SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 13-203030- -00000-0000

Fecha: 2013-08-27 16:20:31 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 19

Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** _____

54. **TÍTULO** TRITERPENOIDES C-17 Y C-3 MODIFICADOS CON ACTIVIDAD INHIBIDORA DE LA MADURACIÓN DEL VIRUS DE INMUNODEFICIENCIA HUMANA

51. **CLASIFICACIÓN INTERNACIONAL** _____

71. **SOLICITANTE** BRISTOL-MYERS SQUIBB COMPANY

DOMICILIO PRINCETON, NEW JERSEY, E.U.A.

74. **APODERADO** ALVARO CORREA

22. **BOGOTÁ, D.C.,** AGOSTO, 27, 2013

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 13-203030- -00000-0000 **de radicación**

Fecha: 2013-08-27 16:20:31 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 19

DIRECCIÓN DE NUEVAS CREACIONES
SOLICITUD FASE NACIONAL -PCT

1	TIPO DE SOLICITUD	☒ Patente de invención ☒ Capítulo I	☐ Patente de Modelo de Utilidad ☐ Capitulo II

2 DATOS SOLICITUD INTERNACIONAL PCT (86)

Solicitud Internacional No.	PCT/US2012/022852	Fecha	27/01/2012
Publicación Internacional No.	WO/2012/106190	Fecha	09/08/2012

3 TÍTULO DE LA INVENCIÓN (200 caracteres o espacios máximos)

TRITERPENOIDES C-17 Y C-3 MODIFICADOS CON ACTIVIDAD INHIBIDORA DE LA MADURACIÓN DEL VIRUS DE INMUNODEFICIENCIA HUMANA

4 CLASIFICACIÓN INTERNACIONAL (CIP)

C07J 63/00 **(2006.01),** ***A61K 31/56*** **(2006.01),** ***A61P 31/18*** **(2006.01)**

5 SOLICITANTE (S) ☐ Esta persona también es inventor. Para datos adicionales utilizar hoja de información complementaria

	APELLIDOS O RAZÓN SOCIAL	NOMBRE	IDENTIFICACIÓN	TIPO
1	**BRISTOL-MYERS SQUIBB COMPANY**			

6 DATOS DEL SOLICITANTE

DIRECCIÓN	**Route 206 and Province Line Road Princeton, New Jersey 08543-4000**	No. TELÉFONO	**6341500**
CIUDAD	**Princeton**	CORREO ELECTRÓNICO	**alvaro.correa@bekermckenzie.com**
DEPARTAMENTO/ESTADO	**New Jersey**	NACIONALIDAD O LUGAR DE CONSTITUCIÓN	**Estados Unidos de América**
PAÍS DE RESIDENCIA	**Estados Unidos de América**		

7 INVENTOR (ES) Para datos adicionales utilizar hoja de información complementaria

	APELLIDOS	NOMBRES	NACIONALIDAD
1.	**REGUEIRO-REN**	**Alicia**	**España**
2.	**LIU**	**Zheng**	**Estados Unidos de América**
3.	**SWIDORSKI**	**Jacob**	**Estados Unidos de América**
4.	**SIN**	**Ny**	**Estados Unidos de América**
5.	**VENABLES**	**Brian Lee**	**Estados Unidos de América**

DIRECCIÓN DE CORREO ELECTRÓNICO:

8 DATOS INVENTOR (ES)

	PAÍS RESIDENCIA	DEPARTAMENTO/ESTADO	CIUDAD	DIRECCIÓN
1.	**Estados Unidos de América**	**Connecticut**	**Wallingford**	**c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492**
2.	**Estados Unidos de América**	**Connecticut**	**Wallingford**	**c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492**
3.	**Estados Unidos de América**	**Connecticut**	**Wallingford**	**c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492**
4.	**Estados Unidos de América**	**Connecticut**	**Wallingford**	**c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492**
5.	**Estados Unidos de América**	**Connecticut**	**Wallingford**	**c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492**

OTRO(S) SOLICITANTE(S) Y/O (OTRO(S)) INVENTOR(ES)

☒ Los demás solicitantes y/o (demás) inventores se indican en una hoja a continuación.

9 ☐ **REPRESENTANTE LEGAL** ☒ **APODERADO**

APELLIDOS	NOMBRES	IDENTIFICACIÓN
CORREA ORDOÑEZ	**Alvaro**	C.C .**79.143.366** T.P .**20.281**

DIRECCIÓN **Av. 82 No. 10-62**

CIUDAD **Bogotá**

PAÍS **Colombia**

No. TELÉFONO **6341500**

CORREO ELECTRÓNICO **alvaro.correa@bekermckenzie.com**

No. RADICACIÓN DE PROTOCOLO DE PODER GENERAL

10 DECLARACIONES DE PRIORIDAD ☒ SI ☐ NO

(33) PAÍS DE ORIGEN	CÓDIGO PAÍS	(31) NÚMERO	(32) FECHA (AAAA/MM/DD)
1. **Estados Unidos de América**	**US**	**61/437,893**	**31/01/2011**
2.			
3.			

11 DECLARACIÓN SOBRE USO DE RECURSOS GENÉTICOS O BIOLÓGICOS

Declaro que el objeto de la presente solicitud de patente fue obtenido a partir de recursos genéticos o biológicos de los que cualquiera de los países miembros de la Comunidad Andina es país de origen.

☐ SI ☒ NO

Nota: En caso afirmativo deberá anexar copia del contrato de acceso de recursos genéticos o productos derivados, o certificado o número de registro, expedido por la Autoridad competente.

12 DECLARACIÓN SOBRE USO DE CONOCIMIENTOS TRADICIONALES

Declaro que el objeto de la presente solicitud de patente fue obtenido a partir de conocimientos tradicionales de comunidades indígenas, afroamericanas o locales de países miembros de la Comunidad Andina.

☐ SI ☒ NO

Nota: En caso afirmativo deberá anexar la licencia o autorización de uso de conocimiento tradicional, o certificado, o número de registro expedido por la Autoridad competente.

13 REDUCCIÓN DE TASAS

Declaro que carezco de medios económicos para presentar la solicitud de patente.

☐ SI ☒ NO

Nota: En caso de ser persona natural y carecer de medios económicos, y por lo tanto, aplique la reducción de tasas a que se refiere la resolución vigente en tarifas, debe firmar la presente solicitud bajo la gravedad de juramento.

Micro, pequeñas y medianas empresas ☐

Universidades públicas o privadas ☐

Entidades sin ánimo de lucro ☐

Debe aportar los documentos que se indican en el numeral 17 de anexos

14 AUTORIZACIÓN DE NOTIFICACIÓN EN LÍNEA ☐ SI ☐ NO

Manifiesto que he leído y entendido perfectamente los términos y condiciones de uso de medios electrónicos para las notificaciones en línea a través de Internet de los actos administrativos proferidos por la Superintendencia de Industria y Comercio que deben ser notificados personalmente y, en consecuencia, autorizo el servicio de notificación a través de internet.

15	**COMPROBANTE DE PAGO O PAGO ELECTRÓNICO**	**N°**	**Fecha**

16 FIRMA DEL SOLICITANTE, DEL APODERADO O DEL REPRESENTANTE LEGAL

Junto a cada firma, indicar el nombre del firmante y su calidad (si tal calidad no es obvia al leer el petitorio)

17 ANEXOS

Documentación Técnica
Solicitud Internacional en castellano

1. ☒ Descripción — N° de folios: 723
2. ☒ Reivindicaciones — N° Reivindicaciones: 20
3. ☐ Dibujos y/o figuras — N° folios: N/A

Documentación Jurídica

9. ☒ Poderes, si fuera el caso.
10. ☒ Documento que legalmente pruebe la cesión del inventor al solicitante o a su causante.
11. ☐ Copia del contrato de acceso de recursos genéticos o productos derivados, certificado o número de registro, si fuera el caso.

4. ☒ Resumen.
5. ☐ Certificado de depósito de material biológico si fuera el caso.
6. ☐ Listado de secuencias de nucleótidos y/o aminoácidos en forma digital si fuera el caso.
7. ☐ Arte final 12 x 12.
8. ☒ Anexo formato digital.

12. ☐ Copia de la licencia o autorización de Conocimientos Tradicionales, certificado o número de registro, si fuera el caso.
13. **Reducción de tasas**

Micro, pequeñas o medinas empresas

☐ Copia simple de la declaración de renta del año inmediatamente anterior, o en su defecto prueba documental idónea.

☐ Documento de constancia de cumplimiento con lo establecido en la ley 905 de 2004.

Universidades públicas o privadas

☐ Copia acto de reconocimiento institucional emitido por el Ministerio de Educación

Entidades sin ánimo de lucro

☐ Copia de registro vigente en Cámara de comercio.
☐ Hoja de información complementaria.
☐ Otros, especificar

14. ☒ Comprobante de pago de la tasa de presentación de la solicitud.
15. ☐ Comprobante de pago por reivindicación de prioridad.
16. ☐ Comprobante de pago de la tasa por concepto de excedente de palabras en la publicación.
17. ☒ Comprobante de pago por reivindicación adicional a 10.

1	(12) TIPO DE SOLICITUD	NUMERO DE RADICACIÓN
☐ Patente de invención ☐ Patente de Modelo de Utilidad		FECHA DE PRESENTACIÓN

4	(71) SOLICITANTE (S)

APELLIDOS O RAZÓN SOCIAL	NOMBRE	IDENTIFICACIÓN	TIPO
2. 3. 4.			

5	DATOS DEL SOLICITANTE

PAÍS DE RESIDENCIA	DEPARTAMENTO/ESTADO	CIUDAD	DIRECCIÓN
2. 3. 4.			

TELÉFONO	FAX	E-MAIL	NACIONALIDAD
2. 3. 4.			

6	(72) INVENTOR (ES)

APELLIDOS	NOMBRE	NACIONALIDAD
6. **SIT**	**Sing-Yuen**	**Estados Unidos de América**
7. **CHEN**	**Yan**	**Estados Unidos de América**
8. **CHEN**	**Jie**	**Estados Unidos de América**
9. **MEANWELL**	**Nicholas A.**	**Estados Unidos de América**
10.		
11.		
12.		

7	DATOS INVENTOR (ES)

DIRECCIÓN	CIUDAD	DEPARTAMENTO/ESTADO	PAÍS RESIDENCIA
6. **c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492**	**Wallingford**	**Connecticut**	**Estados Unidos de América**
7. **c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492**	**Wallingford**	**Connecticut**	**Estados Unidos de América**
8. **c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492**	**Wallingford**	**Connecticut**	**Estados Unidos de América**
9. **c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492**	**Wallingford**	**Connecticut**	**Estados Unidos de América**
10.			
11.			
12.			

9	(30) DECLARACIONES DE PRIORIDAD

Industria y Comercio
SUPERINTENDENCIA

PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA
RELACIÓN DE ANEXOS

Dependencia:	Fecha: ____/ ____/ ____/ AAAA MM DD	Recorrido:
2020	13 8 27	4

Tipo de Radicación: Entrada: ☒ Salida: ☐ Traslado: ☐ Convenio: ☐

Radicador: | Planilla:

ID	*No. Radicación*	*Consecutivo*	*Item*
1	13 - 203030	0	7
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			

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

Observaciones:

Folio + 5 anexan cd

1 CD.

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 13 - 0068811

Bogotá D.C., Julio 10 de 2013 - 16:43:39

RECIBIDO DE : BAKER NI 900.532.339

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	545480596	10/07/2013	117.455.000.00

*** Conceptos Pagados ***

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

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

Responsable: _____
-****-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 13-203030- -00000-0000
Fecha: 2013-08-27 16:20:31 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 19

7

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 13 - 0084066

Bogotá D.C., Agosto 23 de 2013 - 15:55:57

RECIBIDO DE : BAKER NI 900.532.339 R

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
RECIBO DE CA	999999999	56860	11/06/2013		30.000.00
RECIBO DE CA	999999999	68934	10/07/2013		270.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
10	50005-01-01 SOLICITUDES	1607 REIVINDICACION PATENTE UNITARIA ADICIONAL A LAS 10 INIC	30.000.00	300.000.00
				$300.000.00

SON: **TRESCIENTOS MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-****-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 13-203030- -00000-0000
Fecha: 2013-08-27 16:20:31 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 19

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO PROPIETARIOS

PATENTE DE INVENCION ____ PCT X MODELO DE UTILIDAD ____ DISEÑO INDUSTRIAL ___

(21) N° de solicitud: (22) Fecha de solicitud:
(51) Clasificación Internacional :

(71)Solicitante(s)
BRISTOL-MYERS SQUIBB COMPANY

(72) Inventor(es)
REGUEIRO-REN, Alicia; LIU, Zheng; SWIDORSKI, Jacob; SIN, Ny; VENABLES, Brian Lee; SIT, Sing-Yuen; CHEN, Yan; CHEN, Jie; MEANWELL, Nicholas A.

(74) Apoderado: **ALVARO CORREA ORDOÑEZ**

(30) Prioridad	(31) ***No. Prioridad***	32) ***Fecha***	(33) ***País***
	61/437,893	**31/01/2011**	**US**

(85) Fecha inicio fase nacional : **31/08/2013**
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud : **27/01/2012**
No. de solicitud : **PCT/US2012/022852**

(87) Publicación internacional
Fecha : **09/08/2012**
N° publicación : **WO/2012/106190**

(54) Titulo : **TRITERPENOIDES C-17 Y C-3 MODIFICADOS CON ACTIVIDAD INHIBIDORA DE LA MADURACIÓN DEL VIRUS DE INMUNODEFICIENCIA HUMANA**

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO TEMATICO

PATENTE DE INVENCION ____ PCT _X_ MODELO DE UTILIDAD ____ DISEÑO INDUSTRIAL ___

(21) N° de solicitud: (22) Fecha de solicitud:
(51) Clasificación Internacional :

(71)Solicitante(s)
BRISTOL-MYERS SQUIBB COMPANY

(72) Inventor(es)
REGUEIRO-REN, Alicia; LIU, Zheng; SWIDORSKI, Jacob; SIN, Ny; VENABLES, Brian Lee; SIT, Sing-Yuen; CHEN, Yan; CHEN, Jie; MEANWELL, Nicholas A.

(74) Apoderado: **ALVARO CORREA ORDOÑEZ**

(30) Prioridad	(31) *No. Prioridad*	32) *Fecha*	(33) *País*
	61/437,893	**31/01/2011**	**US**

(85) Fecha límite inicio fase nacional : **31/08/2013**
(86) Datos relativos a la presentación de la solic. PCT
Fecha de presentación de la solicitud : **27/01/2012**
No. de solicitud : **PCT/US2012/022852**

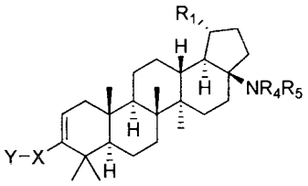
(87) Publicación internacional:
Fecha : **09/08/2012**
No. Publicación : **WO/2012/106190**

(54) Titulo : **TRITERPENOIDES C-17 Y C-3 MODIFICADOS CON ACTIVIDAD INHIBIDORA DE LA MADURACIÓN DEL VIRUS DE INMUNODEFICIENCIA HUMANA**

(57) Resumen :

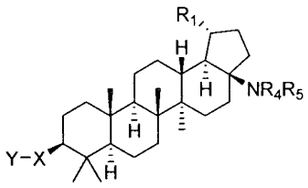
La presente invención se refiere a compuestos que tienen propiedades farmacológicas y que afectan el aspecto biológico, sus composiciones farmacéuticas y métodos de uso. En particular, los triterpenoides C-17 y C-3 modificados que tienen una actividad antiviral única se proporcionan como inhibidores de la maduración del VIH, como se representa mediante los compuestos de las Fórmulas I, II y III:

CONTINUA AL RESPALDO ...



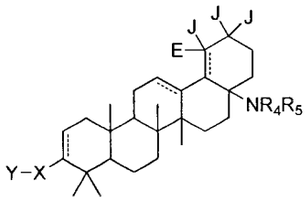
Fórmula I

;



Fórmula II

; y



Fórmula III

Estos compuestos son útiles para el tratamiento del VIH y del SIDA.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

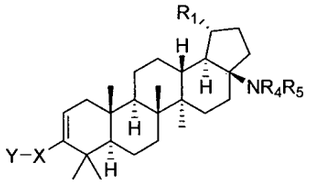
10

(21) N° de solicitud:	(51) Int Cl:
22) Fecha de solicitud:	(71)Solicitante(s) **BRISTOL-MYERS SQUIBB COMPANY**
(30) Prioridad (31) ***No.*** **61/437,893** 32) ***Fecha*** **31/01/2011** (33) ***País*** **US**	(72) Inventor(es) **REGUEIRO-REN, Alicia** **LIU, Zheng** **SWIDORSKI, Jacob** **SIN, Ny** **VENABLES, Brian Lee** **SIT, Sing-Yuen** **CHEN, Yan** **CHEN, Jie** **MEANWELL, Nicholas A.**
	(74) Apoderado: **ALVARO CORREA ORDOÑEZ**
(85) Fecha limite inicio fase nacional : **31/08/2013** (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud : **27/01/2012** No. de solicitud : **PCT/US2012/022852**	(87) Publicación internacional Fecha : **09/08/2012** N° publicación : **WO/2012/106190**

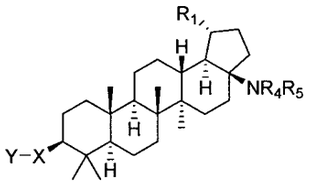
(54) Titulo: **TRITERPENOIDES C-17 Y C-3 MODIFICADOS CON ACTIVIDAD INHIBIDORA DE LA MADURACIÓN DEL VIRUS DE INMUNODEFICIENCIA HUMANA**

Resumen :

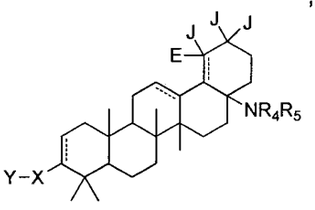
La presente invención se refiere a compuestos que tienen propiedades farmacológicas y que afectan el aspecto biológico, sus composiciones farmacéuticas y métodos de uso. En particular, los triterpenoides C-17 y C-3 modificados que tienen una actividad antiviral única se proporcionan como inhibidores de la maduración del VIH, como se representa mediante los compuestos de las Fórmulas I, II y III:



Fórmula I ;



Fórmula II ; y



Fórmula III

Estos compuestos son útiles para el tratamiento del VIH y del SIDA.

PATENT COOPERATION TREATY

PCT/US2012/022852

Received – BMS IP Dept.
Action Due:
Due Date:
Atty/Agt:
By D. Bragg at May 14, 2012

From the INTERNATI

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

LEVIS, John F.
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, New Jersey 08543-4000
ETATS-UNIS D'AMERIQUE

Date of mailing *(day/month/year)* 11 May 2012 (11.05.2012)	
Applicant's or agent's file reference 11696-WO-PCT	IMPORTANT NOTIFICATION
International application No. PCT/US2012/022852	International filing date *(day/month/year)* 27 January 2012 (27.01.2012)

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
LIU, Zheng c/o Bristol-Myers Squibb Company 5 Research Parkway Wallingford, Connecticut 06492 United States of America	CN	US
	Telephone No.	
	Facsimile No.	
	E-mail address	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☐ the address ☒ the nationality ☐ the residence

Name and Address	State of Nationality	State of Residence
LIU, Zheng c/o Bristol-Myers Squibb Company 5 Research Parkway Wallingford, Connecticut 06492 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	E-mail address ☐ Notifications by e-mail authorized	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☒ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☐ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 90 90	Authorized officer Fujino Kaori e-mail pt07.pct@wipo.int Telephone No. +41 22 338 74 07

Form PCT/IB/306 (January 2009) 1/EW4HXSQHXW65E0

TRATADO DE COOPERACION EN MATERIA DE PATENTES

De la OFICINA INTERNACIONAL

PCT
NOTIFICACION DEL REGISTRO DE UN CAMBIO

(Regla 92bis.1 e Instrucciones Administrativas, Sección 422 del PCT)

Para:

LEVIS, John F.
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, New Jersey 08543-4000
ESTADOS UNIDOS DE AMÉRICA

Fecha de Envío (día/mes/año) 11 Mayo 2012 (11.05.2012)	
Referencia de registro del solicitante o mandatario 11696-WO-PCT	**NOTIFICACION IMPORTANTE**
Solicitud Internacional No. PCT/US2012/022852	Fecha de presentación Internacional (día/mes/año) 27 Enero 2012 (27.01.2012)

1. las siguientes indicaciones aparecen en el registro que se refiere a:

☒ El solicitante ☒ El inventor ☐ El agente ☐ El representante común

Nombre y dirección	Estado de Nacionalidad	Estado de Residencia
LIU, Zheng c/o Bristol-Myers Squibb Company 5 Research Parkway Wallingford, Connecticut 06492 Estados Unidos de América	CN	US
	No. Teléfono	
	No. Fax.	
	Dirección de e-mail	

2. La oficina internacional notifica por la presente que se ha registrado el siguiente cambio que se refiere a:

☐ La persona ☐ El nombre ☐ La dirección ☒ La nacionalidad ☐ La residencia

Nombre y dirección	Estado de Nacionalidad	Estado de Residencia
LIU, Zhen c/o Bristol-Myers Squibb Company 5 Research Parkway Wallingford, Connecticut 06492 Estados Unidos de América	US	US
	No. Teléfono:	
	No. Fax.	
	Dirección de e-mail ☐ Notificaciones por e-mail autorizado	

3. Observaciones Adicionales si las hay:

4. Una copia de esta notificación se ha enviado a:

☒ La oficina receptora
☒ La Autoridad de Búsqueda Internacional
☐ las Autoridades especificadas para la búsqueda suplementaria
☐ La Autoridad del Examen Preliminar Internacional
☒ Las oficinas designadas relacionadas
☐ Las oficinas elegidas relacionadas
☐ Otras:

La Oficina Internacional de WIPO 34, Chemin des Colombettes 1211 Ginebra 20, Suiza Facsímile No. +41 22 338 90 90	Funcionario Autorizado Fujino Kaori e-mail: pt07.pct@wipo.int Teléfono No. +41 22 338 74 07

VIII-2-1	**Declaration: Entitlement to apply for and be granted a patent** Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	In relation to this international application BRISTOL-MYERS SQUIBB COMPANY is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(iv)		an assignment from REGUEIRO-REN, Alicia to BRISTOL-MYERS SQUIBB COMPANY, dated 14 February 2011 (14.02.2011)
VIII-2-1(iv)		an assignment from LIU, Zheng to BRISTOL-MYERS SQUIBB COMPANY, dated 14 February 2011 (14.02.2011)
VIII-2-1(iv)		an assignment from SWIDORSKI, Jacob to BRISTOL-MYERS SQUIBB COMPANY, dated 14 February 2011 (14.02.2011)
VIII-2-1(iv)		an assignment from SIN, Ny to BRISTOL-MYERS SQUIBB COMPANY, dated 22 February 2011 (22.02.2011)
VIII-2-1(iv)		an assignment from VENABLES, Brian Lee to BRISTOL-MYERS SQUIBB COMPANY, dated 22 February 2011 (22.02.2011)
VIII-2-1(iv)		an assignment from SIT, Sing-Yuen to BRISTOL-MYERS SQUIBB COMPANY, dated 16 February 2011 (16.02.2011)
VIII-2-1(iv)		an assignment from CHEN, Yan to BRISTOL-MYERS SQUIBB COMPANY, dated 14 February 2011 (14.02.2011)
VIII-2-1(iv)		an assignment from CHEN, Jie to BRISTOL-MYERS SQUIBB COMPANY, dated 14 February 2011 (14.02.2011)
VIII-2-1(iv)		an assignment from MEANWELL, Nicholas A. to BRISTOL-MYERS SQUIBB COMPANY, dated 14 February 2011 (14.02.2011)

PCT PETITORIO

Original (para PRESENTACIÓN)

VIII-2-1	**Declaración: Derecho para solicitar y ser otorgada una patente** Declaración del derecho del solicitante, como en la presentación internacional, para solicitar y ser otorgada una patente (Reglas 4.17(i) y 51bis.1(a)(ii)), en caso en donde la declaración bajo la Regla 4.17(iv) no es apropiada Nombre	En relación a esta solicitud internacional BRISTOL-MYERS SQUIBB COMPANY tiene el derecho para solicitar y sea otorgada una patente por virtud de lo siguiente:
VIII-2-1(iv)		Una cesión de REGUEIRO-REN, Alicia a BRISTOL-MYERS SQUIBB COMPANY, fechada el 14 de Febrero de 2011 (14.02.2011)
VIII-2-1(iv)		Una cesión de LIU, Zheng a BRISTOL-MYERS SQUIBB COMPANY, fechada el 14 de Febrero de 2011 (14.02.2011)
VIII-2-1(iv)		Una cesión de SWIDORSKI, Jacob a BRISTOL-MYERS SQUIBB COMPANY, fechada el 14 de Febrero de 2011 (14.02.2011)
VIII-2-1(iv)		Una cesión de SIN, Ny a BRISTOL-MYERS SQUIBB COMPANY, fechada el 22 de Febrero de 2011 (22.02.2011)
VIII-2-1(iv)		Una cesión de VENABLES, Brian Lee a BRISTOL-MYERS SQUIBB COMPANY, fechada el 22 de Febrero de 2011 (22.02.2011)
VIII-2-1(iv)		Una cesión de SIT, Sing-Yuen a BRISTOL-MYERS SQUIBB COMPANY, fechada el 16 de Febrero de 2011 (16.02.2011)
VIII-2-1(iv)		Una cesión de CHEN, Yan a BRISTOL-MYERS SQUIBB COMPANY, fechada el 14 de Febrero de 2011 (14.02.2011)
VIII-2-1(iv)		Una cesión de CHEN, Jie a BRISTOL-MYERS SQUIBB COMPANY, fechada el 14 de Febrero de 2011 (14.02.2011)
VIII-2-1(iv)		Una cesión de MEANWELL, Nicholas A. a BRISTOL-MYERS SQUIBB COMPANY, fechada el 14 de Febrero de 2011 (14.02.2011)

15

POD-4002

TRADUCCIÓN OFICIAL N° 0507071 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

PODER OTORGADO POR BRISTOL-MYERS SQUIBB COMPANY

APOSTILLA

1. PAÍS: ESTADOS UNIDOS DE AMÉRICA

2. ESTE DOCUMENTO PÚBLICO HA SIDO FIRMADO POR:
SALLY B. HANSEN

3. QUIEN ACTÚA EN CALIDAD DE NOTARIO PÚBLICO DE NUEVA JERSEY

4. LLEVA EL SELLO DE:
SALLY B. HANSEN, NOTARIO

CERTIFICADO

5. EN TRENTON, NUEVA JERSEY

6. EL 28 DE JUNIO DE 2007

7. POR BRADLEY ABELOW, TESORERO DE NUEVA JERSEY

8. N° A295716

9. SELLO (APARECE ADHERIDO SELLO DORADO)

10. FIRMA (FIRMADO) BRADLEY ABELOW

Texto en inglés y en español mediante el cual **BRISTOL-MYERS SQUIBB COMPANY** domiciliada en Nueva York, Nueva York, otorga poder a **ALVARO CORREA ORDOÑEZ y/o OLGA GEORGETTE OTERO y/o RICARDO METKE y/o JUAN PABLO CONCHA**

Dado y suscrito el 30 de mayo de 2007

(Firmado) Anastasia P. Winslow, Senior Patent Counsel (Abogado de Patentes Senior)

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
RES. 034 de ENERO 11 de 1983
MINISTERIO DE JUSTICIA

1

16

TRADUCCIÓN OFICIAL N° 0507071 al español de un documento escrito en inglés, efectuada por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor e Intérprete Oficial inglés-español-inglés según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia de la República de Colombia

CERTIFICACIÓN NOTARIAL

Texto en inglés y en español mediante el cual el suscrito Notario certifica el 30 de mayo de 2007 la existencia legal de la sociedad **BRISTOL-MYERS SQUIBB COMPANY** así como las funciones y firma de su representante autorizado Anastasia P. Winslow, Senior Patent Counsel (Abogado de Patentes Senior) para lo cual se basó en los documentos relacionados en inglés en el punto 6 de la certificación los cuales se traducen aquí al español, a saber:

Certificación suscrita por el Vicepresidente Senior y el Asesor Legal de Bristol-Myers Squibb Company el 7 de abril de 2007.

Certificado de Constitución Enmendado y Replanteado de Bristol-Myers Squibb Company fechado mayo 24, 2005.

[Firmado] SALLY B. HANSEN, Notario Público

[Sello en tinta que dice: "SALLY B. HANSEN. Notario Público de Nueva Jersey. Mi comisión vence el 6 de junio de 2010"]

[Aparece sello realzado]

La anterior es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

Jaime Armando Garavito Burgos
c.c. N° 19.130.702 de Bogotá
Traductor e Intérprete Oficial según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia

BOGDM5 # 82106

JAIME A. GARAVITO B
TRADUCTOR E INTERPRETE OFICIAL
Res. 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

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APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
SALLY B HANSEN

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
SALLY B HANSEN, NOTARY

CERTIFIED

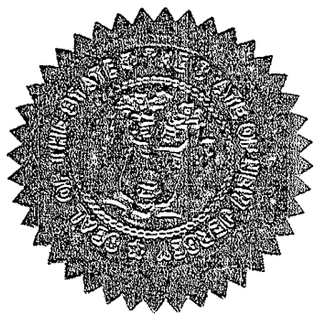
5. AT TRENTON, NEW JERSEY

6. THE 28TH DAY OF JUNE 2007

7. BY: Bradley Abelow, NEW JERSEY TREASURER

8. NO. A295716

9. SEAL/STAMP:



10. SIGNATURE

Bradley Abelow

18

BAKER & MCKENZIE

Raisbeck, Lara, Rodríguez & Rueda
Av. 82 No. 10 - 62 6th Floor
Bogotá, Colombia

NIT: 860.066.640-3
Tel: +57 1 634 1500
Fax: +57 1 376 2211
www.bakernet.com

POWER OF ATTORNEY

The undersigned.

BRISTOL–MYERS SQUIBB COMPANY

domiciled in

Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 United States of America

declares that it hereby grants to

ALVARO CORREA-ORDOÑEZ and/or
OLGA GEORGETTE OTERO and/or
RICARDO METKE and/or
JUAN PABLO CONCHA

with domicile at Av. 82 No. 10 – 62, 6Th floor, of Bogotá D. C., Colombia, a full and sufficient power of attorney to 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, industrial designs, integrated circuits, layout-designs and vegetal varieties; the registration of trademarks, denominations of origin, commercial names, trade emblems, slogans and domain names; its renewal, assignments, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b)Processes of protection to the consumer, unfair competition, oppositions, cancellations, nullity, precautionary injunctions, infringement, granting of licenses, writ mandamus, the protection of trade secrets, and in general the civil, penal, an administrative processes relating to those rights. And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

I hereby ratify all actions previously taken on behalf of this company by the aforementioned attorneys with respect to the mentioned matters.

Done and subscribed in

On the 30 day of May of 2007

Signature of the person issuing the Power

Anastasia P. Winslow
Senior Patent Counsel

PODER DE ABOGADO

La abajo firmada,

BRISTOL–MYERS SQUIBB COMPANY

domiciliada en

Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 Estados Unidos de América

declara por el presente que otorga a

ALVARO CORREA-ORDOÑEZ y/o
OLGA GEORGETTE OTERO y/o
RICARDO METKE y/o
JUAN PABLO CONCHA

con domicilio en la Av. 82 No. 10 – 62 Piso 6 en Bogotá D. C., Colombia, poder especial amplio y suficiente, 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 autoridades 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, diseños industriales, esquemas de trazado de circuitos integrados y variedades vegetales; el registro de marcas, denominaciones de origen, nombres comerciales, enseñas, lemas comerciales y nombres de dominio; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Los procesos para la protección del consumidor, competencia desleal, oposiciones, cancelaciones, nulidades, medidas cautelares, infracciones, concesión de licencias, la tutela, la protección de secretos industriales, y en general procesos civiles, penales, administrativos relacionados con estos derechos. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del caso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

Igualmente, ratifico todo lo actuado hasta el momento en los mismos asuntos, por cualquiera de los mencionados apoderados en representación de ésta sociedad.

Dado y firmado en

A los 30 días del mes de mayo de 2007

Firma de la persona que firma el Poder

4

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NOTARIAL CERTIFICATION

On this 30 day of May

2007 , the undersigned Notary

CERTIFIES

1. That **Name of the person issuing the power**
Anastasia P. Winslow
of legal age and domiciled in
Princeton, NJ USA
Address, city, state, country
set his hand on the foregoing document.

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

3. That the grantor has executed the foregoing document as
Senior Patent Counsel
Position of the person issuing the Power
of the judicial person **BRISTOL-MYERS SQUIBB COMPANY**

4. That the judicial person **BRISTOL-MYERS SQUIBB COMPANY**
having its home office in
Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 United States of America
is duly organized, has present legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.

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

6. That I have based certifications 3, 4 and 5 above on the following authentic documents for such purpose exhibited to me and which I mention specifically, giving their dates and their origin or source:
(Please indicate here the documents such as the articles of incorporation, by laws or resolution from the Board of Directors and their dates, on which the notary relied to grant the certification)
- Certification executed by Sr. Vice President and General Counsel of Bristol-Myers Squibb Company on April 7, 2007
- Amended and Restated Certificate of Incorporation of Bristol-Myers Squibb Company dated May 24, 2005

Notary Public

SALLY B. HANSEN
Notary Public of New Jersey
My Commission Expires June 6, 2010

CERTIFICACION NOTARIAL

A los 30 días del mes de mayo

de 2007 , el suscrito Notario

DA FE

1 Que Anastasia P. Winslow

mayor y domiciliado en Princeton, NJ
Estados Unidos de América

suscribió de su puño y letra el documento que antecede.

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

3 Que el otorgante ha suscrito el referido documento en su carácter de
Abogados de Patentes Senior
de la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**

4 Que la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**
con sede en
Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 Estados Unidos de América
está legalmente constituída, que tiene existencia legal actual y que el acto para el cual se otorga el poder está comprendido entre los que constituyen su objeto social.

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

6. Que he basado las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono específicamente con expresión de sus fechas y de su origen o procedencia:
- Certificación suscrita por el Vicepresidente Senior y el Asesor Legal de Bristol-Myers Squibb Company el 7 de abril de 2007.
- Certificado de Constitución Enmendado y Replanteado de Bristol-Myers Squibb Company fechado el 4 de mayo de 2005.

El Notario Público

5

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 13-203030- -00000-0000

Fecha: 2013-08-27 16:20:31 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 19

PATENTE DE INVENCIÓN ☐ MODELO D

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☐ MODELO DE UTILIDAD PCT ☐ Art.33 Decisión 486/00, Circular Única

- ☐ Indicación que se solicita una PCT
- ☐ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐ (Art. 119 Decisión 486/00)

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ (Art. 92 Decisión 486/00)

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 August 2012 (09.08.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/106190 A1

(51) International Patent Classification:
C07J 63/00 (2006.01) *A61P 31/18* (2006.01)
A61K 31/56 (2006.01)

(21) International Application Number:
PCT/US2012/022852

(22) International Filing Date:
27 January 2012 (27.01.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/437,893 31 January 2011 (31.01.2011) US

(71) Applicant *(for all designated States except US)*: **BRISTOL-MYERS SQUIBB COMPANY** [US/US]; Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 (US).

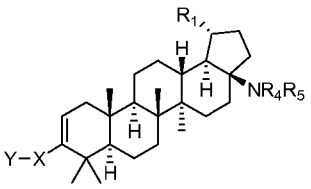
(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **REGUEIRO-REN, Alicia** [ES/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **LIU, Zheng** [US/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **SWIDORSKI, Jacob** [US/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **SIN, Ny** [US/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **VENABLES, Brian Lee** [US/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **SIT, Sing-Yuen** [US/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **CHEN, Yan** [US/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US). **CHEN, Jie** [CN/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492

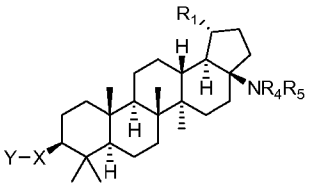
[Continued on next page]

(54) Title: C-17 AND C-3 MODIFIED TRITERPENOIDS WITH HIV MATURATION INHIBITORY ACTIVITY

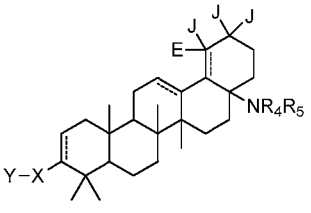
(57) Abstract: Compounds having drug and bio-affecting properties, their pharmaceutical compositions and methods of use are set forth. In particular, C-17 and C-3 modified triterpenoids that possess unique antiviral activity are provided as HIV maturation inhibitors, as represented by compounds of Formulas I, II and III. These compounds are useful for the treatment of HIV and AIDS.



I



II



III

WO 2012/106190 A1

(US). **MEANWELL, Nicholas A.** [US/US]; c/o Bristol-Myers Squibb Company, 5 Research Parkway, Wallingford, Connecticut 06492 (US).

(74) Agents: **LEVIS, John F.** et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, New Jersey 08543-4000 (US).

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

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C-17 AND C-3 MODIFIED TRITERPENOIDS WITH HIV MATURATION INHIBITORY ACTIVITY

FIELD OF THE INVENTION

The present invention relates to novel compounds useful against HIV and, more particularly, to compounds derived from betulinic acid and other structurally-related compounds which are useful as HIV maturation inhibitors, and to pharmaceutical compositions containing same, as well as to methods for their preparation.

BACKGROUND OF THE INVENTION

HIV-1 (human immunodeficiency virus -1) infection remains a major medical problem, with an estimated 45-50 million people infected worldwide at the end of 2010. The number of cases of HIV and AIDS (acquired immunodeficiency syndrome) has risen rapidly. In 2005, approximately 5.0 million new infections were reported, and 3.1 million people died from AIDS. Currently available drugs for the treatment of HIV include nucleoside reverse transcriptase (RT) inhibitors or approved single pill combinations: zidovudine (or AZT or Retrovir®), didanosine (or Videx®), stavudine (or Zerit®), lamivudine (or 3TC or Epivir®), zalcitabine (or DDC or Hivid®), abacavir succinate (or Ziagen®), Tenofovir disoproxil fumarate salt (or Viread®), emtricitabine (or FTC - Emtriva®), Combivir® (contains -3TC plus AZT), Trizivir® (contains abacavir, lamivudine, and zidovudine), Epzicom® (contains abacavir and lamivudine), Truvada® (contains Viread® and Emtriva®); non-nucleoside reverse transcriptase inhibitors: nevirapine (or Viramune®), delavirdine (or Rescriptor®) and efavirenz (or Sustiva®), Atripla® (Truvada® + Sustiva®), and etravirine, and peptidomimetic protease inhibitors or approved formulations: saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, lopinavir, Kaletra®(lopinavir and Ritonavir), darunavir, atazanavir (Reyataz®) and tipranavir (Aptivus®) and

cobicistat, and integrase inhibitors such as raltegravir (Isentress®), and entry inhibitors such as enfuvirtide (T-20) (Fuzeon®) and maraviroc (Selzentry®).

Each of these drugs can only transiently restrain viral replication if used alone. However, when used in combination, these drugs have a profound effect on viremia and disease progression. In fact, significant reductions in death rates among AIDS patients have been recently documented as a consequence of the widespread application of combination therapy. However, despite these impressive results, 30 to 50% of patients may ultimately fail combination drug therapies. Insufficient drug potency, non-compliance, restricted tissue penetration and drug-specific limitations within certain cell types (e.g. most nucleoside analogs cannot be phosphorylated in resting cells) may account for the incomplete suppression of sensitive viruses. Furthermore, the high replication rate and rapid turnover of HIV-1 combined with the frequent incorporation of mutations, leads to the appearance of drug-resistant variants and treatment failures when sub-optimal drug concentrations are present. Therefore, novel anti-HIV agents exhibiting distinct resistance patterns, and favorable pharmacokinetic as well as safety profiles are needed to provide more treatment options. Improved HIV fusion inhibitors and HIV entry coreceptor antagonists are two examples of new classes of anti-HIV agents further being studied by a number of investigators.

HIV attachment inhibitors are a further subclass of antiviral compounds that bind to the HIV surface glycoprotein gp120, and interfere with the interaction between the surface protein gp120 and the host cell receptor CD4. Thus, they prevent HIV from attaching to the human CD4 T-cell, and block HIV replication in the first stage of the HIV life cycle. The properties of HIV attachment inhibitors have been improved in an effort to obtain compounds with maximized utility and efficacy as antiviral agents. In particular, US 7,354,924 and US 2005/0209246 are illustrative of HIV attachment inhibitors.

Another emerging class of compounds for the treatment of HIV are called HIV maturation inhibitors. Maturation is the last of as many as 10 or more steps in HIV replication or the HIV life cycle, in which HIV becomes infectious as a consequence

of several HIV protease-mediated cleavage events in the gag protein that ultimately results in release of the capsid (CA) protein. Maturation inhibitors prevent the HIV capsid from properly assembling and maturing, from forming a protective outer coat, or from emerging from human cells. Instead, non-infectious viruses are produced, preventing subsequent cycles of HIV infection.

Certain derivatives of betulinic acid have now been shown to exhibit potent anti-HIV activity as HIV maturation inhibitors. For example, US 7,365,221 discloses monoacylated betulin and dihydrobetuline derivatives, and their use as anti-HIV agents. As discussed in the '221 reference, esterification of betulinic acid (1) with certain substituted acyl groups, such as 3',3'-dimethylglutaryl and 3',3'-dimethylsuccinyl groups produced derivatives having enhanced activity (Kashiwada, Y., et al., J. Med. Chem. 39:1016-1017 (1996)). Acylated betulinic acid and dihydrobetulinic acid derivatives that are potent anti-HIV agents are also described in U.S. Pat. No. 5,679,828. Esterification of the hydroxyl in the 3 carbon of betulin with succinic acid also produced a compound capable of inhibiting HIV-1 activity (Pokrovskii, A. G., et al., Gos. Nauchnyi Tsentr Virusol. Biotekhnol. "Vector" 9:485-491 (2001)).

Other references to the use of treating HIV infection with compounds derived from betulinic acid include US 2005/0239748 and US 2008/0207573, as well as WO2006/053255, WO2009/100532 and WO2011/007230.

One HIV maturation compound that has been in development has been identified as Bevirimat or PA-457, with the chemical formula of $C_{36}H_{56}O_6$ and the IUPAC name of 3β-(3-carboxy-3-methyl-butanoyloxy) lup-20(29)-en-28-oic acid.

Reference is also made herein to the applications by Bristol-Myers Squibb entitled "MODIFIED C-3 BETULINIC ACID DERIVATIVES AS HIV MATURATION INHIBITORS" USSN 13/151,706 filed on June 2, 2011 and "C-28 AMIDES OF MODIFIED C-3 BETULINIC ACID DERIVATIVES AS HIV MATURATION INHIBITORS" USSN 13/151,722, filed on June 2, 2011. Reference is also made to the application entitled "C-28 AMINES OF C-3 MODIFIED

BETULINIC ACID DERIVATIVES AS HIV MATURATION INHIBITORS" USSN 61/437,870, filed on January 31, 2011.

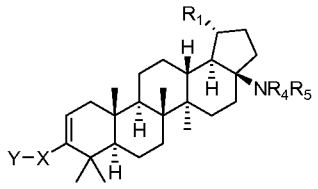
What is now needed in the art are new compounds which are useful as HIV maturation inhibitors, as well as new pharmaceutical compositions containing these compounds.

SUMMARY OF THE INVENTION

The present invention provides compounds of Formulas I, II, and III below, including pharmaceutically acceptable salts thereof, their pharmaceutical formulations, and their use in patients suffering from or susceptible to a virus such as HIV. The compounds of Formulas I – III are effective antiviral agents, particularly as inhibitors of HIV. They are useful for the treatment of HIV and AIDS.

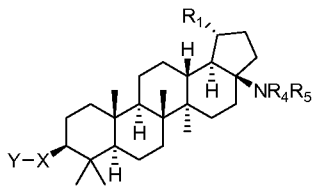
One embodiment of the present invention is directed to a compound, including pharmaceutically acceptable salts thereof, which is selected from the group of:

a compound of formula I



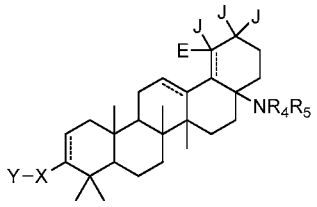
Formula I ;

a compound of formula II



Formula II ; and

a compound of formula III



Formula III ;

wherein R_1 is isopropenyl or isopropyl;

J and E are –H or $–CH_3$, and E is absent when the double bond is present;

X is a phenyl or heteroaryl ring substituted with A, wherein A is at least one member selected from the group of -H, -halo, -hydroxyl, -C_{1-6} alkyl, -C_{1-6} alkoxy, and -$COOR_2$;

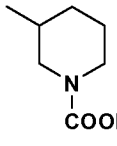
R_2 is -H, -C_{1-6} alkyl, -alkylsubstituted C_{1-6} alkyl or-arylsubstituted C_{1-6} alkyl;

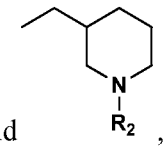
Y is selected from the group of $–COOR_2$, $-C(O)NR_2SO_2R_3$, - $C(O)NHSO_2NR_2R_2$, - $NR_2SO_2R_2$, $-SO_2NR_2R_2$, -C_{3-6} cycloalkyl-$COOR_2$, -C_{2-6} alkenyl-$COOR_2$, -C_{2-6} alkynyl-$COOR_2$, -C_{1-6} alkyl-$COOR_2$, $-NHC(O)(CH_2)_n-COOR_2$, $-SO_2NR_2C(O)R_2$, -tetrazole, and –CONHOH,

wherein n=1-6;

R_3 is -C_{1-6} alkyl or -alkylsubstituted C_{1-6} alkyl;

R_4 is selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} alkyl-$C(OR_3)_2$-C_{3-6} cycloalkyl, -C_{1-6} substituted alkyl, -C_{1-6} alkyl-C_{3-6} cycloalkyl, -C_{1-6} alkyl-Q_1, -C_{1-6} alkyl-C_{3-6} cycloalkyl-Q_1, aryl, heteroaryl, substituted heteroaryl, -COR_6, -$COCOR_6$, -SO_2R_7, -$SO_2NR_2R_2$,



, and


,

wherein Q_1 is selected from the group of heteroaryl, substituted heteroaryl, halogen, -CF_3, -OR_2, -$COOR_2$, -NR_8R_9, -$CONR_{10}R_{11}$ and -SO_2R_7;

R_5 is selected from the group of -H, -C_{1-6} alkyl, -C_{3-6} cycloalkyl, -C_{1-6} alkylsubstituted alkyl, -C_{1-6} alkyl-NR_8R_9, -COR_{10}, -COR_6, -$COCOR_6$, -SO_2R_7 and -$SO_2NR_2R_2$;

with the proviso that only one of R_4 or R_5 can be selected from the group of -COR_6, -$COCOR_6$,-SO_2R_7 and -$SO_2NR_2R_2$;

or R_4 and R_5 are taken together with the adjacent N to form



;

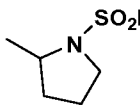
R_6 is selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} alkyl-substitutedalkyl, -C_{3-6} cycloalkyl, -C_{3-6} substitutedcycloalkyl-Q_2, -C_{1-6} alkyl-Q_2, -C_{1-6} alkyl-substitutedalkyl-Q_2,-C_{3-6} cycloalkyl-Q_2, aryl-Q_2, -$NR_{13}R_{14}$, and -OR_{15};

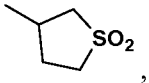
wherein Q_2 is selected from the group of aryl, heteroaryl, substituted heteroaryl, -OR_2, -$COOR_2$, -NR_8R_9, SO_2R_7, -$CONHSO_2R_3$, and -$CONHSO_2NR_2R_2$;

R_7 is selected from the group of -C_{1-6} alkyl, -C_{1-6} substituted alkyl, -C_{3-6} cycloalkyl, aryl, and heteroaryl;

R_8 and R_9 are independently selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} substituted alkyl, aryl, heteroaryl, substituted aryl, substituted heteroaryl, -C_{1-6} alkyl-Q_2, and -$COOR_3$,

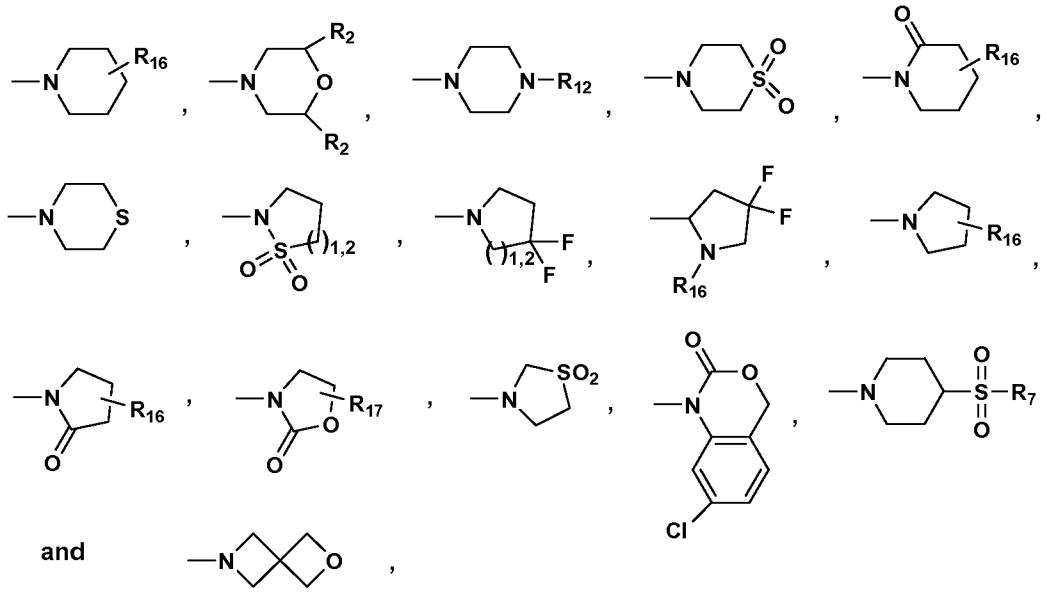
and R_8 and R_9 can also be independently selected from the group of



and


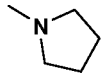
,

or R_8 and R_9 are taken together with the adjacent N to form a cycle selected from the group of:



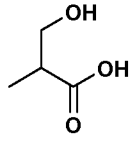
and ,

with the proviso that only one of R_8 or R_9 can be $-COOR_3$;

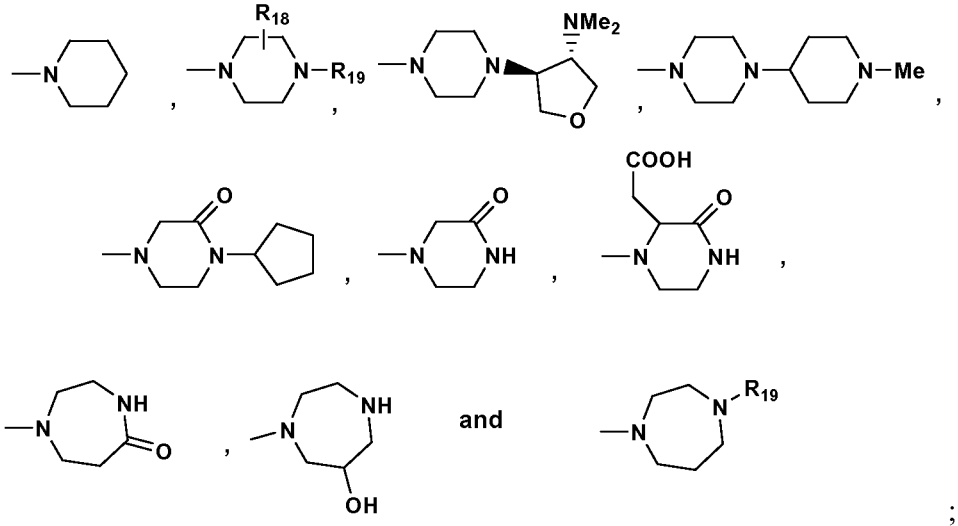
R_{10} and R_{11} are independently selected from the group of -H, $-C_{1-6}$ alkyl, $-C_{1-6}$ substituted alkyl and $-C_{3-6}$ cycloalkyl,
or R_{10} and R_{11} are taken together with the adjacent N to form a cycle such as  ;

R_{12} is selected from the group of $-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-OH; $-C_{1-6}$ alkyl, $-C_{1-6}$ substituted alkyl,$-C_{3-6}$ cycloalkyl, $-COR_7$, $-COONR_{22}R_{23}$, $-SOR_7$, and $-SONR_{24}R_{25}$;

R_{13} and R_{14} are independently selected from the group of -H, $-C_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl, $-C_{1-6}$ substituted alkyl, $-C_{1-6}$ alkyl-Q_3, $-C_{1-6}$ alkyl-C_{3-6} cycloalkyl-Q_3, C_{1-6} substituted alkyl-Q_3 and

 ,

or R_{13} and R_{14} are taken together with the adjacent N to form a cycle selected from the group of:



Q_3 is selected from the group of heteroaryl, substituted heteroaryl, $-NR_{20}R_{21}$, $-CONR_2R_2$, $-COOR_2$, $-OR_2$, and $-SO_2R_3$;

R_{15} is selected from the group of $-C_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl, $-C_{1-6}$ substituted alkyl, $-C_{1-6}$ alkyl-Q_3, $-C_{1-6}$ alkyl-C_{3-6} cycloalkyl-Q_3 and $-C_{1-6}$ substituted alkyl-Q_3;

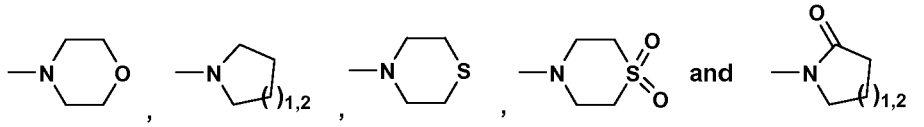
R_{16} is selected from the group of -H, $-C_{1-6}$ alkyl, $-NR_2R_2$, and $-COOR_3$;

R_{17} is selected from the group of -H, $-C_{1-6}$ alkyl, $-COOR_3$, and aryl;

R_{18} is selected from the group of $-COOR_2$ and $-C_{1-6}$ alkyl-$COOR_2$;

R_{19} is selected from the group of -H, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-Q_4, $-COR_3$, $-COOR_3$, wherein Q_4 is selected from the group of $-NR_2R_2$ and $-OR_2$;

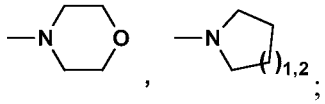
R_{20} and R_{21} are independently selected from the group of -H, $-C_{1-6}$ alkyl, $-C_{1-6}$ substituted alkyl, $-C_{1-6}$ substituted alkyl-OR_2, and $-COR_3$,
or R_{20} and R_{21} are taken together with the adjacent N to form a cycle selected from the group of



with the proviso that only one of R_{20} or R_{21} can be $-COR_3$;

R_{22} and R_{23} are independently selected from the group of H, $-C_{1-6}$ alkyl, $-C_{1-6}$ substituted alkyl, and $-C_{1-6}$ cycloalkyl,

or R_{22} and R_{23} are taken together with the adjacent N to form a cycle selected from the group of



;

R_{24} and R_{25} are independently from the group of H, $-C_{1-6}$ alkyl, $-C_{1-6}$ substituted alkyl, $-C_{1-6}$ alkyl-Q_5, $-C_{1-6}$ cycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl,

and Q_5 is selected from the group of halogen and SO_2R_3.

In a further embodiment, there is provided a method for treating mammals infected with a virus, especially wherein said virus is HIV, comprising administering to said mammal an antiviral effective amount of a compound which is selected from the group of compounds of Formulas I, II, III above, and one or more pharmaceutically acceptable carriers, excipients or diluents. Optionally, the compound of Formulas I, II, and/or III can be administered in combination with an antiviral effective amount of another- AIDS treatment agent selected from the group consisting of: (a) an AIDS antiviral agent; (b) an anti-infective agent; (c) an immunomodulator; and (d) other HIV entry inhibitors.

Another embodiment of the present invention is a pharmaceutical composition comprising an antiviral effective amount of a compound which is selected from the group of compounds of Formulas I, II, and III, and one or more pharmaceutically acceptable carriers, excipients, and diluents; and optionally in combination with an antiviral effective amount of another AIDS treatment agent selected from the group consisting of: (a) an AIDS antiviral agent; (b) an anti-infective agent; (c) an immunomodulator; and (d) other HIV entry inhibitors.

In another embodiment of the invention there is provided one or more methods for making the compounds of Formulas I, II, and III herein.

Also provided herein are intermediate compounds useful in making the compounds of Formulas I, II, and III herein.

The present invention is directed to these, as well as other important ends, hereinafter described.

DETAILED DESCRIPTION OF THE EMBODIMENTS

Since the compounds of the present invention may possess asymmetric centers and therefore occur as mixtures of diastereomers and enantiomers, the present disclosure includes the individual diastereoisomeric and enantiomeric forms of the compounds of Formulas I, II and III in addition to the mixtures thereof.

Definitions

Unless otherwise specifically set forth elsewhere in the application, one or more of the following terms may be used herein, and shall have the following meanings:

"H" refers to hydrogen, including its isotopes, such as deuterium.

The term "$C_{1\text{-}6}$ alkyl" as used herein and in the claims (unless specified otherwise) mean straight or branched chain alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, amyl, hexyl and the like.

"C_1–C_4 fluoroalkyl" refers to F-substituted C_1–C_4 alkyl wherein at least one H atom is substituted with F atom, and each H atom can be independently substituted by F atom;

"Halogen" refers to chlorine, bromine, iodine or fluorine.

An "aryl" or "Ar" group refers to an all carbon monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups having a completely conjugated pi-electron system. Examples, without limitation, of aryl groups are phenyl, napthalenyl and anthracenyl. The aryl group may be substituted or unsubstituted. When substituted the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, O-carbamyl, N-carbamyl, C-amido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethyl, ureido, amino and $-NR^xR^y$, wherein R^x and R^y are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl, C-carboxy, sulfonyl, trihalomethyl, and, combined, a five- or six-member heteroalicyclic ring.

As used herein, a "heteroaryl" group refers to a monocyclic or fused ring (i.e., rings which share an adjacent pair of atoms) group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur and, in addition, having a completely conjugated pi-electron system. Unless otherwise indicated, the heteroaryl group may be attached at either a carbon or nitrogen atom within the heteroaryl group. It should be noted that the term heteroaryl is intended to encompass an N-oxide of the parent heteroaryl if such an N-oxide is chemically feasible as is known in the art. Examples, without limitation, of heteroaryl groups are furyl, thienyl, benzothienyl, thiazolyl, imidazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, benzothiazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyranyl, tetrahydropyranyl, pyrazolyl, pyridyl, pyrimidinyl, quinolinyl, isoquinolinyl, purinyl, carbazolyl, benzoxazolyl, benzimidazolyl, indolyl, isoindolyl, pyrazinyl. diazinyl, pyrazine, triazinyl, tetrazinyl, and tetrazolyl. When substituted the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thioalkoxy, thiohydroxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, O-carbamyl, N-carbamyl, C-amido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethyl, ureido, amino, and $-NR^xR^y$, wherein R^x and R^y are as defined above.

As used herein, a "heteroalicyclic" group refers to a monocyclic or fused ring group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur. Rings are selected from those which provide stable arrangements of bonds and are not intended to encompass systems which would not exist. The rings may also have one or more double bonds. However, the rings do not have a completely conjugated pi-electron system. Examples, without limitation, of heteroalicyclic groups are azetidinyl, piperidyl, piperazinyl, imidazolinyl, thiazolidinyl, 3-pyrrolidin-1-yl, morpholinyl, thiomorpholinyl and tetrahydropyranyl. When substituted the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethanesulfonamido, trihalomethanesulfonyl, silyl, guanyl, guanidino, ureido, phosphonyl, amino and $-NR^xR^y$, wherein R^x and R^y are as defined above.

An "alkyl" group refers to a saturated aliphatic hydrocarbon including straight chain and branched chain groups. Preferably, the alkyl group has 1 to 20 carbon atoms (whenever a numerical range; e.g., "1-20", is stated herein, it means that the group, in this case the alkyl group may contain 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc. up to and including 20 carbon atoms). More preferably, it is a medium size alkyl having 1 to 10 carbon atoms. Most preferably, it is a lower alkyl having 1 to 4 carbon atoms. The alkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more individually selected from trihaloalkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halo, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethanesulfonamido, trihalomethanesulfonyl, and combined, a five- or six-member heteroalicyclic ring.

A "cycloalkyl" group refers to an all-carbon monocyclic or fused ring (i.e., rings which share and adjacent pair of carbon atoms) group wherein one or more rings does not have a completely conjugated pi-electron system. Examples, without limitation, of cycloalkyl groups are cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, cyclohexene, cycloheptane, cycloheptene and adamantane. A cycloalkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more individually selected from alkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halo, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalo- methanesulfonamido, trihalomethanesulfonyl, silyl, amidino, guanidino, ureido, phosphonyl, amino and $-NR^xR^y$ with R^x and R^y as defined above.

An "alkenyl" group refers to an alkyl group, as defined herein, having at least two carbon atoms and at least one carbon-carbon double bond.

An "alkynyl" group refers to an alkyl group, as defined herein, having at least two carbon atoms and at least one carbon-carbon triple bond.

A "hydroxy" group refers to an –OH group.

An "alkoxy" group refers to both an –O-alkyl and an –O-cycloalkyl group as defined herein.

An "aryloxy" group refers to both an –O-aryl and an –O-heteroaryl group, as defined herein.

A "heteroaryloxy" group refers to a heteroaryl-O- group with heteroaryl as defined herein.

A "heteroalicycloxy" group refers to a heteroalicyclic-O- group with heteroalicyclic as defined herein.

A “thiohydroxy” group refers to an –SH group.

A “thioalkoxy” group refers to both an S-alkyl and an –S-cycloalkyl group, as defined herein.

A “thioaryloxy” group refers to both an –S-aryl and an –S-heteroaryl group, as defined herein.

A “thioheteroaryloxy” group refers to a heteroaryl-S- group with heteroaryl as defined herein.

A “thioheteroalicycloxy” group refers to a heteroalicyclic-S- group with heteroalicyclic as defined herein.

A “carbonyl” group refers to a –C(=O)-R” group, where R” is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), as each is defined herein.

An “aldehyde” group refers to a carbonyl group where R” is hydrogen.

A “thiocarbonyl” group refers to a –C(=S)-R” group, with R” as defined herein.

A “Keto” group refers to a –CC(=O)C- group wherein the carbon on either or both sides of the C=O may be alkyl, cycloalkyl, aryl or a carbon of a heteroaryl or heteroalicyclic group.

A “trihalomethanecarbonyl” group refers to a $Z_3CC(=O)$- group with said Z being a halogen.

A “C-carboxy” group refers to a –C(=O)O-R” groups, with R” as defined herein.

An "O-carboxy" group refers to a R"C(-O)O-group, with R" as defined herein.

A "carboxylic acid" group refers to a C-carboxy group in which R" is hydrogen.

A "trihalomethyl" group refers to a $-CZ_3$, group wherein Z is a halogen group as defined herein.

A "trihalomethanesulfonyl" group refers to an $Z_3CS(=O)_2$- groups with Z as defined above.

A "trihalomethanesulfonamido" group refers to a $Z_3CS(=O)_2NR^x$- group with Z as defined above and R^x being H or (C_{1-6})alkyl.

A "sulfinyl" group refers to a –S(=O)-R" group, with R" being (C_{1-6})alkyl.

A "sulfonyl" group refers to a $-S(=O)_2R$" group with R" being (C_{1-6})alkyl.

A "S-sulfonamido" group refers to a $-S(=O)_2NR^XR^Y$, with R^X and R^Y independently being H or (C_{1-6})alkyl.

A "N-Sulfonamido" group refers to a $R"S(=O)_2NR_X$- group, with R_x being H or (C_{1-6})alkyl.

A "O-carbamyl" group refers to a $-OC(=O)NR^xR^y$ group, with R^X and R^Y independently being H or (C_{1-6})alkyl.

A "N-carbamyl" group refers to a $R^xOC(=O)NR^y$ group, with R^x and R^y independently being H or (C_{1-6})alkyl.

A "O-thiocarbamyl" group refers to a $-OC(=S)NR^xR^y$ group, with R^x and R^y independently being H or (C_{1-6})alkyl.

A "N-thiocarbamyl" group refers to a $R^xOC(=S)NR^y$- group, with R^x and R^y independently being H or (C_{1-6})alkyl.

An "amino" group refers to an $-NH_2$ group.

A "C-amido" group refers to a $-C(=O)NR^xR^y$ group, with R^x and R^y independently being H or (C_{1-6})alkyl.

A "C-thioamido" group refers to a $-C(=S)NR^xR^y$ group, with R^x and R^y independently being H or (C_{1-6})alkyl.

A "N-amido" group refers to a $R^xC(=O)NR^y$- group, with R^x and R^y independently being H or (C_{1-6})alkyl.

An "ureido" group refers to a $-NR^xC(=O)NR^yR^{y2}$ group, with R^x, R^y, and R^{y2} independently being H or (C_{1-6})alkyl.

A "guanidino" group refers to a $-R^xNC(=N)NR^yR^{y2}$ group, with R^x, R^y, and R^{y2} independently being H or (C_{1-6})alkyl.

A "amidino" group refers to a $R^xR^yNC(=N)$- group, with R^x and R^y independently being H or (C_{1-6})alkyl.

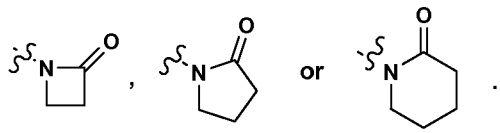
A "cyano" group refers to a $-CN$ group.

A "silyl" group refers to a $-Si(R")_3$, with R" being (C_{1-6})alkyl or phenyl.

A "phosphonyl" group refers to a $P(=O)(OR^x)_2$ with R^x being (C_{1-6})alkyl.

A "hydrazino" group refers to a $-NR^xNR^yR^{y2}$ group, with R^x, R^y, and R^{y2} independently being H or (C_{1-6})alkyl.

A "4, 5, or 6 membered ring cyclic N-lactam" group refers to



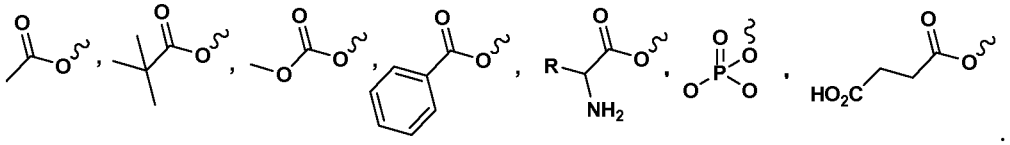
Any two adjacent R groups may combine to form an additional aryl, cycloalkyl, heteroaryl or heterocyclic ring fused to the ring initially bearing those R groups.

It is known in the art that nitrogen atoms in heteroaryl systems can be "participating in a heteroaryl ring double bond", and this refers to the form of double bonds in the two tautomeric structures which comprise five-member ring heteroaryl groups. This dictates whether nitrogens can be substituted as well understood by chemists in the art. The disclosure and claims of the present disclosure are based on the known general principles of chemical bonding. It is understood that the claims do not encompass structures known to be unstable or not able to exist based on the literature.

Pharmaceutically acceptable salts and prodrugs of compounds disclosed herein are within the scope of the invention. The term "pharmaceutically acceptable salt" as used herein and in the claims is intended to include nontoxic base addition salts. Suitable salts include those derived from organic and inorganic acids such as, without limitation, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, tartaric acid, lactic acid, sulfinic acid, citric acid, maleic acid, fumaric acid, sorbic acid, aconitic acid, salicylic acid, phthalic acid, and the like. The term "pharmaceutically acceptable salt" as used herein is also intended to include salts of acidic groups, such as a carboxylate, with such counterions as ammonium, alkali metal salts, particularly sodium or potassium, alkaline earth metal salts, particularly calcium or magnesium, and salts with suitable organic bases such as lower alkylamines (methylamine, ethylamine, cyclohexylamine, and the like) or with substituted lower alkylamines (e.g. hydroxyl-substituted alkylamines such as diethanolamine, triethanolamine or tris(hydroxymethyl)- aminomethane), or with bases such as piperidine or morpholine.

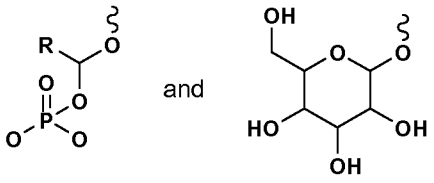
As stated above, the compounds of the invention also include "prodrugs". The term "prodrug" as used herein encompasses both the term "prodrug esters" and the term "prodrug ethers". The term "prodrug esters" as employed herein includes esters and carbonates formed by reacting one or more hydroxyls of compounds of Formula I with either alkyl, alkoxy, or aryl substituted acylating agents or phosphorylating agent employing procedures known to those skilled in the art to generate acetates, pivalates, methylcarbonates, benzoates, amino acid esters, phosphates, half acid esters such as malonates, succinates or glutarates, and the like. In certain embodiments, amino acid esters may be especially preferred.

Examples of such prodrug esters include



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The term "prodrug ethers" include both phosphate acetals and O-glucosides. Representative examples of such prodrug ethers include

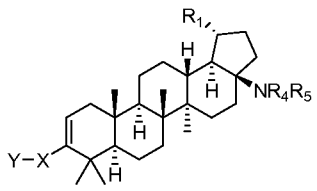


and

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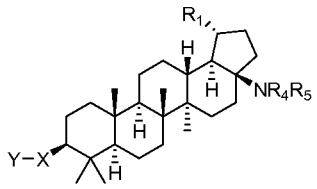
As set forth above, the invention is directed to a compound, including pharmaceutically acceptable salts thereof, which is selected from the group of:

a compound of formula I



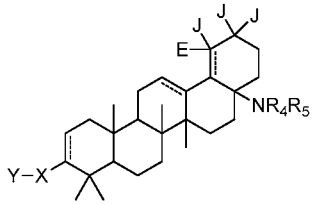
Formula I ;

a compound of formula II



Formula II ; and

a compound of formula III



Formula III ;

wherein R_1 is isopropenyl or isopropyl;

J and E are –H or $–CH_3$, and E is absent when the double bond is present;

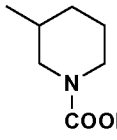
X is a phenyl or heteroaryl ring substituted with A, wherein A is at least one member selected from the group of -H, -halo, -hydroxyl, -C_{1-6} alkyl, -C_{1-6} alkoxy, and -$COOR_2$;

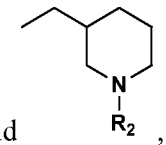
R_2 is -H, -C_{1-6} alkyl, -alkylsubstituted C_{1-6} alkyl or-arylsubstituted C_{1-6} alkyl;

Y is selected from the group of –$COOR_2$, -$C(O)NR_2SO_2R_3$, -$C(O)NHSO_2NR_2R_2$, -$NR_2SO_2R_2$, -$SO_2NR_2R_2$, -C_{3-6} cycloalkyl-$COOR_2$, -C_{2-6} alkenyl-$COOR_2$, -C_{2-6} alkynyl-$COOR_2$, -C_{1-6} alkyl-$COOR_2$, -$NHC(O)(CH_2)_n$-$COOR_2$, -$SO_2NR_2C(O)R_2$, -tetrazole, and –CONHOH,
wherein n=1-6;

R_3 is -C_{1-6} alkyl or -alkylsubstituted C_{1-6} alkyl;

R_4 is selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} alkyl-$C(OR_3)_2$-C_{3-6} cycloalkyl, -C_{1-6} substituted alkyl, -C_{1-6} alkyl-C_{3-6} cycloalkyl, -C_{1-6} alkyl-Q_1, -C_{1-6} alkyl-C_{3-6} cycloalkyl-Q_1, aryl, heteroaryl, substituted heteroaryl,-COR_6, -$COCOR_6$, -SO_2R_7, -$SO_2NR_2R_2$,



, and


,

wherein Q_1 is selected from the group of heteroaryl, substituted heteroaryl, halogen, -CF_3, -OR_2, -$COOR_2$, -NR_8R_9, -$CONR_{10}R_{11}$ and -SO_2R_7;

R_5 is selected from the group of -H, -C_{1-6} alkyl, -C_{3-6} cycloalkyl, -C_{1-6} alkylsubstituted alkyl, -C_{1-6} alkyl-NR_8R_9, -COR_{10}, -COR_6, -$COCOR_6$, -SO_2R_7 and -$SO_2NR_2R_2$;

with the proviso that only one of R_4 or R_5 can be selected from the group of -COR_6, -$COCOR_6$,-SO_2R_7 and -$SO_2NR_2R_2$;

or R_4 and R_5 are taken together with the adjacent N to form



;

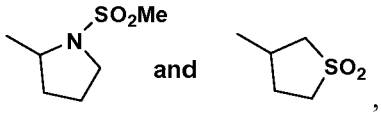
R_6 is selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} alkyl-substitutedalkyl, -C_{3-6} cycloalkyl, -C_{3-6} substitutedcycloalkyl-Q_2, -C_{1-6} alkyl-Q_2, -C_{1-6} alkyl-substitutedalkyl-Q_2,-C_{3-6} cycloalkyl-Q_2, aryl-Q_2, -$NR_{13}R_{14}$, and -OR_{15};

wherein Q_2 is selected from the group of aryl, heteroaryl, substituted heteroaryl, -OR_2, -$COOR_2$, -NR_8R_9, SO_2R_7, -$CONHSO_2R_3$, and -$CONHSO_2NR_2R_2$;

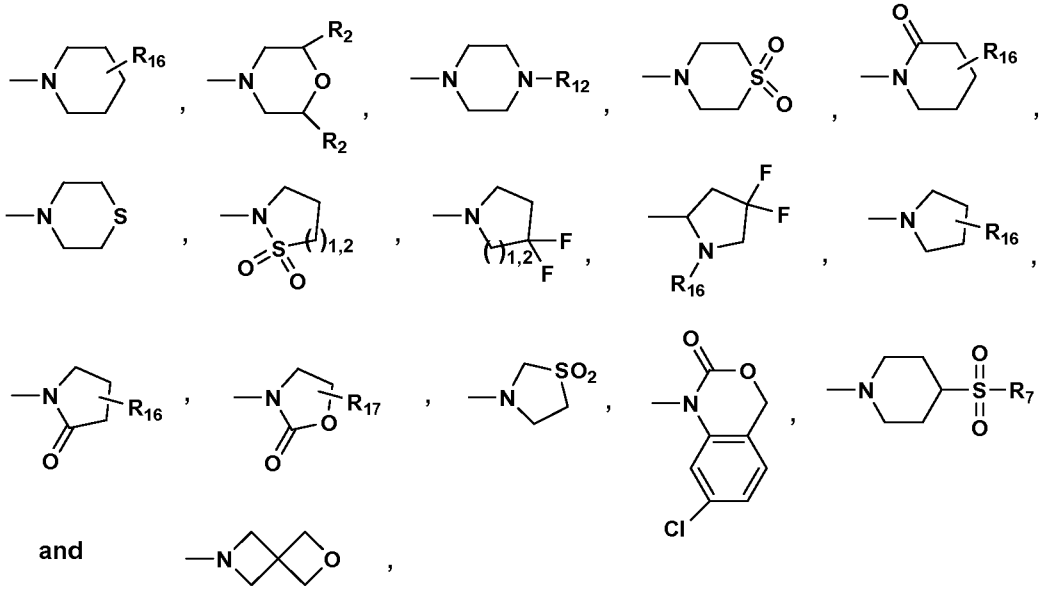
R_7 is selected from the group of -C_{1-6} alkyl, -C_{1-6} substituted alkyl, -C_{3-6} cycloalkyl, aryl, and heteroaryl;

R_8 and R_9 are independently selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} substituted alkyl, aryl, heteroaryl, substituted aryl, substituted heteroaryl, -C_{1-6} alkyl-Q_2, and -$COOR_3$,

and R_8 and R_9 can also be independently selected from the group of



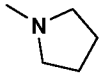
or R_8 and R_9 are taken together with the adjacent N to form a cycle selected from the group of:



with the proviso that only one of R_8 or R_9 can be $-COOR_3$;

R_{10} and R_{11} are independently selected from the group of -H, $-C_{1-6}$ alkyl, $-C_{1-6}$ substituted alkyl and $-C_{3-6}$ cycloalkyl,

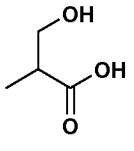
or R_{10} and R_{11} are taken together with the adjacent N to form a cycle such as



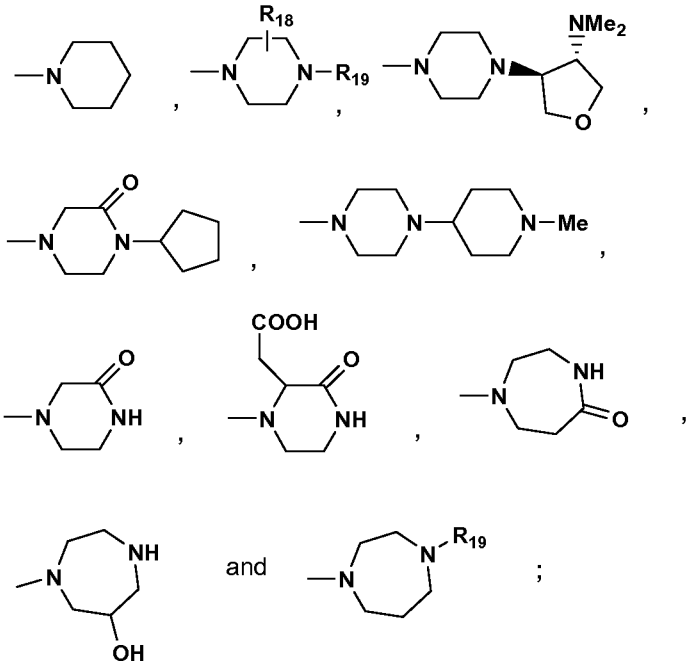
;

R_{12} is selected from the group of $-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-OH, $-C_{1-6}$ alkyl, $-C_{1-6}$ substituted alkyl,$-C_{3-6}$ cycloalkyl, $-COR_7$, $-COONR_{22}R_{23}$, $-SOR_7$, and $-SONR_{24}R_{25}$;

R_{13} and R_{14} are independently selected from the group of -H, $-C_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl, $-C_{1-6}$ substituted alkyl, $-C_{1-6}$ alkyl-Q_3, $-C_{1-6}$ alkyl-C_{3-6} cycloalkyl-Q_3, C_{1-6} substituted alkyl-Q_3 and



or R_{13} and R_{14} are taken together with the adjacent N to form a cycle selected from the group of:



Q_3 is selected from the group of heteroaryl, substituted heteroaryl, $-NR_{20}R_{21}$, $-CONR_2R_2$, $-COOR_2$, $-OR_2$, and $-SO_2R_3$;

R_{15} is selected from the group of $-C_{1-6}$ alkyl, $-C_{3-6}$ cycloalkyl, $-C_{1-6}$ substituted alkyl, $-C_{1-6}$ alkyl-Q_3, $-C_{1-6}$ alkyl-C_{3-6} cycloalkyl-Q_3 and $-C_{1-6}$ substituted alkyl-Q_3;

R_{16} is selected from the group of -H, $-C_{1-6}$ alkyl, $-NR_2R_2$, and $-COOR_3$;

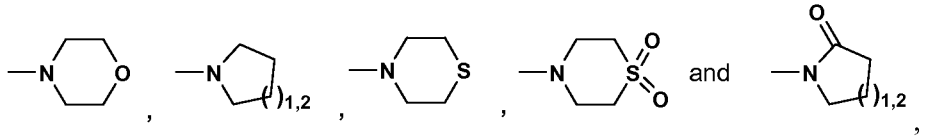
R_{17} is selected from the group of -H, $-C_{1-6}$ alkyl, $-COOR_3$, and aryl;

R_{18} is selected from the group of $-COOR_2$ and $-C_{1-6}$ alkyl-$COOR_2$;

R_{19} is selected from the group of -H, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-Q_4, $-COR_3$, $-COOR_3$,

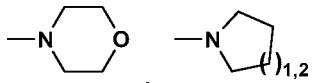
wherein Q_4 is selected from the group of $-NR_2R_2$ and $-OR_2$;

R_{20} and R_{21} are independently selected from the group of -H, $-C_{1-6}$ alkyl, $-C_{1-6}$ substituted alkyl, $-C_{1-6}$ substituted alkyl-OR_2, and $-COR_3$,
or R_{20} and R_{21} are taken together with the adjacent N to form a cycle selected from the group of



with the proviso that only one of R_{20} or R_{21} can be $-COR_3$;

R_{22} and R_{23} are independently selected from the group of H, $-C_{1-6}$ alkyl, $-C_{1-6}$ substituted alkyl, and $-C_{1-6}$ cycloalkyl,
or R_{22} and R_{23} are taken together with the adjacent N to form a cycle selected from the group of



R_{24} and R_{25} are independently from the group of H, $-C_{1-6}$ alkyl, $-C_{1-6}$ substituted alkyl, $-C_{1-6}$ alkyl-Q_5, $-C_{1-6}$ cycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl,
and Q_5 is selected from the group of halogen and SO_2R_3.

Even more preferred compounds include those wherein R_1 is isopropenyl.

More preferred compounds include those which are encompassed by Formula I. Of these, those wherein X is a phenyl ring are even more preferred. Even more preferred are compounds of Formula I wherein X is a phenyl ring and Y is in the para position.

Also preferred are compounds of Formula I wherein A is at least one member selected from the group of –H, -OH, -halo, $-C_{1-3}$ alkyl, and $-C_{1-3}$ alkoxy, wherein –halo is selected from the group of –Cl, -F and –Br, with –F being more preferred. It is even more preferred that A is –H.

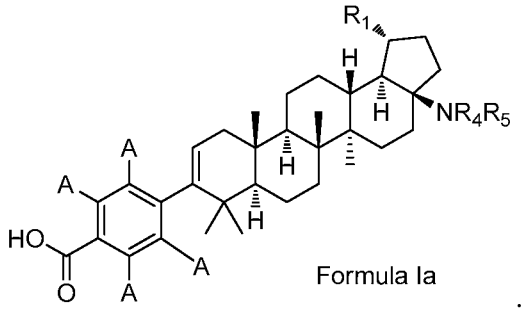
Also preferred are compounds of Formula I wherein Y is $-COOR_2$, and more preferably –COOH.

Also preferred are compounds wherein R_4 is selected from the group of –H, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-Q_1, and $-COR_6$. Especially preferred are compounds wherein R_4 is $-C_{1-6}$ alkyl-Q_1 or $-COR_6$.

It is also preferred that R_5 is –H.

In addition, it is preferred that Q_1 is $-NR_8R_9$.

In another preferred embodiment there is provided a compound of Formula Ia below wherein X is a phenyl ring and Y is –COOH in the para position:

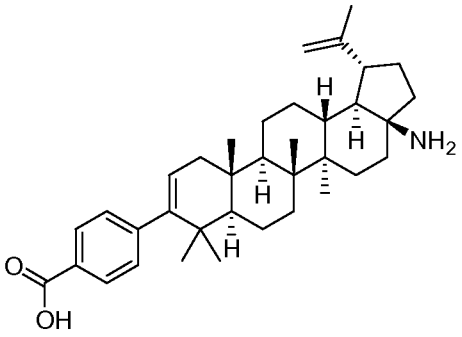


Formula Ia

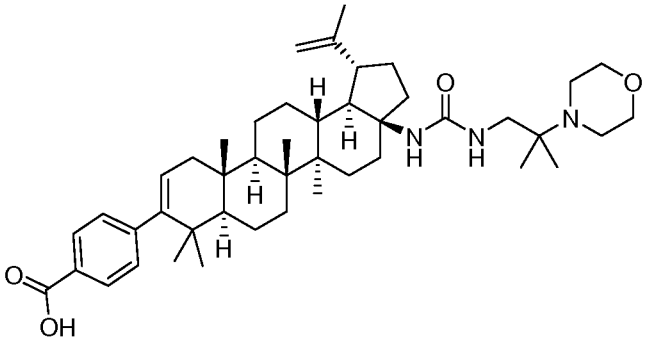
In this embodiment, it is also preferred that A is at least one member selected from the group of –H, -halo, -OH, $-C_{1-3}$ alkyl and $-C_{1-3}$ alkoxy. It is particularly preferred that A is at least one member selected from the group of –H, -fluoro, -chloro, -OH, -methyl and –methoxy, with –H being even more preferred.

In addition, in a further embodiment of the invention compounds of Formula II are preferred, as are compounds of Formula III.

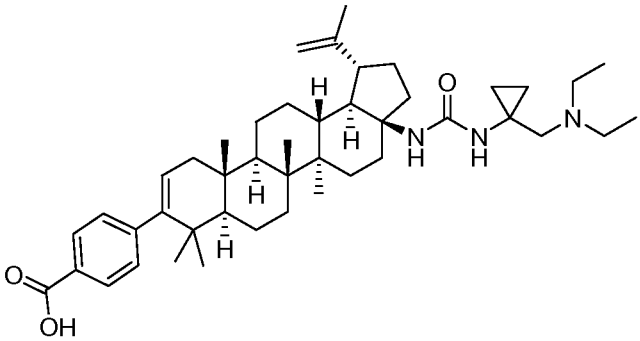
Other compounds, including pharmaceutically acceptable salts thereof, which are preferred as part of the invention include the following:


H
H
NH2
H
O
OH

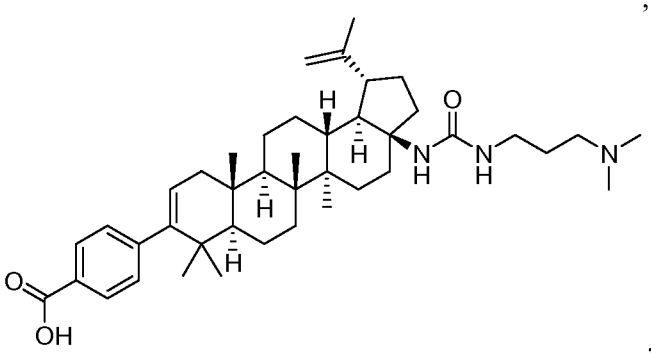
,


H
H
O
N
H
N
H
O
N
H
H
O
OH

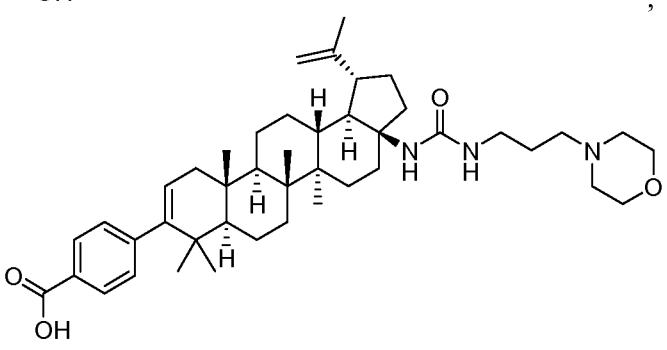
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H
H
O
N
H
N
H
N
H
H
O
OH

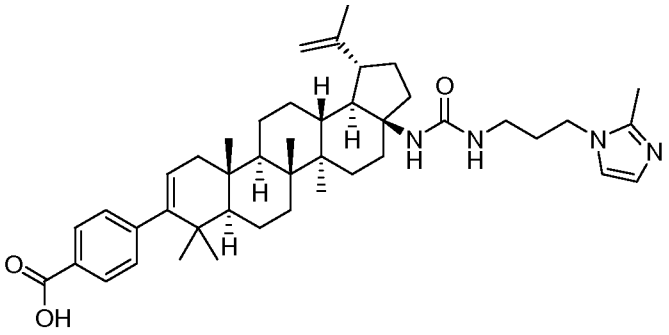
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H
H
O
N
H
N
H
N
H
H
O
OH

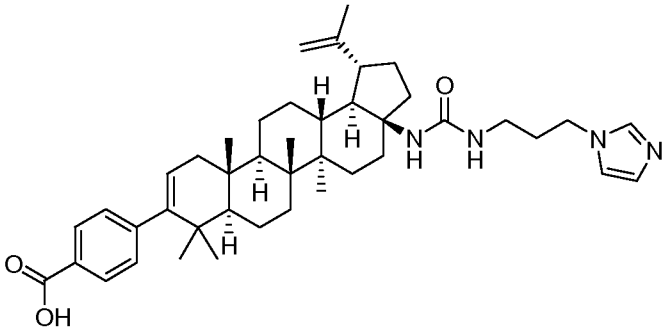
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H
H
O
N
H
N
H
N
O
H
H
O
OH

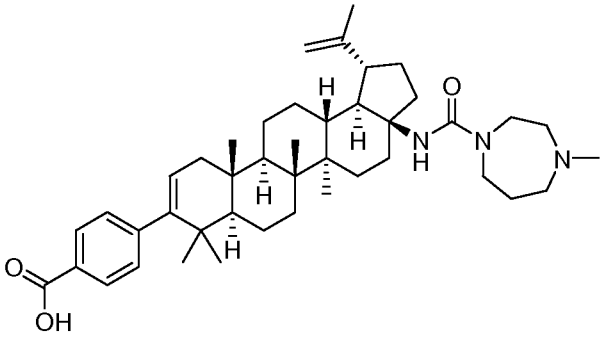
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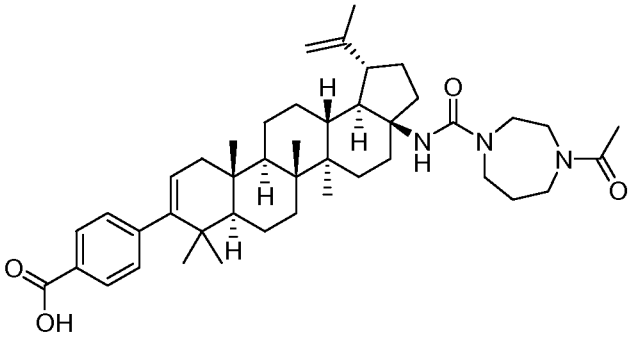
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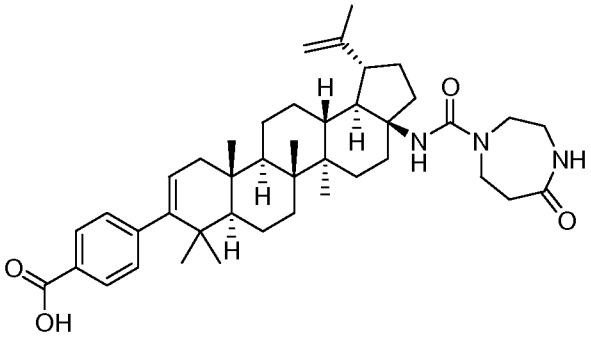
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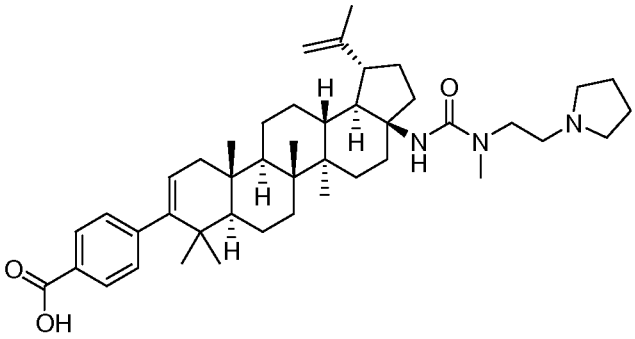
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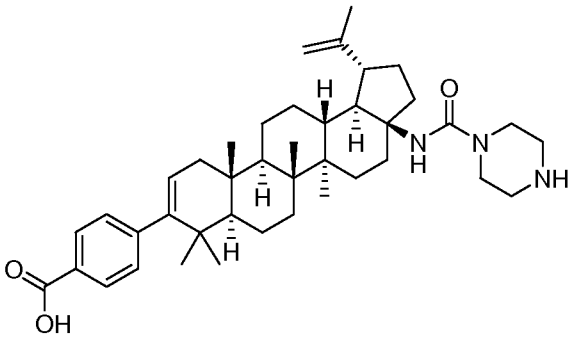
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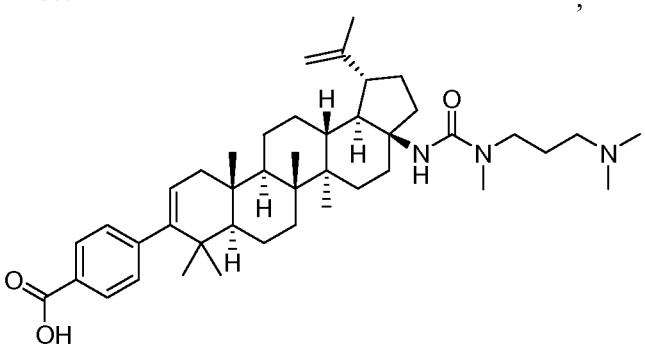
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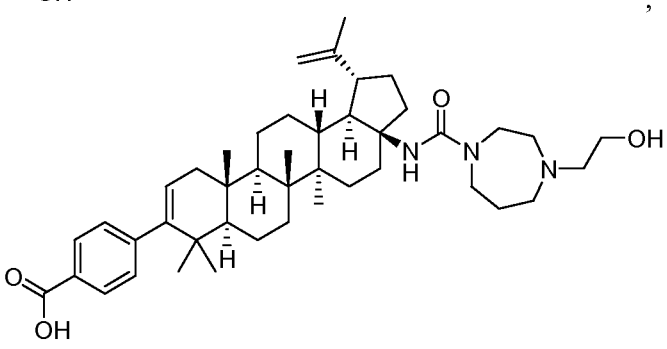
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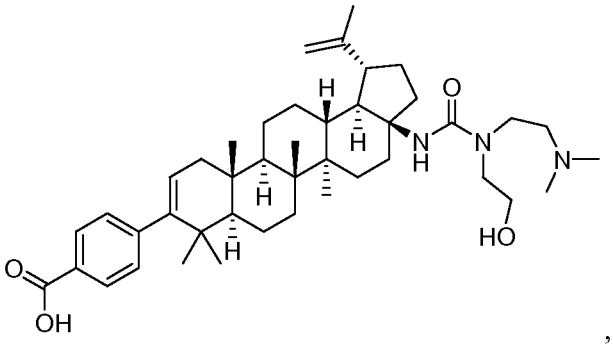
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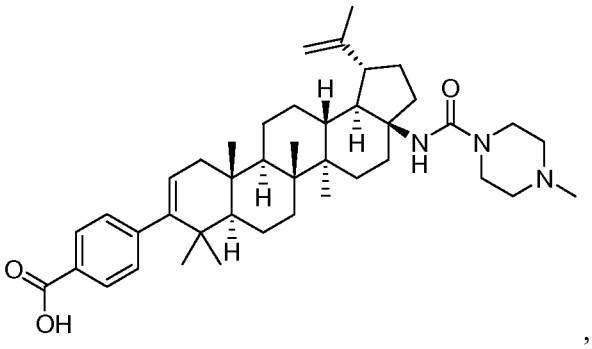
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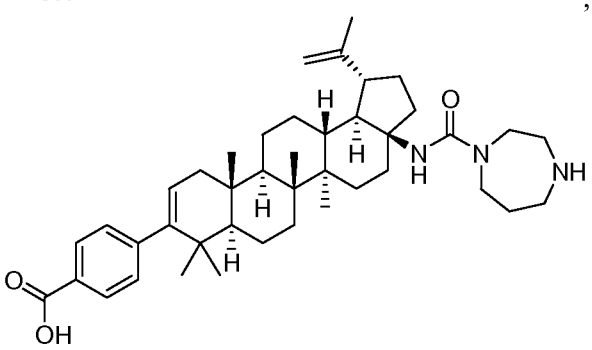
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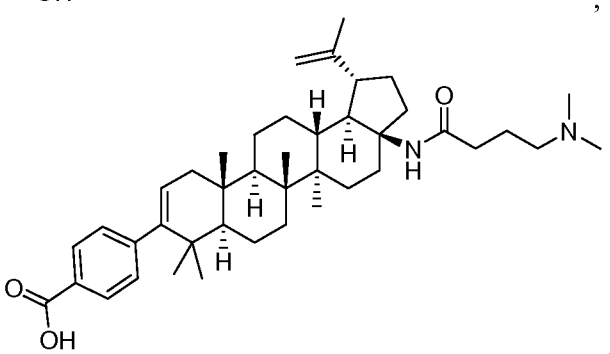
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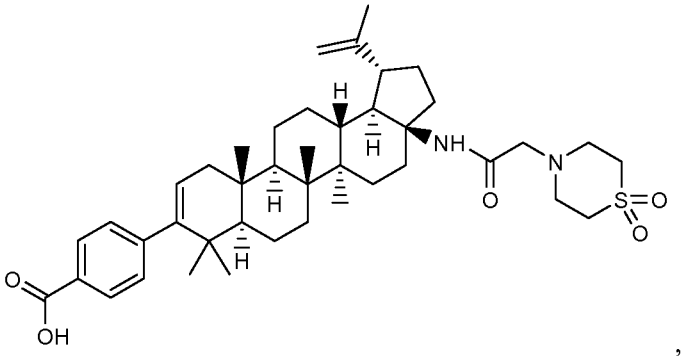
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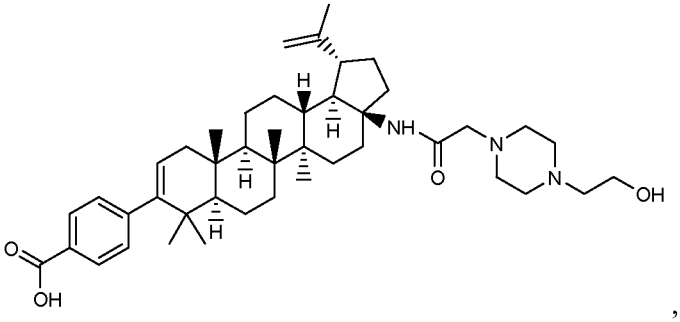
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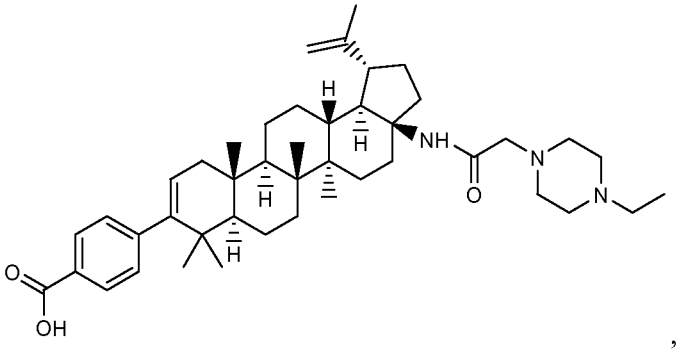
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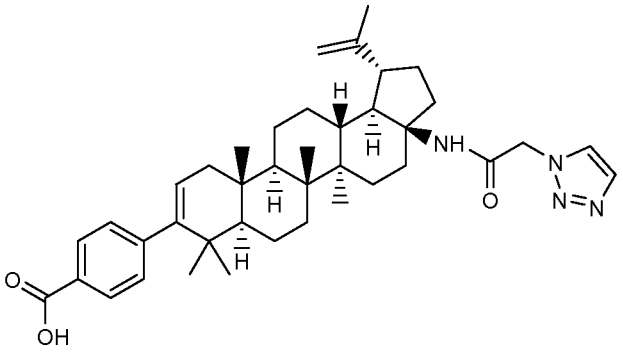


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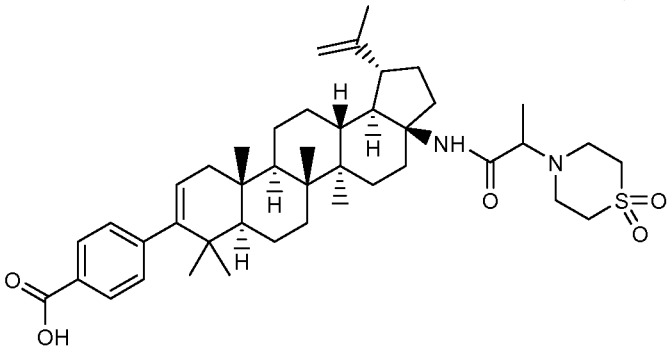


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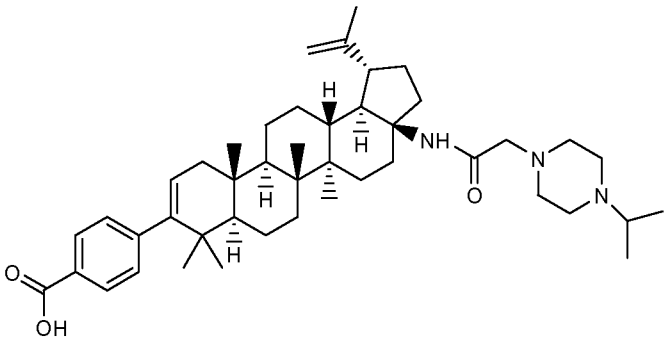
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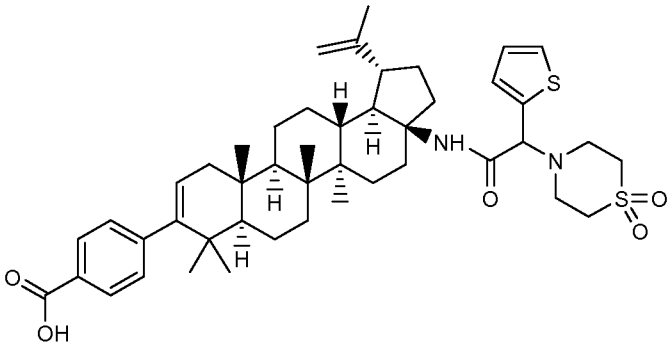
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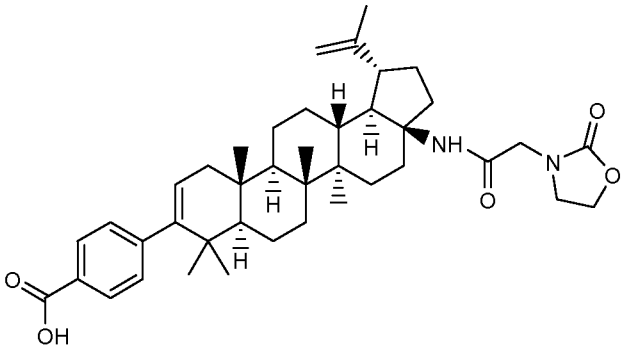
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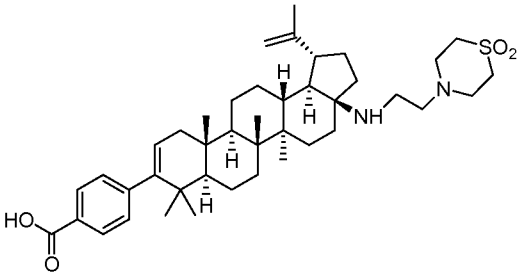
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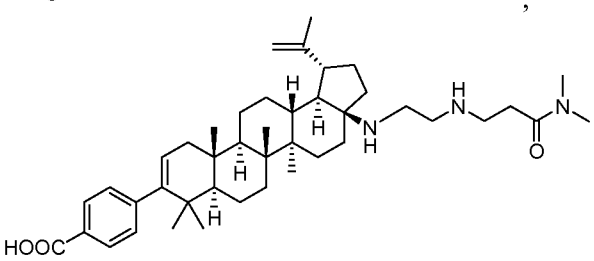
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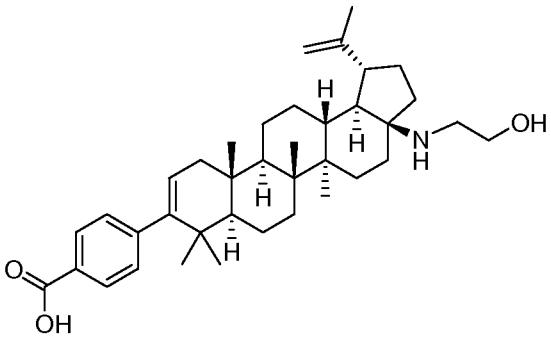
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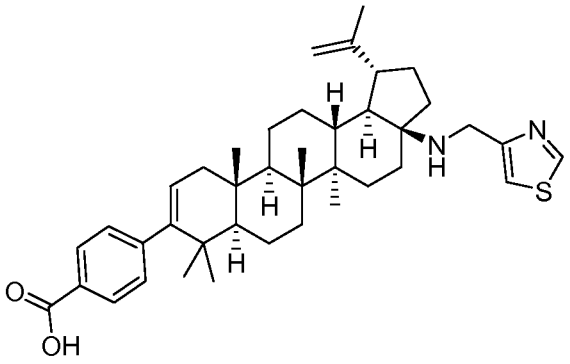
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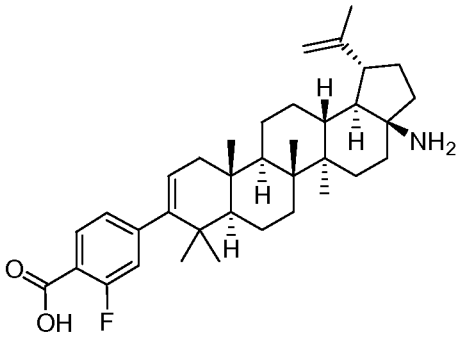
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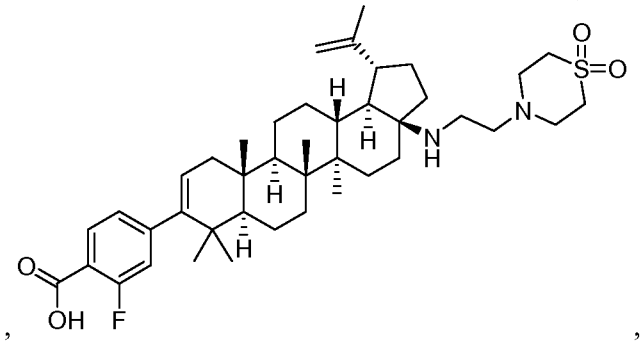
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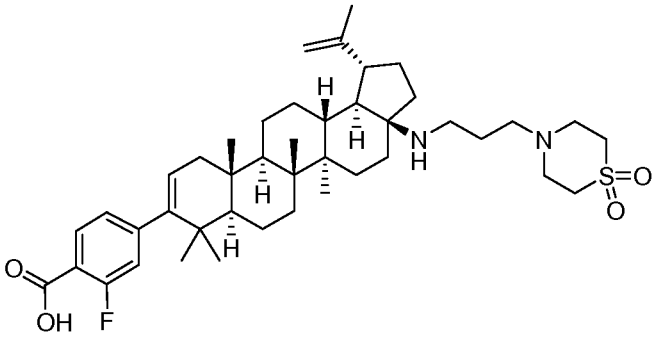
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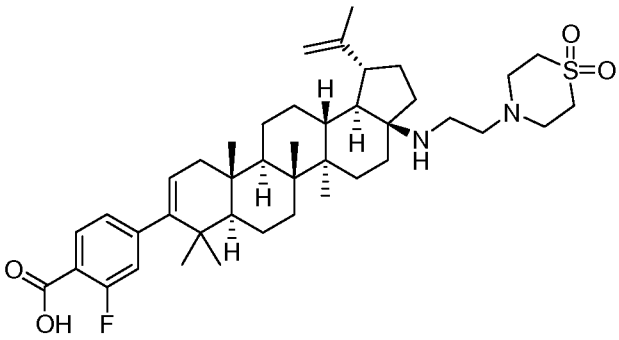


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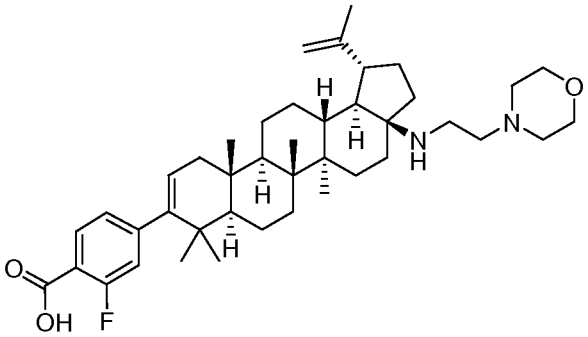


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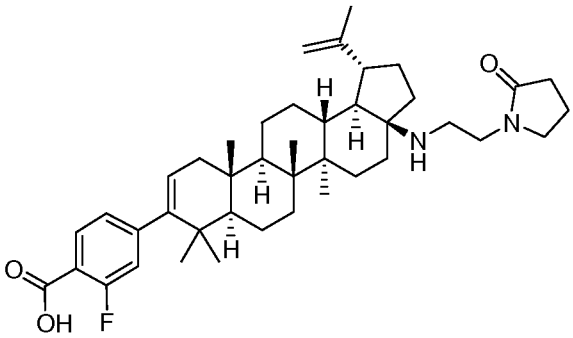
Also preferred are the following compounds, including pharmaceutically acceptable salts thereof:



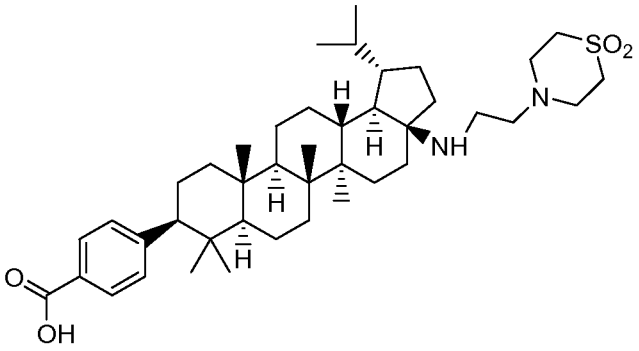
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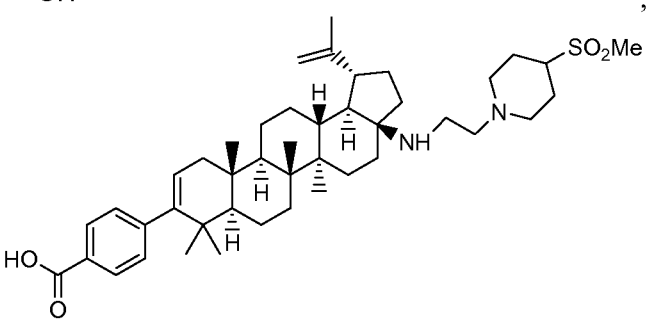
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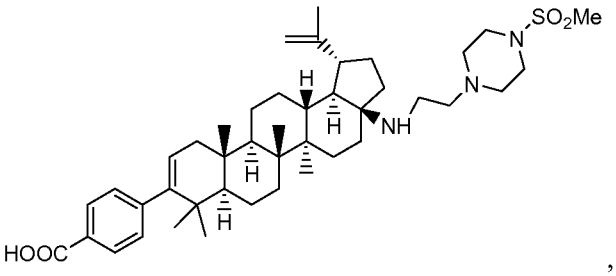
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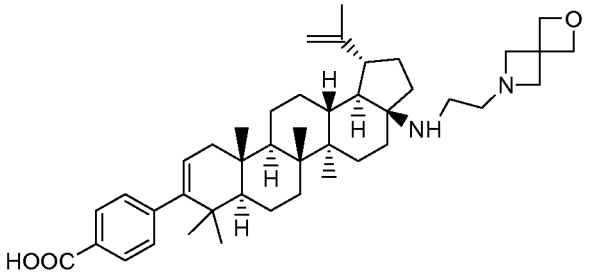
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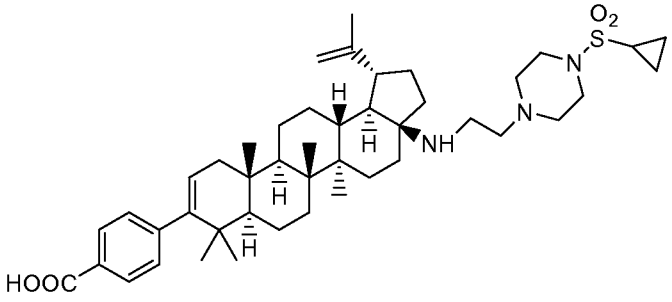


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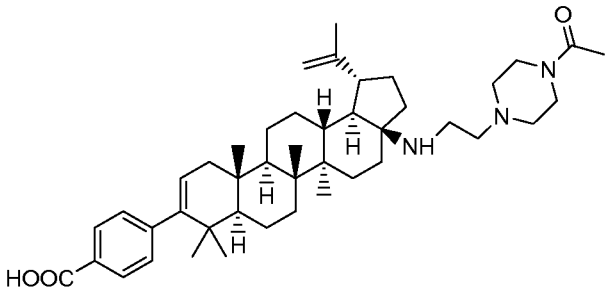


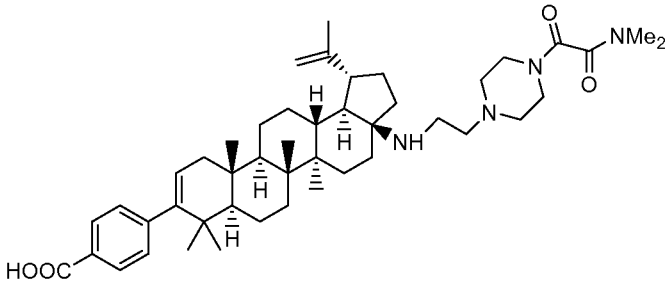
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The compounds of the present invention, according to all the various embodiments described above, may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, and by other means, in dosage unit formulations containing non-toxic pharmaceutically acceptable carriers, excipients and diluents available to the skilled artisan. One or more adjuvants may also be included.

Thus, in accordance with the present invention, there is further provided a method of treatment, and a pharmaceutical composition, for treating viral infections

such as HIV infection and AIDS. The treatment involves administering to a patient in need of such treatment a pharmaceutical composition which contains an antiviral effective amount of one or more of the compounds of Formulas I, II, and/or III, together with one or more pharmaceutically acceptable carriers, excipients or diluents. As used herein, the term "antiviral effective amount" means the total amount of each active component of the composition and method that is sufficient to show a meaningful patient benefit, i.e., inhibiting, ameliorating, or healing of acute conditions characterized by inhibition of the HIV infection. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously. The terms "treat, treating, treatment" as used herein and in the claims means preventing, ameliorating or healing diseases associated with HIV infection.

The pharmaceutical compositions of the invention may be in the form of orally administrable suspensions or tablets; as well as nasal sprays, sterile injectable preparations, for example, as sterile injectable aqueous or oleaginous suspensions or suppositories. Pharmaceutically acceptable carriers, excipients or diluents may be utilized in the pharmaceutical compositions, and are those utilized in the art of pharmaceutical preparations.

When administered orally as a suspension, these compositions are prepared according to techniques typically known in the art of pharmaceutical formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents, and lubricants known in the art.

The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile,

bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

The compounds herein set forth can be administered orally to humans in a dosage range of about 1 to 100 mg/kg body weight in divided doses, usually over an extended period, such as days, weeks, months, or even years. One preferred dosage range is about 1 to 10 mg/kg body weight orally in divided doses. Another preferred dosage range is about 1 to 20 mg/kg body weight in divided doses. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Also contemplated herein are combinations of the compounds of Formulas I, II, and /or III herein set forth, together with one or more other agents useful in the treatment of AIDS. For example, the compounds of this disclosure may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of the AIDS antivirals, immunomodulators, antiinfectives, or vaccines, such as those in the following non-limiting table:

ANTIVIRALS

Drug Name	*Manufacturer*	*Indication*
097	Hoechst/Bayer	HIV infection, AIDS, ARC (non-nucleoside reverse trans-criptase (RT) inhibitor)
Amprenavir 141 W94 GW 141	Glaxo Wellcome	HIV infection, AIDS, ARC (protease inhibitor)
Abacavir (1592U89) GW 1592	Glaxo Wellcome	HIV infection, AIDS, ARC (RT inhibitor)
Acemannan	Carrington Labs (Irving, TX)	ARC
Acyclovir	Burroughs Wellcome	HIV infection, AIDS, ARC
AD-439	Tanox Biosystems	HIV infection, AIDS, ARC
AD-519	Tanox Biosystems	HIV infection, AIDS, ARC
Adefovir dipivoxil AL-721	Gilead Sciences Ethigen (Los Angeles, CA)	HIV infection ARC, PGL HIV positive, AIDS
Alpha Interferon	Glaxo Wellcome	Kaposi's sarcoma, HIV in combination w/Retrovir
Ansamycin LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC

Antibody which Neutralizes pH Labile alpha aberrant Interferon	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC
AR177	Aronex Pharm	HIV infection, AIDS, ARC
Beta-fluoro-ddA	Nat'l Cancer Institute	AIDS-associated diseases
BMS-234475 (CGP-61755)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (protease inhibitor)
CI-1012	Warner-Lambert	HIV-1 infection
Cidofovir	Gilead Science	CMV retinitis, herpes, papillomavirus
Curdlan sulfate	AJI Pharma USA	HIV infection
Cytomegalovirus Immune globin	MedImmune	CMV retinitis
Cytovene	Syntex	Sight threatening
Ganciclovir		CMV peripheral CMV retinitis
Darunavir	Tibotec- J & J	HIV infection, AIDS, ARC (protease inhibitor)
Delaviridine	Pharmacia-Upjohn	HIV infection, AIDS, ARC (RT inhibitor)
Dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic
ddC Dideoxycytidine	Hoffman-La Roche	HIV infection, AIDS, ARC

ddI Dideoxyinosine	Bristol-Myers Squibb	HIV infection, AIDS, ARC; combination with AZT/d4T
DMP-450	AVID (Camden, NJ)	HIV infection, AIDS, ARC (protease inhibitor)
Efavirenz (DMP 266, Sustiva®) (-)6-Chloro-4-(S)-cyclopropylethynyl-4(S)-trifluoro-methyl-1,4-dihydro-2H-3,1-benzoxazin-2-one, STOCRINE	Bristol Myers Squibb	HIV infection, AIDS, ARC (non-nucleoside RT inhibitor)
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
Etravirine	Tibotec/ J & J	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
Famciclovir	Smith Kline	herpes zoster, herpes simplex
GS 840	Gilead	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
HBY097	Hoechst Marion Roussel	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
Hypericin	VIMRx Pharm.	HIV infection, AIDS, ARC
Recombinant Human Interferon Beta	Triton Biosciences (Almeda, CA)	AIDS, Kaposi's sarcoma, ARC

Interferon alfa-n3	Interferon Sciences	ARC, AIDS
Indinavir	Merck	HIV infection, AIDS, ARC, asymptomatic HIV positive, also in combination with AZT/ddI/ddC
ISIS 2922	ISIS Pharmaceuticals	CMV retinitis
KNI-272	Nat'l Cancer Institute	HIV-assoc. diseases
Lamivudine, 3TC	Glaxo Wellcome	HIV infection, AIDS, ARC (reverse transcriptase inhibitor); also with AZT
Lobucavir	Bristol-Myers Squibb	CMV infection
Nelfinavir	Agouron Pharmaceuticals	HIV infection, AIDS, ARC (protease inhibitor)
Nevirapine	Boeheringer Ingleheim	HIV infection, AIDS, ARC (RT inhibitor)
Novapren	Novaferon Labs, Inc. (Akron, OH)	HIV inhibitor
Peptide T Octapeptide Sequence	Peninsula Labs (Belmont, CA)	AIDS
Trisodium Phosphonoformate	Astra Pharm. Products, Inc.	CMV retinitis, HIV infection, other CMV infections
PNU-140690	Pharmacia Upjohn	HIV infection, AIDS, ARC (protease inhibitor)

Probucol	Vyrex	HIV infection, AIDS
RBC-CD4	Sheffield Med. Tech (Houston, TX)	HIV infection, AIDS, ARC
Ritonavir	Abbott	HIV infection, AIDS, ARC (protease inhibitor)
Saquinavir	Hoffmann-LaRoche	HIV infection, AIDS, ARC (protease inhibitor)
Stavudine; d4T Didehydrodeoxy-Thymidine	Bristol-Myers Squibb	HIV infection, AIDS, ARC
Tipranavir	Boehringer Ingelheim	HIV infection, AIDS, ARC (protease inhibitor)
Valaciclovir	Glaxo Wellcome	Genital HSV & CMV infections
Virazole Ribavirin	Viratek/ICN (Costa Mesa, CA)	asymptomatic HIV positive, LAS, ARC
VX-478	Vertex	HIV infection, AIDS, ARC
Zalcitabine	Hoffmann-LaRoche	HIV infection, AIDS, ARC, with AZT
Zidovudine; AZT	Glaxo Wellcome	HIV infection, AIDS, ARC, Kaposi's sarcoma, in combination with other therapies
Tenofovir disoproxil, fumarate salt (Viread®)	Gilead	HIV infection, AIDS, (reverse transcriptase inhibitor)
Emtriva® (Emtricitabine) (FTC)	Gilead	HIV infection, AIDS, (reverse transcriptase inhibitor)

Combivir®	GSK	HIV infection, AIDS, (reverse transcriptase inhibitor)
Abacavir succinate (or Ziagen®)	GSK	HIV infection, AIDS, (reverse transcriptase inhibitor)
Reyataz® (or atazanavir)	Bristol-Myers Squibb	HIV infection AIDs, protease inhibitor
Fuzeon® (Enfuvirtide or T-20)	Roche / Trimeris	HIV infection AIDs, viral Fusion inhibitor
Lexiva® (or Fosamprenavir calcium)	GSK/Vertex	HIV infection AIDs, viral protease inhibitor
Selzentry Maraviroc; (UK 427857)	Pfizer	HIV infection AIDs, (CCR5 antagonist, in development)
Trizivir®	GSK	HIV infection AIDs, (three drug combination)
Sch-417690 (vicriviroc)	Schering-Plough	HIV infection AIDs, (CCR5 antagonist, in development)
TAK-652	Takeda	HIV infection AIDs, (CCR5 antagonist, in development)
GSK 873140 (ONO-4128)	GSK/ONO	HIV infection AIDs, (CCR5 antagonist, in development)
Integrase Inhibitor MK-0518 Raltegravir	Merck	HIV infection AIDs

Truvada®	Gilead	Combination of Tenofovir disoproxil fumarate salt (Viread®) and Emtriva® (Emtricitabine)
Integrase Inhibitor GS917/JTK-303 Elvitegravir	Gilead/Japan Tobacco	HIV Infection AIDs in development
Triple drug combination Atripla®	Gilead/Bristol-Myers Squibb	Combination of Tenofovir disoproxil fumarate salt (Viread®), Emtriva® (Emtricitabine), and Sustiva® (Efavirenz)
Festinavir® 4'-ethynyl-d4T	Oncolys BioPharma BMS	HIV infection AIDs in development
CMX-157 Lipid conjugate of nucleotide tenofovir	Chimerix	HIV infection AIDs
GSK1349572 Integrase inhibitor	GSK	HIV infection AIDs

IMMUNOMODULATORS

Drug Name	*Manufacturer*	*Indication*
AS-101	Wyeth-Ayerst	AIDS
Bropirimine	Pharmacia Upjohn	Advanced AIDS
Acemannan	Carrington Labs, Inc. (Irving, TX)	AIDS, ARC
CL246,738	Wyeth Lederle Labs	AIDS, Kaposi's sarcoma
FP-21399	Fuki ImmunoPharm	Blocks HIV fusion with CD4+ cells

Gamma Interferon	Genentech	ARC, in combination w/TNF (tumor necrosis factor)
Granulocyte Macrophage Colony Stimulating Factor	Genetics Institute Sandoz	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Hoechst-Roussel Immunex	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Schering-Plough	AIDS, combination w/AZT
HIV Core Particle Immunostimulant	Rorer	Seropositive HIV
IL-2 Interleukin-2	Cetus	AIDS, in combination w/AZT
IL-2 Interleukin-2	Hoffman-LaRoche Immunex	AIDS, ARC, HIV, in combination w/AZT
IL-2 Interleukin-2 (aldeslukin)	Chiron	AIDS, increase in CD4 cell counts
Immune Globulin Intravenous (human)	Cutter Biological (Berkeley, CA)	Pediatric AIDS, in combination w/AZT
IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
Imuthiol Diethyl Dithio Carbamate	Merieux Institute	AIDS, ARC
Alpha-2 Interferon	Schering Plough	Kaposi's sarcoma w/AZT, AIDS

Methionine-Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC
MTP-PE Muramyl-Tripeptide	Ciba-Geigy Corp.	Kaposi's sarcoma
Granulocyte Colony Stimulating Factor	Amgen	AIDS, in combination w/AZT
Remune	Immune Response Corp.	Immunotherapeutic
rCD4 Recombinant Soluble Human CD4	Genentech	AIDS, ARC
rCD4-IgG hybrids		AIDS, ARC
Recombinant Soluble Human CD4	Biogen	AIDS, ARC
Interferon Alfa 2a	Hoffman-La Roche	Kaposi's sarcoma AIDS, ARC, in combination w/AZT
SK&F106528 Soluble T4	Smith Kline	HIV infection
Thymopentin	Immunobiology Research Institute (Annandale, NJ)	HIV infection
Tumor Necrosis Factor; TNF	Genentech	ARC, in combination w/gamma Interferon

ANTI-INFECTIVES

Drug Name	*Manufacturer*	*Indication*
Clindamycin with	Pharmacia Upjohn	PCP

Primaquine		
Fluconazole	Pfizer	Cryptococcal meningitis, candidiasis
Pastille Nystatin Pastille	Squibb Corp.	Prevention of oral candidiasis
Ornidyl Eflornithine	Merrell Dow	PCP
Pentamidine Isethionate (IM & IV)	LyphoMed (Rosemont, IL)	PCP treatment
Trimethoprim		Antibacterial
Trimethoprim/sulfa		Antibacterial
Piritrexim	Burroughs Wellcome	PCP treatment
Pentamidine Isethionate for Inhalation	Fisons Corporation	PCP prophylaxis
Spiramycin	Rhone-Poulenc diarrhea	Cryptosporidial
Intraconazole-R51211	Janssen-Pharm.	Histoplasmosis; cryptococcal meningitis
Trimetrexate	Warner-Lambert	PCP
Daunorubicin	NeXstar, Sequus	Kaposi's sarcoma
Recombinant Human Erythropoietin	Ortho Pharm. Corp.	Severe anemia assoc. with AZT therapy
Recombinant Human	Serono	AIDS-related

Growth Hormone		wasting, cachexia
Megestrol Acetate	Bristol-Myers Squibb	Treatment of anorexia assoc. W/AIDS
Testosterone	Alza, Smith Kline	AIDS-related wasting
Total Enteral Nutrition	Norwich Eaton Pharmaceuticals	Diarrhea and malabsorption related to AIDS

Additionally, the compounds of the disclosure herein set forth may be used in combination with HIV entry inhibitors. Examples of such HIV entry inhibitors are discussed in DRUGS OF THE FUTURE 1999, 24(12), pp. 1355-1362; CELL, Vol. 9, pp. 243-246, Oct. 29, 1999; and DRUG DISCOVERY TODAY, Vol. 5, No. 5, May 2000, pp. 183-194 and *Inhibitors of the entry of HIV into host cells*. Meanwell, Nicholas A.; Kadow, John F. Current Opinion in Drug Discovery & Development (2003), 6(4), 451-461. Specifically the compounds can be utilized in combination with attachment inhibitors, fusion inhibitors, and chemokine receptor antagonists aimed at either the CCR5 or CXCR4 coreceptor. HIV attachment inhibitors are also set forth in US 7,354,924 and US 2005/0209246.

It will be understood that the scope of combinations of the compounds of this application with AIDS antivirals, immunomodulators, anti-infectives, HIV entry inhibitors or vaccines is not limited to the list in the above Table but includes, in principle, any combination with any pharmaceutical composition useful for the treatment of AIDS.

Preferred combinations are simultaneous or alternating treatments with a compound of the present disclosure and an inhibitor of HIV protease and/or a non-nucleoside inhibitor of HIV reverse transcriptase. An optional fourth component in the combination is a nucleoside inhibitor of HIV reverse transcriptase, such as AZT, 3TC, ddC or ddI. A preferred inhibitor of HIV protease is Reyataz® (active ingredient Atazanavir). Typically a dose of 300 to 600mg is administered once a day. This may be co-administered with a low dose of Ritonavir (50 to 500mgs). Another preferred

inhibitor of HIV protease is Kaletra®. Another useful inhibitor of HIV protease is indinavir, which is the sulfate salt of N-(2(R)-hydroxy-1-(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(3-pyridyl-methyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide ethanolate, and is synthesized according to U.S. 5,413,999. Indinavir is generally administered at a dosage of 800 mg three times a day. Other preferred protease inhibitors are nelfinavir and ritonavir. Another preferred inhibitor of HIV protease is saquinavir which is administered in a dosage of 600 or 1200 mg tid. Preferred non-nucleoside inhibitors of HIV reverse transcriptase include efavirenz. These combinations may have unexpected effects on limiting the spread and degree of infection of HIV. Preferred combinations include those with the following (1) indinavir with efavirenz, and, optionally, AZT and/or 3TC and/or ddI and/or ddC; (2) indinavir, and any of AZT and/or ddI and/or ddC and/or 3TC, in particular, indinavir and AZT and 3TC; (3) stavudine and 3TC and/or zidovudine; (4) tenofovir disoproxil fumarate salt and emtricitabine.

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

GENERAL CHEMISTRY (METHODS OF SYNTHESIS)

The present invention comprises compounds of Formulas I, II, and III, their pharmaceutical formulations, and their use in patients suffering from or susceptible to HIV infection. The compounds of Formulas I, II, and III also include pharmaceutically acceptable salts thereof. General procedures to construct compounds of Formulas I, II, and III and intermediates useful for their synthesis are described in the following Schemes (after the Abbreviations).

Abbreviations

One or more of the following abbreviations, most of which are conventional abbreviations well known to those skilled in the art, may be used throughout the description of the disclosure and the examples:

Bz_2O = benzoic anhydride

TBTU = O-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate

HATU = 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate methanaminium

DCE = dichloroethane

DCM = dichloromethane

CDI = carbonyl diimidazole

prep. HPLC = preparative high performance liquid chromatography

rt = room temperature

DIPEA = diisopropylethylamine

DMAP = 4-dimethylaminopyridine

DMSO = dimethylsulfoxide

THF = tetrahydrofuran

KHMDS = potassium bis(trimethylsilyl)amide

min = minute(s)

h = hour(s)

sat. = saturated

TEA = triethylamine

EtOAc = ethyl acetate

TFA = trifluoroacetic acid

PCC = pyridinium chlorochromate

TLC = thin layer chromatography

Tf_2NPh = (trifluoromethylsulfonyl)methanesulfonamide

dioxane = 1,4-dioxane

PG = protective group

atm = atmosphere(s)

mol = mole(s)

mmol= milimole(s)

mg = milligram(s)

µg = microgram(s)

µl = microliter(s)

µm= micrometer(s)

mm= millimeter(s)

HOAc= acetic acid

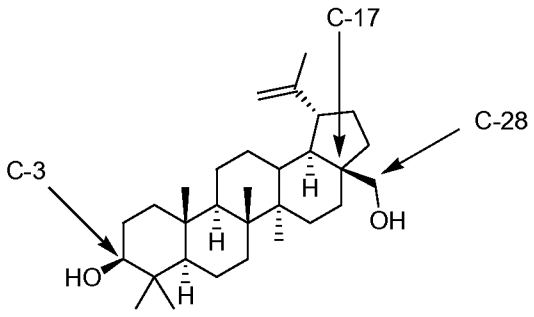
MeOH= methanol

DMF= *N,N*-dimethylformamide

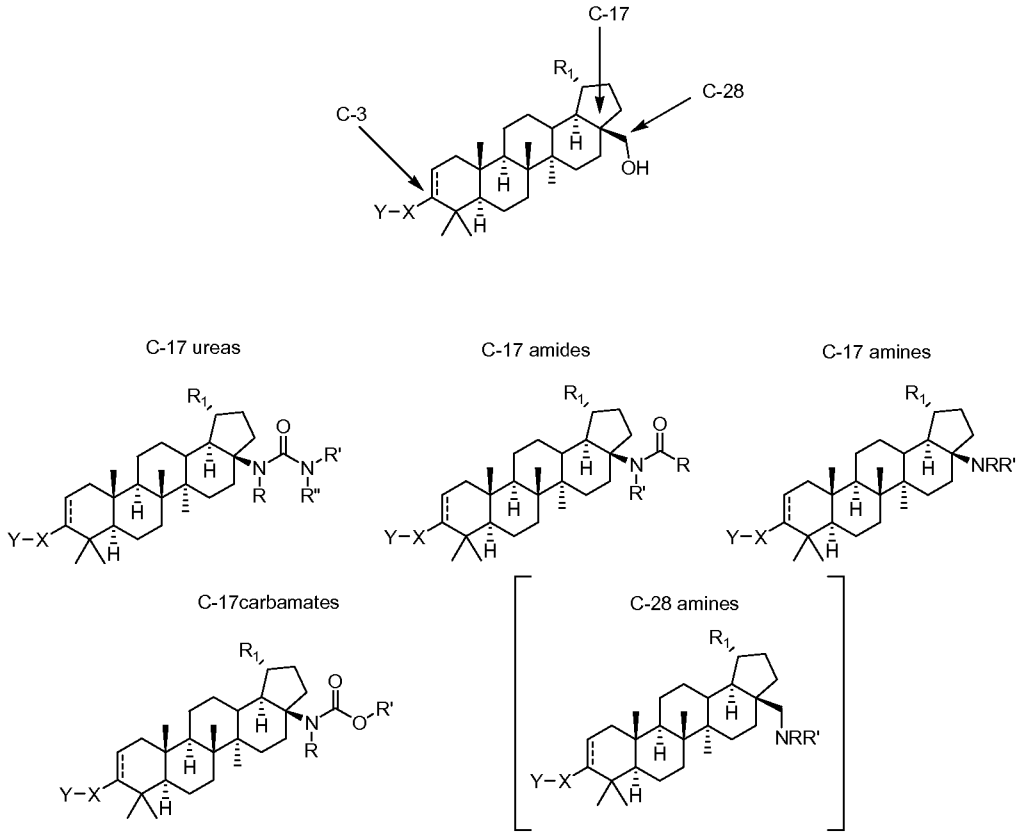
TBAF= tetrabutylammonium fluoride

TBDMSCl= *tert*-butyldimethylsilyl chloride

The terms "C-3" and "C-28" refer to certain positions of a triterpene core as numbered in accordance with IUPAC rules (positions depicted below with respect to an illustrative triterpene: betulin):



The same numbering is maintained when referring to the compound series in schemes and general descriptions of methods.



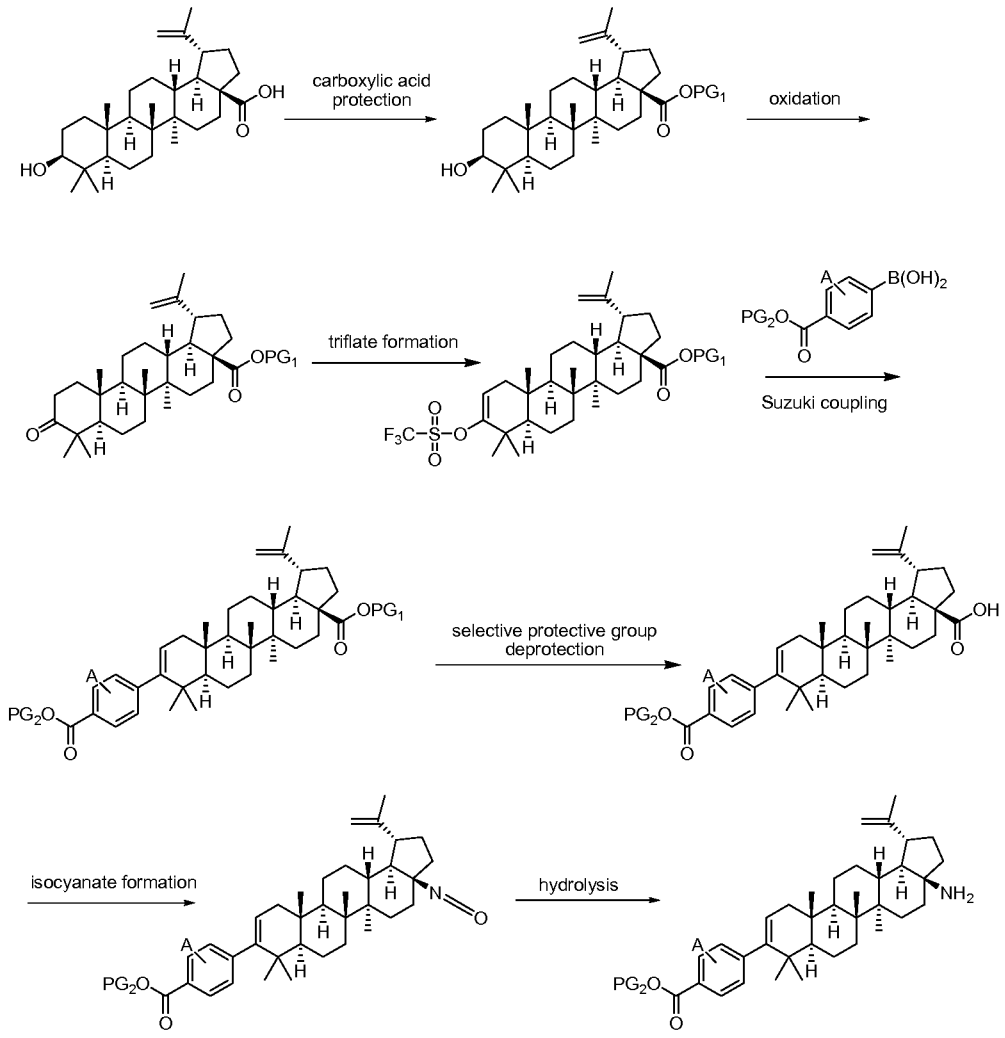
Preparation of Compounds of Formulas I, II, and III General Chemistry Schemes:

Preparation of Compounds of Formulas I, II and III General Chemistry Schemes:

Compounds of Formula I can be prepared from commercially available (Aldrich, others) betulinic acid by chemistry described in the following schemes. Compounds of Formula II and III are described thereafter.

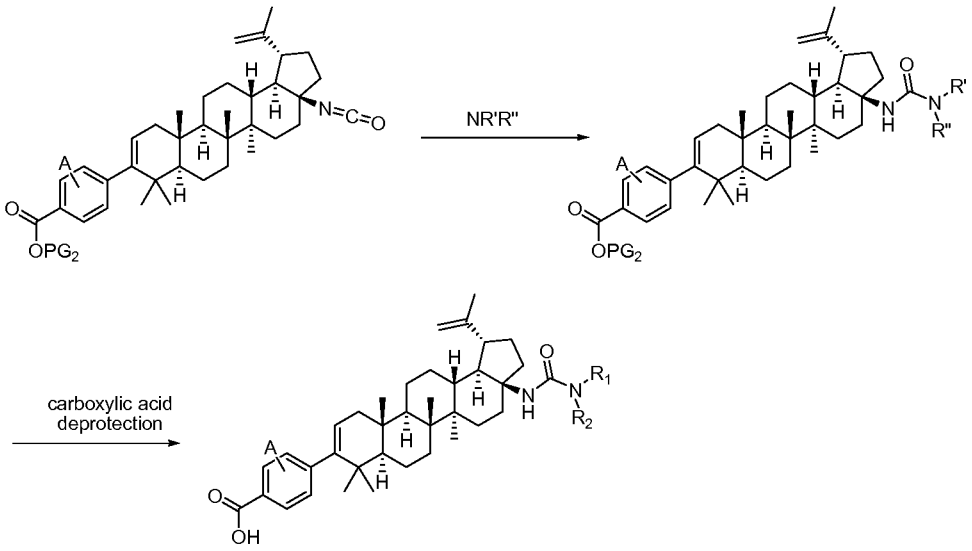
General reaction schemes are set forth as follows:

Scheme 1



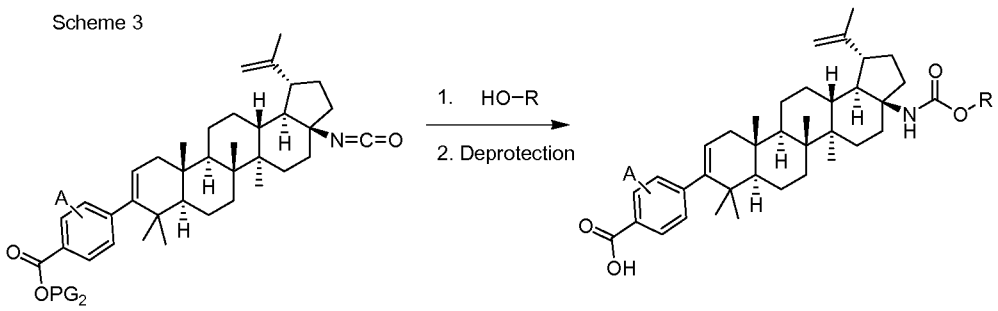
Scheme 1 describes the preparation of the key intermediate C-17 primary amine from betulinic acid. The carboxylic acid present in betulinic acid was protected with a suitable protective group. Standard oxidation (i.e. PCC, Dess-Martin) of the C-3 hydroxyl group produces the C-3 ketone which is then converted into the triflate using conditions know to those skilled in the art. Palladium-catalyzed cross coupling with a boronic acid derivative (Stille coupling using stannanes can also be used) afforded the corresponding C-3-modified betulinic acid derivatives. The C-28 carboxylic ester was then selectively deprotected and submitted to Curtius rearrangement conditions to afford the C-17 primary amine. This reaction can be carried out in one single step or stepwise via isolation of the isocyanate intermediate, as shown in Scheme 1.

Scheme 2



The isocyanate can be further modified to prepare ureas as shown in Scheme 2. Addition of an amine to a solution of the isocyanate in a solvent such as THF or dioxane in the presence of Hunig's base or TEA at room temperature or heating if necessary, affords the corresponding C-17 urea. Hydrolysis of the benzoic ester affords the benzoic acid derivative.

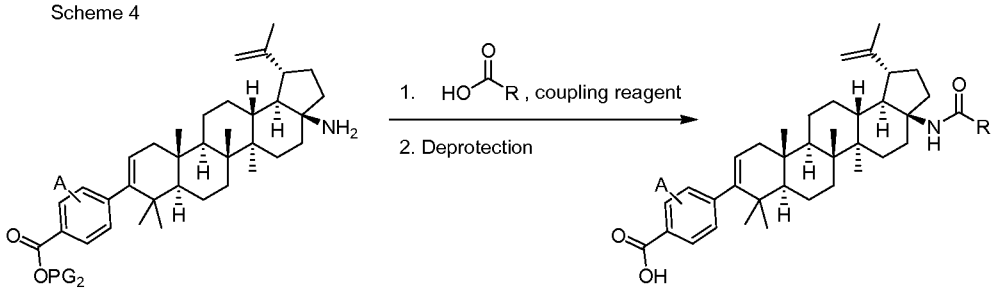
Scheme 3



Similarly, carbamates can be prepared by adding an alcohol to the isocyanate in a solution of THF or dioxane in the presence of a base such as sodium hydride at room temperature or heating when necessary followed by hydrolysis of the carboxylic ester. The deprotection may also happen under the conditions of the first reaction, so no additional step may be needed.

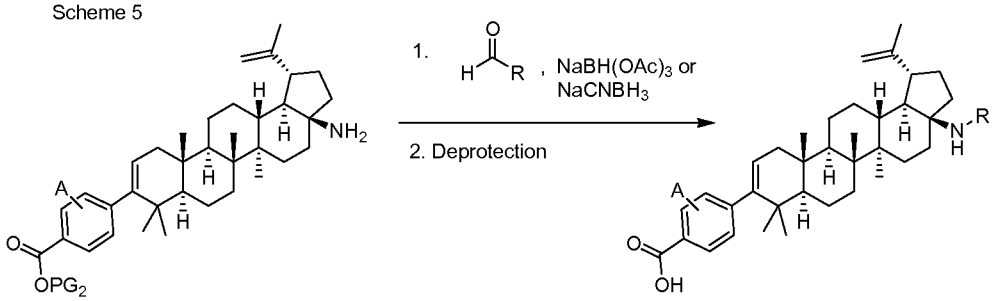
The C-17 primary amine can be further modified using standard methods, known to those skill in the art. Some examples are shown in the following schemes.

Scheme 4



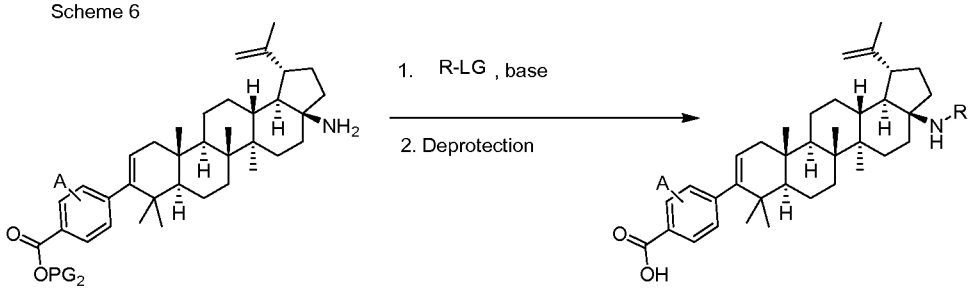
C-17 amides can be prepared by reacting a carboxylic acid with the C-17 primary amine in the presence of an adequate coupling reagent such as HATU, DCC, and others known to those skilled in the art, in the presence of a base such as Hunig's base, TEA, etc., in the appropriate solvent (DCM, THF, DMF, etc.). Hydrolysis of the carboxylic ester affords the benzoic acid. Alternatively, some amides can be prepared by treating the C-17 primary amine with the corresponding carboxylic acid chloride reagent instead of an acid. Similarly, sulfonamides can be prepared from the C-17 primary amine by using a sulfonyl chloride as the sulfonylating agent.

Scheme 5



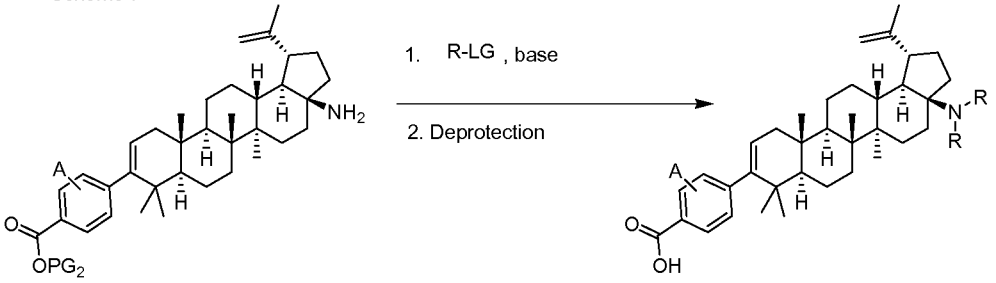
The C-17 primary amine can be treated with an aldehyde under reductive amination conditions (e.g. $NaBH(OAc)_3$)in the presence of AcOH/NaOAc or $Ti(OPr)_4$ in a solvent such as THF, 1,4-dioxane, DCE or DCM) to afford C-17 secondary amines. Hydrolysis of the carboxylic ester renders the benzoic acid compound.

Scheme 6



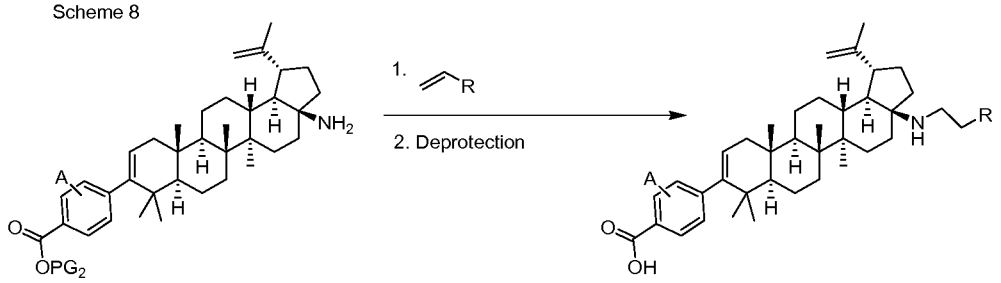
Some C-17 amines can be prepared by alkylation of the C-17 primary amine with an alkylating agent (R-LG), where LG is a leaving group such as, but not limited to Br, Cl, I, mesylate, tosylate or triflate in the presence of a base. Heating may be needed in some cases. Hydrolysis of the carboxylic ester renders the benzoic acid product.

Scheme 7



In some cases, by prolonging the reaction times and heating the reaction mixture, the dialkylated product can also be formed.

Scheme 8

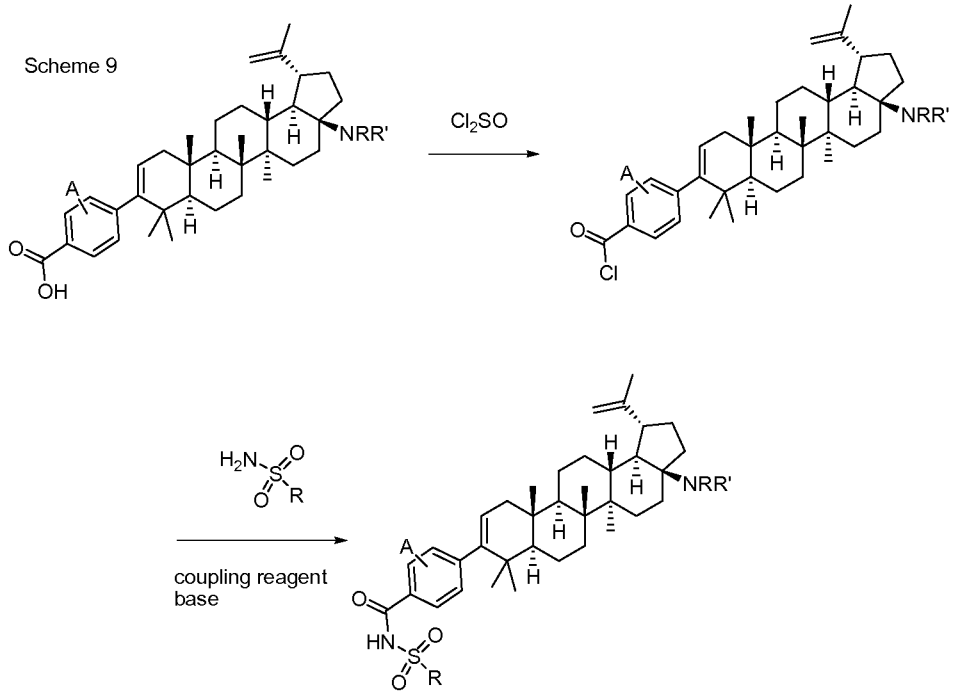


Alternatively, some C-17 amines can be prepared by 1,4-addition to Michael acceptors followed by hydrolysis of the ester.

Substituents R, R' and R" may contain functional groups (i.e. COOH, COOR, OH, NHR) that can be further modified by methods know to those skilled in the art. The modification can be carried out before or after the final deprotection of the carboxylic acid is performed depending on the nature of the functional group.

Alternatively, the C-17 secondary amine can be further modified (i.e. alkylated, acylated, sulfonylated, etc.) using some of the methods described above or other standard methods known to those skilled in the art. Saturation of the isopropenyl group can be accomplished by hydrogenation under standard conditions of the final products.

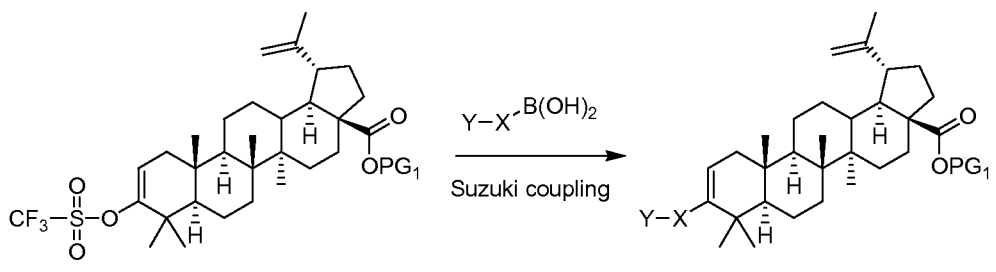
Scheme 9



The benzoic acid can be further modified by methods known to those skilled in the art. An example of such modifications is shown in scheme 9: The free benzoic acid can be converted into the corresponding acid chloride and then treated with the corresponding nucleophile, for example a sulfonyl amide or urea sulfamide, in the presence of a base to afford a sulfonyl amide or acylsulfamide derivative.

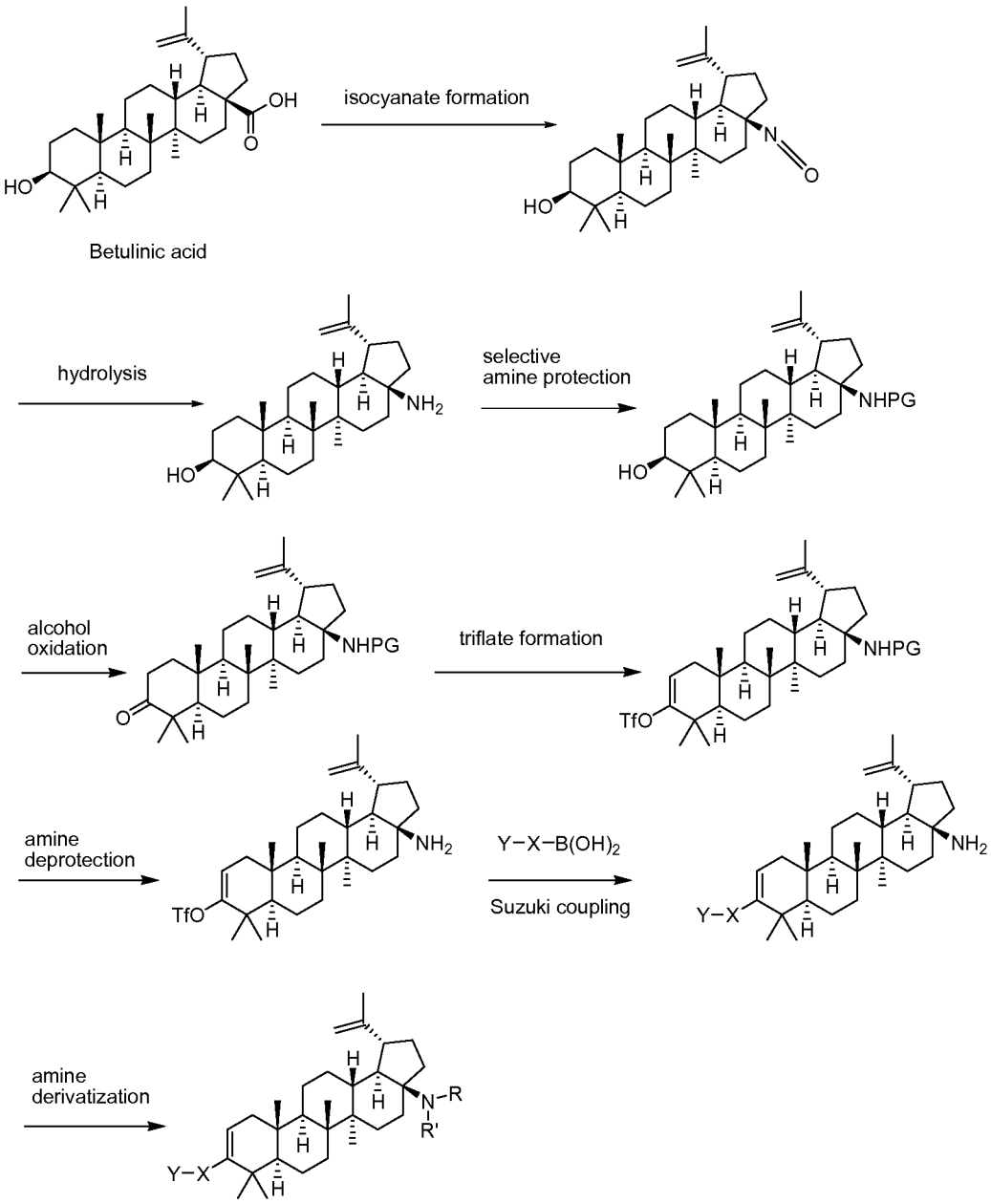
Compounds of formula I where the modification in the C-3 position differs from benzoic acid can be prepared by selecting the corresponding boronic acid in the palladium-catalyzed cross coupling step shown in Scheme 1 (Scheme 10). Then the C-28 position can be modified using the chemistry methods described in the above schemes to obtain the corresponding C-17 amino derivatives.

Scheme 10



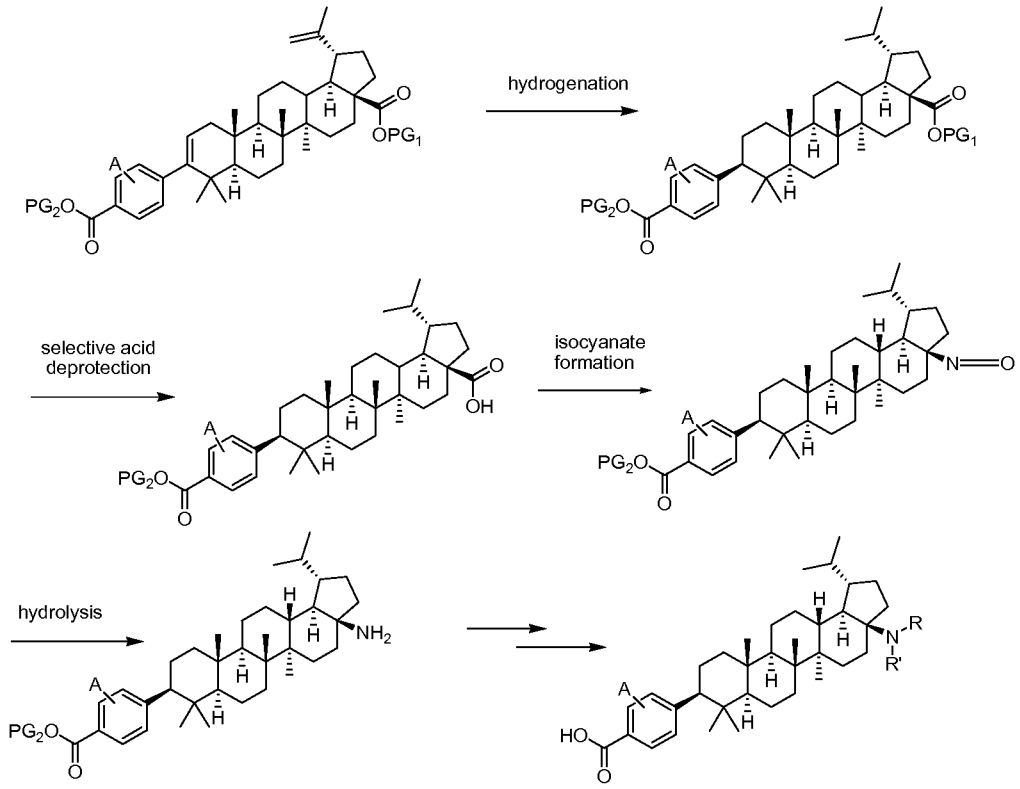
Alternatively, compounds of formula I can be prepared from betulinic acid as described in Scheme 11. Curtius rearrangement of betulinic acid can be accomplished without protection of the C-3 hydroxyl group to render the C-17 isocyanate which upon acid hydrolysis affords the C-17 amine. The C-17 amine is then selectively protected with an amine protective group (i.e F-moc, Boc) to then perform the oxidation of the C-3 hydroxy group to a ketone under standard conditions (i.e. PCC, Dess-Martin reagent, etc). Conversion of the ketone into its triflate can be accomplished by methods known to those skilled in the art. The protective group in the amino group is then taken off to produce the C-17 unsubstituted amine. Installation of the C-3 moiety is accomplished via Suzuki coupling of the triflate with the corresponding boronic acid as described above. The C-17 amino group can then be derivatized as shown above in previous schemes (alkyaltion, acylation, etc).

Scheme 11



Compounds of formula II can be prepared using the chemistry methods described above for compounds of formula I, with one extra step which consists of saturation of the double bonds, as shown below in Scheme 12:

Scheme 12



Compounds of formula III can be prepared in the same manner described above for compounds of formula I and II using oleanoic or ursolic acid as starting materials instead of betulinic acid.

EXAMPLES

The following examples illustrate typical syntheses of the compounds of Formulas I, II and III as described generally above. These examples are illustrative only and are not intended to limit the disclosure in any way. The reagents and starting materials are readily available to one of ordinary skill in the art.

Chemistry

Typical Procedures and Characterization of Selected Examples:

Unless otherwise stated, solvents and reagents were used directly as obtained from commercial sources, and reactions were performed under a nitrogen atmosphere. Flash chromatography was conducted on Silica gel 60 (0.040-0.063 particle size; EM Science supply). ^{1}H NMR spectra were recorded on Bruker DRX-500f at 500 MHz (or Bruker AV 400 MHz, Bruker DPX-300B or Varian Gemini 300 at 300 MHz as stated). The chemical shifts were reported in ppm on the δ scale relative to δTMS = 0. The following internal references were used for the residual protons in the following solvents: $CDCl_3$ (δ_H 7.26), CD_3OD (δ_H 3.30), Acetic-d4 (*Acetic Acid d4*) (δ_H 11.6, 2.07), DMSO mix or DMSO-D6_$CDCl_3$ (($_H$ 2.50 and 8.25) (ratio 75%:25%), and DMSO-D6 (δ_H 2.50). Standard acronyms were employed to describe the multiplicity patterns: s (singlet), br. s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad), app (apparent). The coupling constant (*J*) is in Hertz. All Liquid Chromatography (LC) data were recorded on a Shimadzu LC-10AS liquid chromatograph using a SPD-10AV UV-Vis detector with Mass Spectrometry (MS) data determined using a Micromass Platform for LC in electrospray mode.

LC/MS methods:

Method 1

Start%B = 0, Final%B = 100 over 2 minute gradient, hold at 100%B
Flow Rate = 4 mL / min
Wavelength = 220 nm
Solvent A = 95% water, 5% methanol, 10 mM ammonium acetate
Solvent B = 5% water, 95% methanol, 10 mM ammonium acetate
Column = Phenomenex Luna C18, 5 μm, 3.0 x 50 mm

Method 2

Start%B = 0, Final%B = 100 over 2 minute gradient, hold at 100%B
Flow Rate = 1 mL / min
Wavelength = 220 nm
Solvent A = 90% water, 10% acetonitrile, 0.1% TFA
Solvent B = 10% water, 90% acetonitrile, 0.1% TFA
Column = Phenomenex Luna C18, 3μm, 2.0 x 30 mm

Method 3

Start%B = 0, Final%B = 100 over 2 minute gradient, hold at 100%B
Flow Rate = 4 mL / min
Wavelength = 220 nm
Solvent A = 95% water, 5% methanol, 10 mM ammonium acetate
Solvent B = 5% water, 95% methanol, 10 mM ammonium acetate
Column = Waters Xbridge C18, 5 μm, 4.6 x 50 mm

Method 4

Start%B = 0, Final%B = 100 over 2 minute gradient, hold at 100%B
Flow Rate = 0.8 mL / min
Wavelength = 220 nm
Solvent A = 95% water, 5% methanol, 10 mM ammonium acetate
Solvent B = 5% water, 95% methanol, 10 mM ammonium acetate
Column = Waters Xbridge C18, 3.5 μm, 2.1 x 50 mm

Method 5

Start%B = 15, Final%B = 100 over 2 minute gradient, hold at 100%B
Flow Rate = 1 mL / min
Wavelength = 220 nm
Solvent A = 95% water, 5% acetonitrile, 10 mM ammonium acetate
Solvent B = 5% water, 95% acetonitrile, 10 mM ammonium acetate
Column = Phenomenex Luna C18, 3 μm, 2.0 x 30 mm

Method 6

Start%B = 0, Final%B = 100 over 2 minute gradient, hold at 100%B
Flow Rate = 1 ml/min
Wavelength = 220 nm
Solvent A = 95% water, 5% acetonitrile, 10mM ammonium acetate
Solvent B = 5% water, 95% acetonitrile, 10mM ammonium acetate
Column = Phenomenex Luna C18, 3 μm, 2.0 x 30 mm

Method 7

Start%B = 25, Final%B = 100 over 2 minute gradient, hold at 100%B
Flow Rate = 1 ml/min
Wavelength = 220 nm
Solvent A = 95% water, 5% acetonitrile, 10mM ammonium acetate
Solvent B = 5% water, 95% acetonitrile, 10mM ammonium acetate
Column = Phenomenex Luna C18, 3 μm, 2.0 x 30 mm

Method 8
Start%B = 0, Final%B = 100 over 4 minute gradient, hold at 100%B
Flow Rate = 5 ml/min
Wavelength = 220 nm
Solvent A = 90% water, 10% methanol, 0.1% TFA
Solvent B = 10% water, 90% methanol, 0.1% TFA
Column = Phenomenex Luna C18, 10 μm 3.0 x 50 mm

Method 9
Start%B = 20, Final%B = 100 over 2 minute gradient, hold at 100%B
Flow Rate = 1 ml/min
Wavelength = 220 nm
Solvent A = 95% water, 5% acetonitrile, 10 mM ammonium acetate
Solvent B = 5% water, 95% acetonitrile, 10 mM ammonium acetate
Column = Phenomenex Luna C18, 3 μm, 2.0 x 30 mm

Method 10
Start%B = 0, Final%B = 100 over 2 minute gradient, hold at 100%B
Flow Rate = 1 mL / min
Wavelength = 220 nm
Solvent A = 95% water, 5% methanol, 10 mM ammonium acetate
Solvent B = 5% water, 95% methanol, 10 mM ammonium acetate
Column = Phenomenex Luna C18, 3 μm, 2.0 x 30 mm

Method 11
Start%B = 0, Final%B = 100 over 2 minute gradient, hold at 100%B

Flow Rate = 1 mL / min

Wavelength = 220 nm

Solvent A = 90% water, 10% methanol, 0.1% TFA

Solvent B = 10% water, 90% methanol, 0.1% TFA

Column = Phenomenex Luna C18, 3 µm, 2.0 x 30 mm

Method 12

Start%B = 30, Final%B = 100 over 1 minute gradient

Flow Rate = 0.8 mL / min

Wavelength = 220 nm

Solvent A = 90% water, 10% methanol, 0.1% TFA

Solvent B = 10% water, 90% methanol, 0.1% TFA

Column = Xbridge Phenyl 2.1 x 50 mm 2.5 µm

Method 13

Start%B = 20, Final%B = 100 over 2 minute gradient

Flow Rate = 0.8 mL / min

Wavelength = 254 nm

Solvent A = 90% water, 10% methanol, 0.1% TFA

Solvent B = 10% water, 90% methanol, 0.1% TFA

Column = Xbridge Phenyl 2.1 x 50 mm 2.5 µm

Method 14

Start%B = 0, Final%B = 100 over 4 minute gradient, hold at 100%B

Flow Rate = 1 mL / min

Wavelength = 220 nm

Solvent A = 95% water, 5% acetonitrile, 10 mM ammonium acetate

Solvent B = 5% water, 95% acetonitrile, 10 mM ammonium acetate

Column = Waters BEH C18, 1.7 µm, 2.0 x 50 mm

Method 15

Start%B = 0, Final%B = 100 over 4 minute gradient, hold at 100%B

Flow Rate = 0.5 mL / min

Wavelength = 220 nm
Solvent A = 95% water, 5% methanol, 10 mM ammonium acetate
Solvent B = 5% water, 95% methanol, 10 mM ammonium acetate
Column = Waters BEH C18, 1.7 μm, 2.0 x 50 mm

Method 16

Start%B = 0, Final%B = 100 over 4 minute gradient, hold at 100%B
Flow Rate = 1 mL / min
Wavelength = 220 nm
Solvent A = 90% water, 10% methanol, 0.1% TFA
Solvent B = 10% water, 90% methanol, 0.1% TFA
Column = Phenomenex Luna C18, 3 μm, 2.0 x 30 mm

Method 17

Start%B = 10%, Final%B = 100 over 1 minute gradient, hold at 100%B
Flow Rate = 0.8 mL / min
Wavelength = 220 nm
Solvent A = 90% water, 10% methanol, 0.1% TFA
Solvent B = 10% water, 90% methanol, 0.1% TFA
Column = Phenomenex-luna , 2.0 x 30 mm, 3.0 μm

Prep HPLC methods:

Prep HPLC Method 1
Start%B = 35, Final%B = 100 over 10 minute gradient, hold at 100%B for 8 minutes
Flow Rate = 100 mL / min
Solvent A = 90% water, 10% acetonitrile, 0.1% TFA
Solvent B = 10% water, 90% acetonitrile, 0.1% TFA
Column = Phenomenex Luna C8(2), 10 μm, 50 x 250 mm (100A)

Prep HPLC Method 2
Start%B = 15, Final%B = 100 over 12 minute gradient, hold at 100%B for 6 minutes
Flow Rate = 50 mL / min

Solvent A = 90% water, 10% acetonitrile, 0.1% TFA

Solvent B = 10% water, 90% acetonitrile, 0.1% TFA

Column = Waters Sunfire C18, 5 µm, 30 x 100 mm

Prep HPLC Method 3

Start%B = 20, Final%B = 100 over 8 minute gradient, hold at 100%B for 10 minutes

Flow Rate = 50 mL / min

Solvent A = 90% water, 10% acetonitrile, 0.1% TFA

Solvent B = 10% water, 90% acetonitrile, 0.1% TFA

Column = Waters Sunfire C18, 5 µm, 30 x 100 mm

Prep HPLC Method 4

Start%B = 20, Final%B = 100 over 15 minute gradient, hold at 100%B for 8 minutes

Flow Rate = 100 mL / min

Solvent A = 90% water, 10% acetonitrile, 0.1% TFA

Solvent B = 10% water, 90% acetonitrile, 0.1% TFA

Column = Phenomenex Luna C8(2), 10 µm, 50 x 250 mm (100A)

Prep HPLC Method 5:

Start%B = 15, Final%B = 100 over 20 minute gradient, hold at 100%B for 4 minutes

Flow Rate = 50 mL / min

Solvent A = 90% water, 10% acetonitrile, 0.1% TFA

Solvent B = 10% water, 90% acetonitrile, 0.1% TFA

Column = Waters Sunfire C18, 5 µm, 30 x 100 mm

Prep HPLC Method 6

Start%B = 30, Final%B = 100 over 20 minute gradient, hold at 100%B for 6 minutes

Flow Rate = 40 mL / min

Solvent A = 90% water, 10% methanol, 0.1% TFA

Solvent B = 10% water, 90% methanol, 0.1% TFA

Column = Phenomenex Luna C18(2), 5 µm, 30 x 100 mm

Prep HPLC Method 7

Start%B = 0, Final%B = 100 over 30 minute gradient, hold at 100%B for 8 minutes
Flow Rate = 50 mL / min
Solvent A = 90% water, 10% acetonitrile, 0.1% TFA
Solvent B = 10% water, 90% acetonitrile, 0.1% TFA
Column = Waters Xbridge Phenyl, 5 μm, 30 x 100 mm

Prep HPLC Method 8
Start%B = 0, Final%B = 100 over 15 minute gradient, hold at 100%B for 10 minutes
Flow Rate = 50 mL / min
Solvent A = 90% water, 10% acetonitrile, 0.1% TFA
Solvent B = 10% water, 90% acetonitrile, 0.1% TFA
Column = Waters Xbridge Phenyl, 5 μm, 30 x 100 mm

Prep HPLC Method 9
Start%B = 30, Final%B = 100 over 20 minute gradient, hold at 100%B for 10 minutes
Flow Rate = 50 mL / min
Solvent A = 90% water, 10% acetonitrile, 0.1% TFA
Solvent B = 10% water, 90% acetonitrile, 0.1% TFA
Column = Waters Sunfire C18, 5 μm, 30 x 100 mm

Prep HPLC Method 10
Start%B = 0, Final%B = 100 over 20 minute gradient, hold at 100%B for 4 minutes
Flow Rate = 50 mL / min
Solvent A = 90% water, 10% acetonitrile, 0.1% TFA
Solvent B = 10% water, 90% acetonitrile, 0.1% TFA
Column = Waters Xbridge Phenyl, 5 μm, 30 x 100 mm

Prep HPLC Method 11
Start % B = 20,Final % B = 100 over 10 min gradient, hold at 100% B for 15 min
Flow Rate = 50 ml/min
Wavelength = 220
Solvent Pair = Water - Methanol- TFA
Solvent A = 90% Water -10% Methanol-0.1% TFA
Solvent B = 10% Water -90% Methanol-0.1% TFA

Column = Waters Sunfire C18, 5 μm, 30 x 150 mm

Analytical HPLC Methods:

Analytical HPLC Method 1

Start % B = 10

Final % B = 100

Gradient Time = 15 min

Flow Rate = 1 ml/min

Wavelength1 = 220

Wavelength2 = 254

Solvent A = 10mM amm. bicarb (pH=9.5)/95%water/5%methanol

Solvent B = 10mM amm. bicarb (pH=9.5)/5%water/95%methanol

Column = Xbridge Phenyl 3.5um, 3.0x150mm

Analytical HPLC Method 2

Start % B = 10

Final % B = 100

Gradient Time = 15 min

Flow Rate = 1 ml/min

Wavelength1 = 220

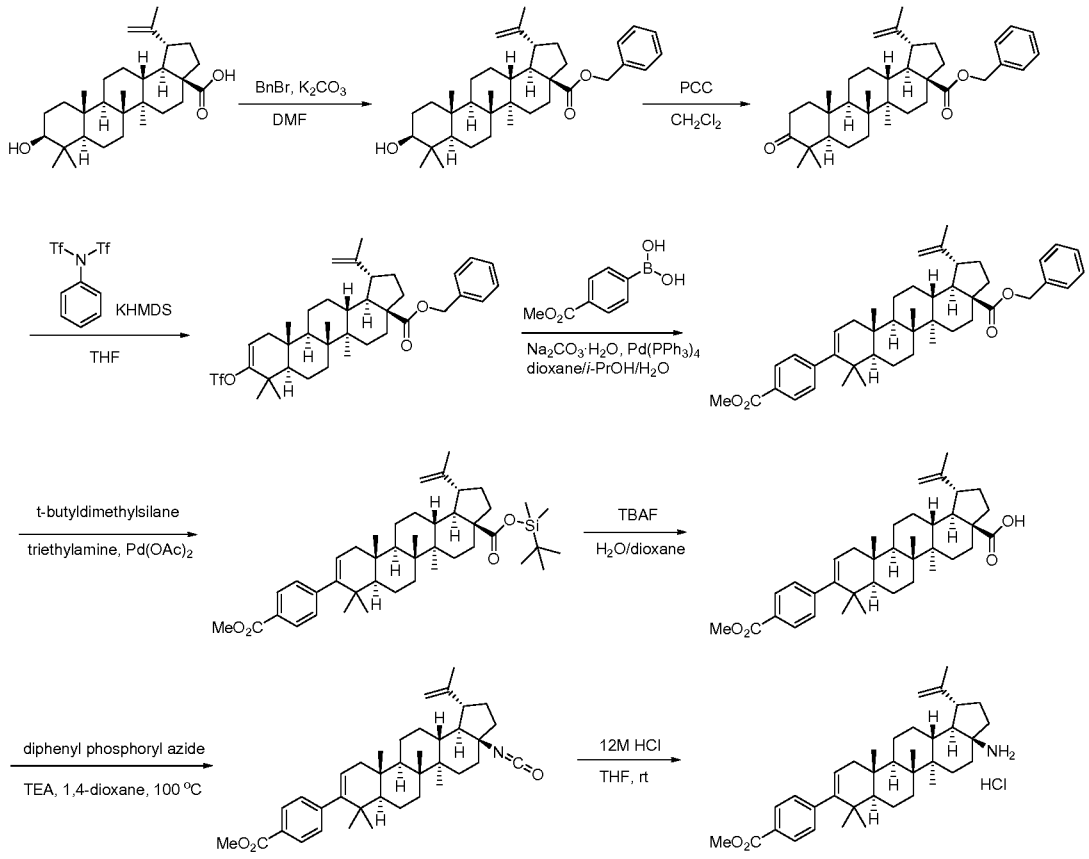
Wavelength2 = 254

Solvent A = 0.1%TFA/95%water/5%acetonitrile

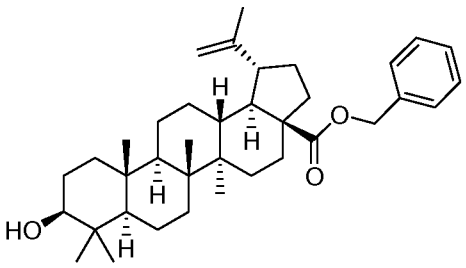
Solvent B = 0.1%TFA/5%water/95%acetonitrile

Column = Xbridge Phenyl 3.5um, 3.0x150mm

Preparation of compounds:



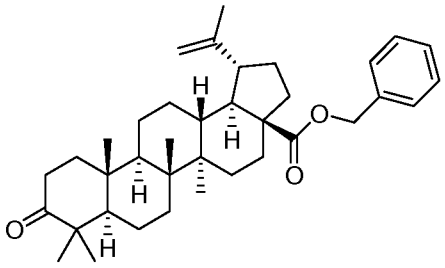
Preparation of (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-benzyl 9-hydroxy-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysene-3a-carboxylate.



To a suspension of betulinic acid (12 g, 26.3 mmol) and potassium carbonate (7.26 g, 52.6 mmol) in DMF (150 mL) was added benzyl bromide (3.28 mL, 27.6 mmol). The mixture was heated to 60 °C for 3.5 h, and then it was cooled to rt. Solids started to precipitate upon cooling. The mixture was diluted water (200 mL) and the solids that formed were collected by filtration to give the title compound (13.92 g, 25.5 mmol, 97% yield) as a white solid. ^{1}H NMR (500 MHz,

CHLOROFORM-d) δ ppm 7.39-7.28 (m, 5 H), 5.16-5.06 (m, 2 H), 4.71 (d, *J*=1.83 Hz, 1 H), 4.59 (s, 1 H), 3.17 (ddd, *J*=11.44, 5.65, 5.49 Hz, 1 H), 3.01 (td, *J*=10.99, 4.88 Hz, 1 H), 2.27 (ddd, *J*=12.36, 3.20, 3.05 Hz, 1 H), 2.21-2.13(m, 1 H), 1.93 - 1.81 (m, 2 H), 1.67 (s, 3 H), 0.95 (s, 3 H), 0.93 (s, 3 H), 1.71 - 0.82 (m, 20 H), 0.79 (s, 3 H), 0.75 (s, 3 H), 0.74 (s, 3 H).

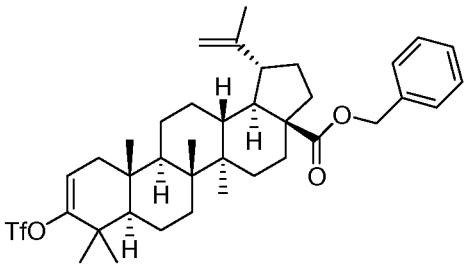
Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-benzyl 5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysene-3a-carboxylate.



To a solution of (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-benzyl 9-hydroxy-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysene-3a-carboxylate (7.1 g, 12.98 mmol) in dichloromethane (100 mL) was added PCC (4.20 g, 19.48 mmol). After stirring for five minutes, the mixture turned a deep crimson color. The mixture was further stirred for 5.5 h. The mixture was filtered through a pad of celite and silica gel which was washed with dichloromethane and then with a 1:1 mixture of ethyl acetate: hexanes. The filtrate was concentrated under reduced pressure to give the title compound (6.92 g, 12.7 mmol, 98% yield) as a white foam. ^{1}H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 7.38 - 7.28 (m, 5 H), 5.17 - 5.06 (m, 2 H), 4.72 (d, *J*=1.83 Hz, 1 H), 4.59 (s, 1 H), 3.01 (td, *J*=10.99, 4.88 Hz, 1 H), 2.51 - 2.43 (m, 1 H), 2.42 - 2.34 (m, 1 H), 2.28 (dt, *J*=12.59, 3.17 Hz, 1 H), 2.21 (td, *J*=12.28, 3.51 Hz, 1 H), 1.94 - 1.82 (m, 3 H), 1.67 (s, 3 H), 1.05 (s, 3 H), 1.01 (s, 3 H), 1.73 – 0.95 (m, 17 H), 0.94 (s, 3 H), 0.89 (s, 3 H), 0.78 (s, 3 H).

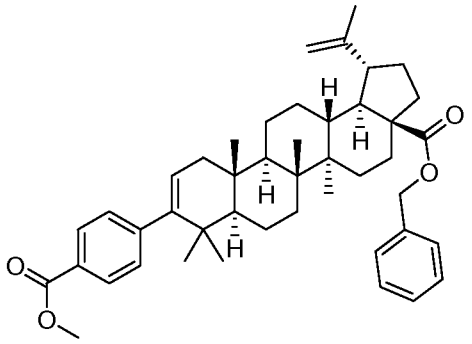
Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-benzyl 5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-9-(trifluoromethylsulfonyloxy)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysene-3a-carboxylate.



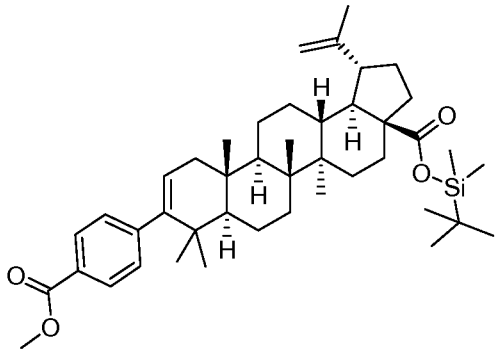
A solution of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-benzyl 5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysene-3a-carboxylate (29.0 g, 53.2 mmol) in THF (200 mL) was cooled to -78 °C. To the solution was added KHMDS (0.5 M in toluene) (213 mL, 106 mmol). The yellow solution was stirred at -78 °C for 25 minutes and a solution of 1,1,1-trifluoro-*N*-phenyl-*N*-(trifluoromethyl)sulfonyl methanesulfonamide (20.92 g, 58.6 mmol) in THF (70 mL) and toluene (30 mL) was added via cannula. The solution was stirred at -78 °C for 3 h. Then, an additional 1.0 g of 1,1,1-trifluoro-*N*-phenyl-*N*-(trifluoromethyl)sulfonyl methanesulfonamide was added and the mixture was stirred at -78 °C. After stirring for 1 h, the mixture was quenched with water (300 mL) and the mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were dried with $MgSO_4$. The drying agent was removed by filtration, and the filtrate was concentrated under reduced pressure to give the title compound (40.0 g, 59.1 mmol) as a yellow solid. Product Rf = 0.57 by silica gel TLC, 5% EtOAc in hexanes, visualized using Hanessian's stain. ^{1}H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 7.29-7.41 (m, 5 H), 5.54 (dd, *J* = 6.71, 1.53 Hz, 1 H), 5.13-5.18 (m, 1 H), 5.05-5.12 (m, 1 H), 4.72 (d, *J* = 1.53 Hz, 1 H), 4.59 (s, 1 H), 3.02 (td, *J* = 10.99, 4.58 Hz, 1 H), 2.25-2.31 (m, 1 H), 2.22 (td, *J* = 12.21, 3.36 Hz, 1 H), 2.14 (dd, *J* = 17.09, 6.71 Hz, 1 H), 1.81-1.96 (m, 2 H), 1.67 (s, 3 H), 1.10 (s, 3 H), 1.00 (s, 3 H), 0.94 (s, 3 H), 0.91-1.77 (m, 17 H), 0.88 (s, 3 H), 0.77 (s, 3 H).

Preparation of (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-benzyl 9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysene-3a-carboxylate.



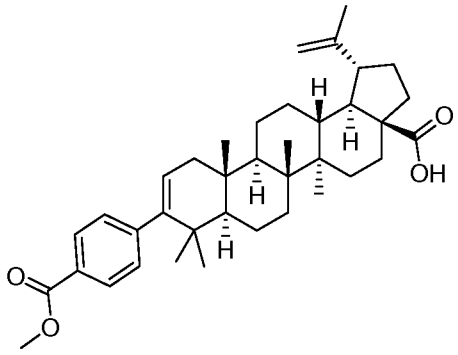
To a solution of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13bR)-benzyl 5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-9-(trifluoromethylsulfonyloxy)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysene-3a-carboxylate (6.21 g, 9.18 mmol) in dioxane (25 mL) was added 2-propanol (25 mL) and water (15 mL) followed by sodium carbonate monohydrate (3.42 g, 27.5 mmol), 4-methoxycarbonylphenylboronic acid (2.478 g, 13.77 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.318 g, 0.275 mmol). The flask was attached to a reflux condenser, flushed with N_2 and heated to reflux overnight. The mixture was then cooled to rt and diluted with water (75 mL). The mixture was extracted with ethyl acetate (3 x 75 mL) and washed with brine (75 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was adsorbed to silica gel and purified by silica gel flash chromatography using a 0-20% ethyl acetate in hexanes gradient. The fractions containing the expected product were combined and concentrated under reduced pressure to give the title compound (4.16 g, 6.28 mmol, 68.4% yield) as a white foam. ^{1}H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 7.92 (d, *J*=8.24 Hz, 2 H), 7.40 - 7.29 (m, 5 H), 7.19 (d, *J*=8.24 Hz, 2 H), 5.28 (dd, *J*=6.10, 1.83 Hz, 1 H), 5.19 - 5.07 (m, 2 H), 4.73 (d, *J*=1.83 Hz, 1 H), 4.60 (s, 1 H), 3.90 (s, 3 H), 3.04 (td, *J*=10.91, 4.73 Hz, 1 H), 2.20 - 2.32 (m, 2 H), 2.09 (dd, *J*=17.24, 6.26 Hz, 1 H), 1.95 - 1.82 (m, 2 H), 1.69 (s, 3 H), 0.97 (s, 3 H), 0.95 (s, 3 H), 0.92 (s, 3 H), 0.91 (s, 3 H), 1.75 – 0.87 (m, 17 H), 0.82 (s, 3 H).

Preparation of (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-*tert*-butyldimethylsilyl 9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysene-3a-carboxylate.



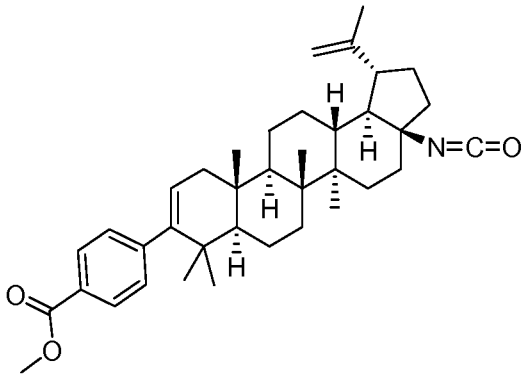
To a solution of (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-benzyl 9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysene-3a-carboxylate (3.82 g, 5.76 mmol) in dichloroethane (100 mL) was added triethylamine (1.285 mL, 9.22 mmol), *tert*-butyldimethylsilane (1.912 mL, 11.52 mmol), and palladium(II) acetate (0.647 g, 2.88 mmol). The mixture was flushed with N_2 and heated to 60 °C. After 2 h, the reaction was cooled to rt, filtered through a pad of celite and silica gel to remove the solids which were washed with 25% EtOAc in hexanes. The filtrate was concentrated under reduced pressure and treated with acetic acid (25 mL), THF (10 mL) and water (3 mL). After stirring for 1 h the solids formed were collected by filtration and washed with water to give the title compound (3.62 g, 5.27 mmol, 91% yield) as a white solid. ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.94 (d, *J*=8.28 Hz, 2 H), 7.21 (d, *J*=8.28 Hz, 2 H), 5.30 (dd, *J*=6.15, 1.63 Hz, 1 H), 4.75 (d, *J*=1.76 Hz, 1 H), 4.62 (s, 1 H), 3.92 (s, 4 H), 3.08 (td, *J*=10.92, 4.27 Hz, 1 H), 2.35 - 2.22 (m, 2 H), 2.17 - 2.06 (m, 1 H), 2.02 – 1.84 (m, 2 H), 1.71 (s, 3 H), 1.01 (s, 6 H), 0.99 (br. s., 3 H), 0.98 (s, 9 H), 0.94 (s, 6 H), 1.78 – 0.90 (m, 16 H), 0.32 - 0.28 (m, 6 H).

Preparation of (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysene-3a-carboxylic acid.



To solution of (1R,3aS,5aR,5bR,7aR,11aS,11bR, 13aR,13bR)-*tert*-butyldimethylsilyl 9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysene-3a-carboxylate (3.12 g, 4.54 mmol) in dioxane (25 mL) was added TBAF (75% wt in water) (2.375 g, 6.81 mmol) and the mixture was stirred at rt for 4 h. The reaction mixture was diluted with 1N HCl (25 mL) and water (5 mL) and extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and partially concentrated under reduced pressure to about 10 mL volume. To the partially concentrated mixture was added 1N HCl (50 mL). The solids that formed were collected by filtration and washed with water to give the title compound (2.58 g, 4.50 mmol, 99% yield) as a white solid. LCMS: m/e 571.47 $(M-H)^-$, 3.60 min (method 1). ^1H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 9.80 (br. s., 1 H), 7.92 (d, *J*=8.24 Hz, 2 H), 7.18 (d, *J*=8.24 Hz, 2 H), 5.32 - 5.26 (m, 1 H), 4.75 (s, 1 H), 4.62 (br. s., 1 H), 3.90 (s, 3 H), 3.07 – 2.99 (m, 1 H), 2.33 - 2.21 (m, 2 H), 2.10 (dd, *J*=17.09, 6.10 Hz, 1 H), 2.06 – 1.94 (m, 2 H), 1.70 (s, 3 H), 1.01 (br. s., 3 H), 1.00 (br. s., 3 H), 0.98 (s, 3 H), 0.91 (s, 6 H), 1.79 – 0.89 (m, 17 H).

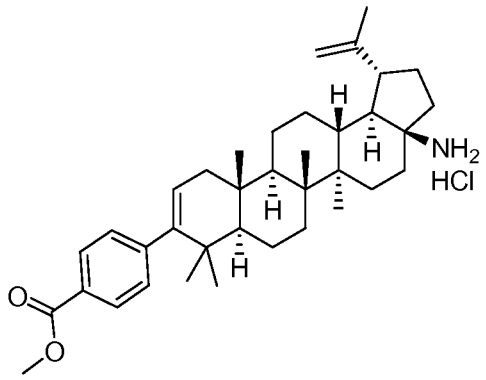
Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.



To a slurry of (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysene-3a-carboxylic acid (10 g, 17.46 mmol) in 1,4-dioxane (200 mL) was added triethylamine (4.38 mL, 31.4 mmol) followed by diphenyl phosphoryl azide (5.82 mL, 26.2 mmol). The resulting white slurry was heated to 100 °C. After 5 h, the reaction was allowed to cool to rt and was then diluted with EtOAc and washed with 1N NaOH (2 x 70 mL). The combined aqueous layer was extracted with EtOAc (2 x 150 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated to a slurry (75 mL) which was stored in a refrigerator overnight. The slurry was filtered and the white solid product was washed with Et_2O. The liquid filtrate was concentrated to a yellow slurry which was filtered and washed with Et_2O to give more white solid product. The two batches of white solid were combined and dried *in vacuo* to give the title compound (8.6 g, 15.09 mmol, 86% yield) as a white solid. ^{1}H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 8.0 (2 H, d, *J*=8.2 Hz), 7.2 (2 H, d, *J*=8.2 Hz), 5.3 (1 H, d, *J*=4.6 Hz), 4.8 (1 H, s), 4.7 (1 H, s), 3.9 (3 H, s), 2.6 (1 H, td, *J*=10.8, 5.8 Hz), 2.1 - 2.2 (2 H, m), 1.8 - 2.0 (4 H, m), 1.7 - 1.8 (1 H, m), 1.7 (3 H, s), 1.5 - 1.7 (5 H, m), 1.4 - 1.5 (5 H, m), 1.3 - 1.4 (2 H, m), 1.2 - 1.3 (2 H, m), 1.1 (3 H, s), 1.1 - 1.1 (1 H, m), 1.0 (3 H, s), 1.0 (3 H, s), 1.0 (3 H, br. s.), 1.0 (3 H, br. s.). ^{13}C NMR (*CHLOROFORM-d*) δ ppm 14.2, 15.4, 16.2, 19.2, 19.5, 20.8, 21.0, 24.7, 27.4, 29.0, 29.2, 33.3, 36.0, 37.2, 39.0, 39.0, 40.3, 41.5, 41.8, 47.8, 49.0, 49.2, 51.7, 52.6, 66.8, 71.3, 110.2, 121.3, 123.7, 127.6, 128.2, 129.8, 146.0, 148.4, 148.6, 166.9.

Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

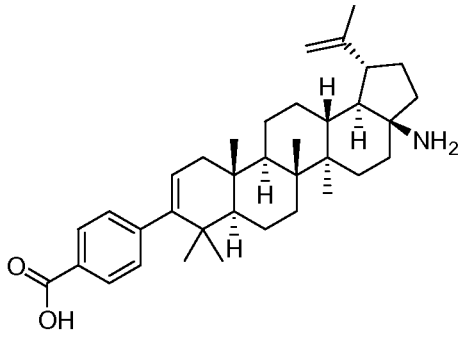
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.



To a cloudy solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (5.47 g, 9.60 mmol) in THF (100 mL) was added concentrated hydrochloric acid (19.83 mL, 240 mmol) . The resulting homogeneous mixture was stirred at rt for 72 h, the reaction mixture was concentrated to dryness to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate, HCl (4.98 g, 8.58 mmol, 89% yield) as a white solid. LCMS: m/e 544.5 $(M+H)^+$, 3.26 min (method 6). ^1H NMR (500 MHz, 1:1 *$CDCl_3$:MeOD, MeOD* lock) δ ppm 7.9 (2 H, d, *J*=8.5 Hz), 7.3 (1 H, t, *J*=7.8 Hz), 7.2 (2 H, d, *J*=8.5 Hz), 7.1 (1 H, t, *J*=7.3 Hz), 5.3 (1 H, d, *J*=4.6 Hz), 4.8 (1 H, s), 4.7 (1 H, br. s.), 3.9 (2 H, s), 3.6 (2 H, dt, *J*=15.6, 6.6 Hz), 3.3 (1 H, dt, *J*=3.1, 1.6 Hz), 2.6 (1 H, td, *J*=11.0, 6.1 Hz), 2.1 (1 H, dd, *J*=17.1, 6.4 Hz), 2.0 (1 H, d, *J*=13.4 Hz), 1.9 - 2.0 (1 H, m), 1.8 - 1.9 (2 H, m), 1.7 - 1.7 (3 H, m), 1.6 - 1.7 (3 H, m), 1.5 - 1.6 (3 H, m), 1.5 - 1.5 (2 H, m), 1.4 (1 H, br. s.), 1.3 - 1.4 (1 H, m), 1.2 - 1.3 (1 H, m), 1.1 - 1.2 (2 H, m), 1.1 - 1.1 (1 H, m), 1.0 (3 H, s), 1.0 (3 H, s), 0.9 (3 H, s), 0.9 (3 H, s).

Example 1

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

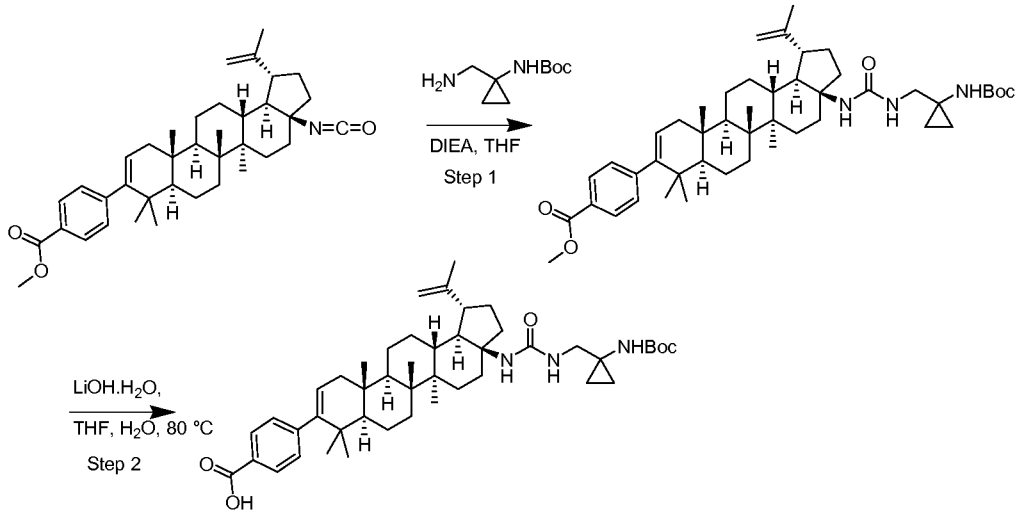


The title compound was formed as a byproduct during the preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate. Purification by reverse phase preparative HPLC gave an off-white solid (100 mg, 3.5% yield) mono-TFA salt. LCMS: m/z 530 ($M+H^+$), retention time 2.29 min (method 11). ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (br. s., 3 H) 0.95 (br. s., 3 H) 1.02 (s, 3 H) 1.06 (s, 3 H) 1.09 - 1.22 (m, 4 H) 1.22 - 1.30 (m, 1 H) 1.30 - 1.47 (m, 3 H) 1.49 - 1.57 (m, 4 H) 1.58 - 1.72 (m, 6 H) 1.73 (s, 3 H) 1.74 - 1.91 (m, 4 H) 1.91 - 1.99 (m, 1 H) 2.02 - 2.18 (m, 2 H) 2.51 - 2.63 (m, 1 H) 4.71 (s, 1 H) 4.81 (s, 1 H) 5.29 (d, *J*=4.88 Hz, 1 H) 7.20 (d, *J*=8.24 Hz, 2 H) 7.92 (d, *J*=8.24 Hz, 2 H).

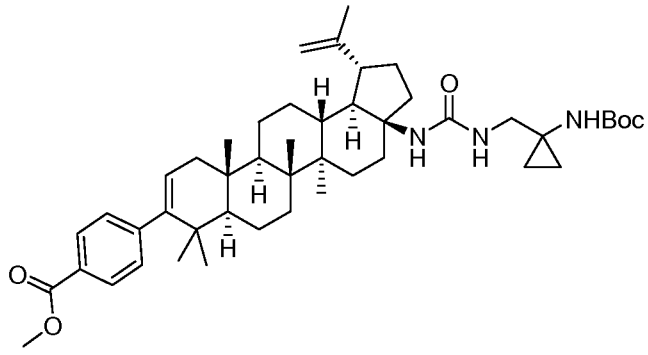
Section 1. Ureas

Example 2

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1-(*tert*-butoxycarbonylamino)cyclopropyl)methylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



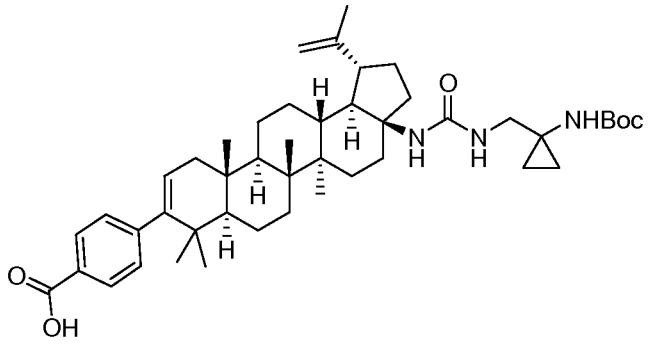
Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1-(*tert*-butoxycarbonylamino)cyclopropyl)methylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.



To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

cyclopenta[a]chrysen-9-yl)benzoate (600 mg, 1.053 mmol) and *N,N*-diisopropyethyllamine (0.734 mL, 4.21 mmol) in THF (6 mL) was added *tert*-butyl 1-(aminomethyl)cyclopropylcarbamate (294 mg, 1.579 mmol). The resulting mixture was stirred at rt. After 16 h, the solvent was concentrated. The crude material was dissolved in THF (1 mL) and MeOH (2 mL), filtered and purified by reverse phase preparative HPLC (method 1) to give the title compound (499.5 mg, 58% yield) as a white solid. LCMS: m/e 756.7 $(M+H)^+$, 2.75 min (method 7). ^{1}H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 8.0 (2 H, d, *J*=8.5 Hz), 7.2 (2 H, d, *J*=8.5 Hz), 5.3 - 5.3 (1 H, m), 5.1 (1 H, br. s.), 4.8 (1 H, s), 4.7 (1 H, s), 3.9 (3 H, s), 3.5 - 3.5 (1 H, m), 3.4 (1 H, d, *J*=14.3 Hz), 2.8 (1 H, br. s.), 2.6 (1 H, d, *J*=12.8 Hz), 2.4 (1 H, dd, *J*=12.2, 8.2 Hz), 2.1 (1 H, dd, *J*=17.4, 6.4 Hz), 1.9 - 2.1 (2 H, m), 1.8 (1 H, d, *J*=13.4 Hz), 1.7 - 1.8 (1 H, m), 1.7 (3 H, s), 1.7 - 1.7 (2 H, m), 1.5 - 1.7 (3 H, m), 1.5 (9 H, s), 1.4 - 1.5 (5 H, m), 1.2 - 1.3 (1 H, m), 1.1 - 1.2 (2 H, m), 1.1 (3 H, s), 1.0 (3 H, s), 1.0 (3 H, s), 0.9 (6 H, s), 0.8 - 0.9 (3 H, m). ^{13}C NMR (*CHLOROFORM-d*) δ ppm 14.1, 15.4, 16.1, 19.0, 19.5, 20.7, 20.8, 24.8, 27.0, 28.1, 29.1, 29.2, 29.4, 31.4, 33.2, 35.1, 36.0, 36.6, 37.2, 40.4, 41.4, 41.6, 46.0, 49.1, 49.6, 51.7, 52.5, 77.3, 80.1, 109.9, 123.7, 127.6, 128.2, 129.8, 146.0, 148.4, 149.2, 167.0.

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1-(*tert*-butoxycarbonylamino)cyclopropyl)methylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

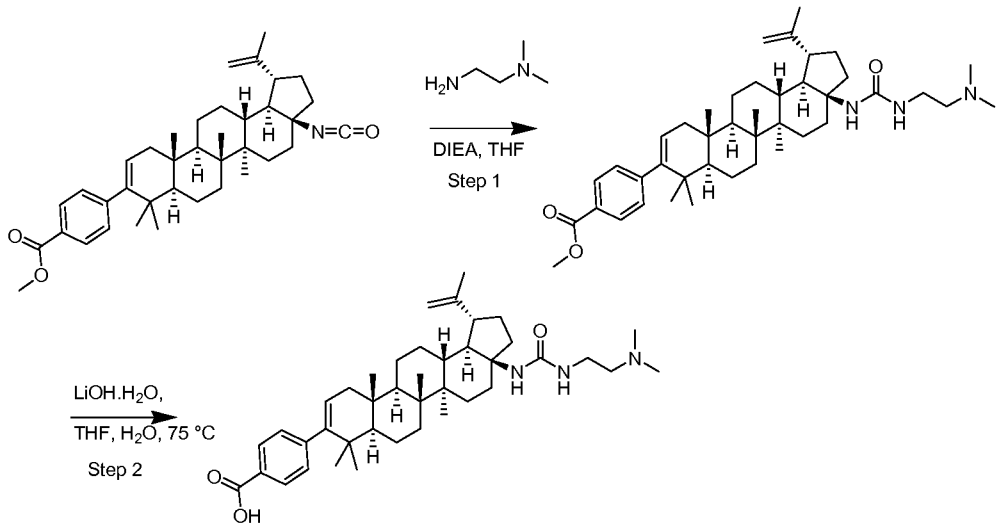


To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-((1-(*tert*-butoxycarbonylamino)cyclopropyl)methyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

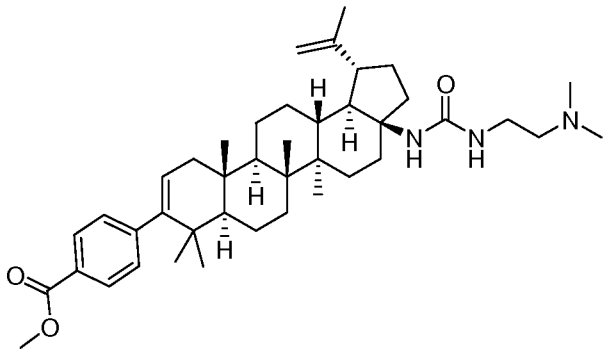
octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (91 mg, 0.12 mmol) in THF (5 mL) was added a solution of lithium hydroxide monohydrate (20.2 mg, 0.481 mmol) in water (1.00 mL). The reaction mixture was stirred at 80 °C for 3 h. The reaction was concentrated and purified by reversed phase preparative HPLC using prep HPLC method 2. HPLC fractions containing product peaks were treated with saturated aqueous $NaHCO_3$ solution (100 mL), combined and concentrated. The resulting residue was triturated with H_2O (8 mL) and extracted with a mixture of THF (30 mL) and EtOAc (50 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to give the title compound (58.1 mg, 0.069 mmol, 57.7% yield) as a white solid. LCMS: m/e 742.6 $(M+H)^+$, 2.13 min (method 6). ^1H NMR (500 MHz, *MeOD*) δ ppm 7.9 (2 H, d, *J*=7.9 Hz), 7.2 (2 H, d, *J*=8.2 Hz), 5.3 (1 H, d, *J*=6.1 Hz), 4.8 (1 H, s), 4.6 (1 H, s), 3.9 - 4.0 (1 H, m), 3.3 (2 H, d, *J*=9.5 Hz), 2.7 (1 H, br. s.), 2.6 (1 H, d, *J*=13.4 Hz), 2.4 (1 H, dd, *J*=11.7, 8.7 Hz), 2.2 (1 H, dd, *J*=17.2, 6.3 Hz), 1.9 - 2.0 (3 H, m), 1.7 - 1.8 (2 H, m), 1.7 (3 H, s), 1.7 - 1.7 (1 H, m), 1.5 - 1.6 (3 H, m), 1.5 - 1.5 (6 H, m), 1.5 (9 H, s), 1.4 (2 H, d, *J*=2.1 Hz), 1.2 - 1.4 (6 H, m), 1.2 (3 H, s), 1.1 - 1.1 (2 H, m), 1.0 (6 H, br. s.), 1.0 (3 H, s), 1.0 (3 H, s), 0.9 - 0.9 (1 H, m). ^{13}C NMR (*MeOD*) δ ppm 11.2, 13.9, 15.5, 16.1, 18.4, 18.6, 20.0, 20.7, 21.6, 23.9, 25.6, 27.5, 27.8, 29.1, 29.1, 29.8, 29.9, 30.0, 33.8, 35.7, 36.5, 37.6, 37.7, 40.8, 41.9, 42.1, 49.9, 49.9, 53.3, 63.8, 67.3, 79.2, 109.5, 124.1, 128.7, 130.1, 146.8, 150.4, 157.5, 159.2.

Example 3

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimethylamino)ethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



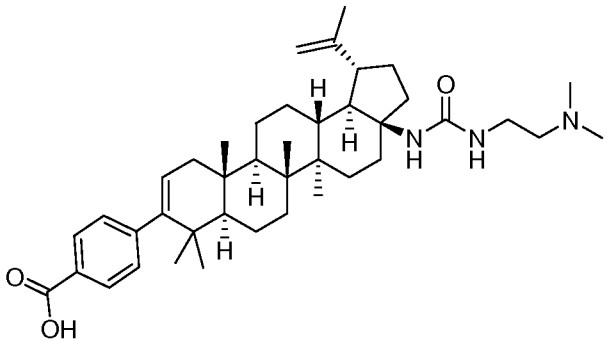
Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimethylamino)ethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.



To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (610.0 mg, 1.071 mmol) in THF (10 mL) was added *N,N*-diisopropylethylamine (0.559 mL, 3.21 mmol) and *N,N*-dimethylethylenediamine (0.353 mL, 3.21 mmol). The reaction mixture was stirred at 25 °C. After 18 h, the reaction mixture was diluted with EtOAc (50 mL) and treated with 1N HCl (5 mL). The mixture was concentrated to a paste and then triturated with EtOAc, filtered and washed with Et_2O. The white solid was saved and the liquid filtrate was concentrated and the trituration and filtration steps were

repeated twice more. The combined white solid product was dried in a vacuum oven to give the title compound (650.0 mg, 0.958 mmol, 90% yield). LCMS: m/e 658.4 $(M+H)^+$, 4.25 min (method 8). ^{1}H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 7.9 (2 H, d, *J*=8.5 Hz), 7.2 (2 H, d, *J*=8.2 Hz), 5.3 (1 H, dd, *J*=6.3, 1.7 Hz), 4.8 (1 H, s), 4.6 (1 H, s), 3.9 (3 H, s), 3.7 - 3.8 (1 H, m), 3.5 - 3.6 (1 H, m), 3.2 (2 H, br. s.), 2.9 (6 H, br. s.), 2.7 - 2.7 (1 H, m), 2.6 (1 H, d, *J*=13.4 Hz), 2.4 (1 H, dd, *J*=11.6, 8.2 Hz), 2.1 (1 H, dd, *J*=17.2, 6.3 Hz), 2.0 - 2.1 (1 H, m), 1.8 - 1.9 (1 H, m), 1.8 (1 H, d, *J*=12.8 Hz), 1.7 (3 H, s), 1.7 (1 H, d, *J*=6.7 Hz), 1.6 - 1.7 (1 H, m), 1.5 - 1.6 (2 H, m), 1.5 (4 H, d, *J*=2.7 Hz), 1.3 - 1.4 (5 H, m), 1.2 - 1.3 (1 H, m), 1.1 (3 H, s), 1.0 - 1.1 (2 H, m), 1.0 (3 H, s), 1.0 - 1.0 (3 H, m), 0.9 (6 H, s). ^{13}C NMR (*CHLOROFORM-d*) δ ppm 14.2, 15.8, 16.3, 18.4, 19.2, 19.5, 20.7, 21.1, 25.0, 27.1, 29.1, 29.5, 29.6, 33.3, 35.3, 35.4, 36.0, 37.2, 37.3, 40.3, 41.4, 41.7, 43.4, 46.7, 49.3, 51.7, 52.6, 53.4, 58.9, 63.9, 77.3, 109.8, 123.9, 127.6, 128.2, 129.8, 145.9, 148.5, 149.4, 157.5, 167.0.

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimethylamino)ethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

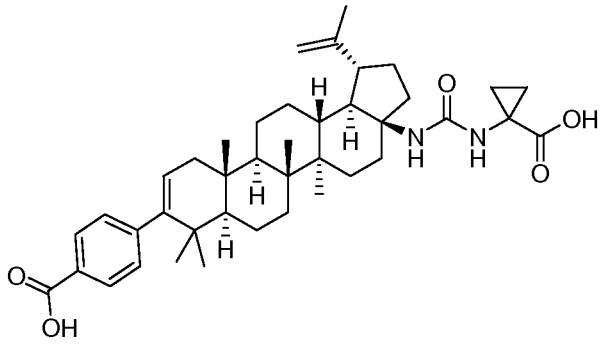


To a cloudy solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimethylamino)ethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.255 g, 0.388 mmol) in THF (5 mL) was added a solution of lithium hydroxide monohydrate (0.049 g, 1.16 mmol) in water (1.00 mL). The reaction mixture was heated to 75 °C for 18 h. Then, the reaction was treated with 1N HCl (1 mL) and concentrated *in vacuo*, absorbed onto silica gel (3.5

g), loaded onto a silica gel column (12 g cartridge) and eluted with 90:10 DCM:MeOH to give the title compound (237 mg, 0.368 mmol, 95% yield) as a white solid. LCMS: m/e 644.4 $(M+H)^+$, 3.95 min (method 8). ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.9 (2 H, d, *J*=8.2 Hz), 7.2 (2 H, d, *J*=8.2 Hz), 5.9 (1 H, s), 5.3 - 5.3 (1 H, m), 4.8 (1 H, d, *J*=1.8 Hz), 4.6 (1 H, s), 3.7 - 3.8 (1 H, m), 3.4 - 3.6 (2 H, m), 3.4 (1 H, s), 3.2 - 3.3 (2 H, m), 2.9 (6 H, s), 2.7 (1 H, td, *J*=11.1, 5.0 Hz), 2.6 (1 H, dd, *J*=10.2, 3.2 Hz), 2.4 (1 H, dd, *J*=12.1, 8.1 Hz), 2.2 (1 H, dd, *J*=17.4, 6.4 Hz), 1.9 - 2.0 (2 H, m), 1.8 (1 H, d, *J*=13.4 Hz), 1.7 (3 H, s), 1.7 (1 H, br. s.), 1.7 - 1.7 (1 H, m), 1.6 - 1.6 (2 H, m), 1.5 - 1.6 (4 H, m), 1.4 - 1.4 (5 H, m), 1.3 - 1.4 (3 H, m), 1.2 (3 H, s), 1.1 - 1.1 (1 H, m), 1.0 - 1.1 (6 H, m), 1.0 (3 H, s), 1.0 (3 H, s). ^{13}C NMR (*MeOD*) δ ppm 14.5, 16.3, 16.8, 19.2, 20.6, 21.3, 22.2, 26.3, 28.2, 29.7, 30.4, 30.5, 34.5, 36.2, 36.4, 37.1, 38.2, 38.4, 41.5, 42.6, 42.8, 43.6, 48.1, 49.0, 49.3, 49.3, 50.4, 50.6, 54.0, 55.6, 59.9, 64.9, 110.3, 111.1, 124.8, 129.3, 130.7, 147.5, 150.9, 160.4.

Example 4

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(1-carboxycyclopropyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

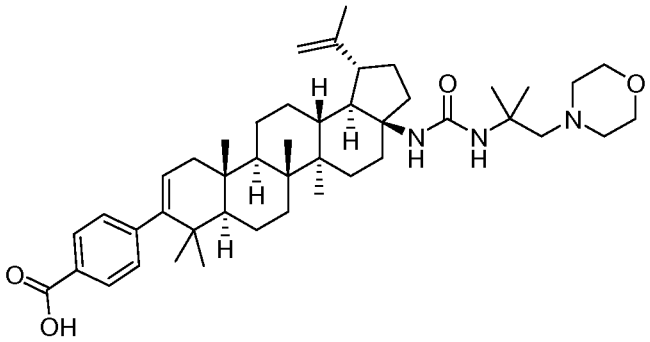


The title compound was prepared in 25% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-

3a-(3-(2-(dimethylamino)ethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 1-aminocyclopropane-1-carboxylic acid ethyl ester hydrochloride was used instead of *N,N*-dimethylethylenediamine in Step 1. LCMS: m/e 657.3 $(M+H)^+$, 4.18 min (method 8). ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.9 (2 H, d, *J*=8.2 Hz), 7.2 (2 H, d, *J*=8.2 Hz), 5.3 - 5.3 (1 H, m), 4.8 (1 H, br. s.), 4.6 (1 H, br. s.), 3.7 - 3.8 (1 H, m), 3.6 - 3.6 (1 H, m), 3.5 - 3.6 (1 H, m), 2.5 - 2.7 (2 H, m), 2.4 (1 H, dd, *J*=12.1, 8.4 Hz), 2.2 (1 H, dd, *J*=17.1, 6.4 Hz), 2.0 (1 H, d, *J*=11.9 Hz), 1.9 (2 H, dt, *J*=6.6, 3.2 Hz), 1.8 - 1.9 (2 H, m), 1.7 - 1.8 (4 H, m), 1.4 - 1.7 (7 H, m), 1.4 (3 H, td, *J*=13.1, 4.0 Hz), 1.3 (3 H, t, *J*=11.7 Hz), 1.2 (3 H, s), 1.1 - 1.1 (3 H, m), 1.1 (3 H, d, *J*=2.4 Hz), 1.0 (3 H, s), 1.0 (2 H, s), 0.9 (1 H, m).

Example 5

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(2-methyl-1-morpholinopropan-2-yl)ureido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

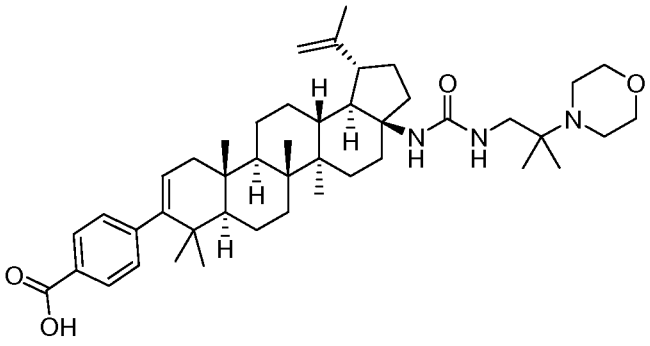


The title compound was prepared in 16% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimethylamino)ethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-methyl-2-morpholinopropan-1-

amine was used instead of *N,N*-dimethylethylenediamine in Step 1. LCMS: m/e 714.3 $(M+H)^+$, 3.97 min (method 8). ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.9 (2 H, d, *J*=8.2 Hz), 7.2 (2 H, d, *J*=8.2 Hz), 5.3 (1 H, d, *J*=4.6 Hz), 4.7 (1 H, br. s.), 2.5 - 2.7 (1 H, m), 2.2 (1 H, dd, *J*=16.9, 6.0 Hz), 2.1 (1 H, dd, *J*=13.3, 9.9 Hz), 1.9 - 2.0 (2 H, m), 1.8 - 1.9 (3 H, m), 1.8 (3 H, br. s.), 1.7 - 1.8 (1 H, m), 1.6 - 1.7 (5 H, m), 1.5 - 1.6 (3 H, m), 1.4 (2 H, d, *J*=13.4 Hz), 1.3 - 1.4 (1 H, m), 1.2 (3 H, br. s.), 1.1 (3 H, br. s.), 1.1 (3 H, br. s.), 1.0 (3 H, br. s.), 1.0 (3 H, br. s.).

Example 6

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(2-methyl-2-morpholinopropyl)ureido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

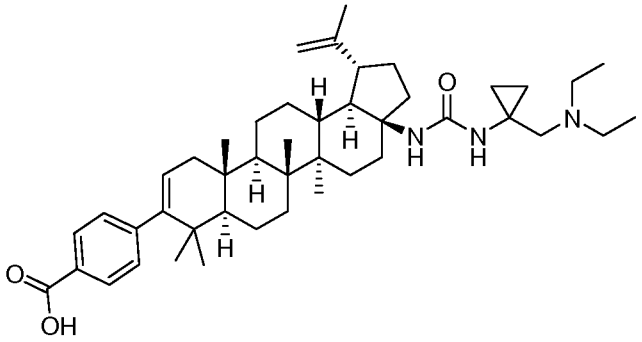


The title compound was prepared in 20% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimethylamino)ethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-methyl-2-morpholinopropan-1-amine was used instead of *N,N*-dimethylethylenediamine in Step 1. LCMS: m/e 714.3 $(M+H)^+$, 3.95 min (method 8). ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.9 (2 H, d, *J*=8.2 Hz), 7.2 (2 H, d, *J*=8.2 Hz), 5.3 (1 H, d, *J*=6.1 Hz), 4.8 (1 H, s), 4.7 (1 H, s), 4.1 (2 H, d, *J*=12.2 Hz), 3.7 - 3.9 (2 H, m), 3.5 - 3.6 (2 H, m), 3.4 - 3.5 (2 H, m), 3.2 (2 H,

t, *J*=11.9 Hz), 2.6 - 2.7 (2 H, m), 2.4 (1 H, dd, *J*=12.1, 8.4 Hz), 2.2 (1 H, dd, *J*=17.1, 6.1 Hz), 2.0 (1 H, t, *J*=10.8 Hz), 1.8 - 1.9 (1 H, m), 1.8 (1 H, br. s.), 1.7 (3 H, s), 1.7 (1 H, td, *J*=13.3, 3.4 Hz), 1.6 - 1.6 (2 H, m), 1.5 - 1.6 (4 H, m), 1.4 - 1.5 (3 H, m), 1.4 - 1.4 (6 H, m), 1.3 (1 H, d, *J*=9.5 Hz), 1.1 (3 H, s), 1.1 (3 H, br. s.), 1.1 (3 H, br. s.), 1.0 (3 H, s), 1.0 (3 H, s).

Example 7

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(1-((diethylamino)methyl)cyclopropyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

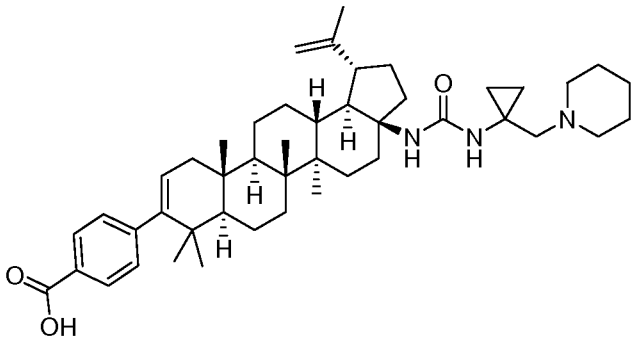


The title compound was prepared in 25% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimethylamino)ethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 1-((diethylamino)methyl)cyclopropanamine, 2 HCl was used instead of *N,N*-dimethylethylenediamine in Step 1. LCMS: m/e 698.3 $(M+H)^+$, 3.97 min (method 8). ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.9 - 8.0 (2 H, m), 7.2 - 7.3 (2 H, m), 5.3 (1 H, dd, *J*=4.0, 1.8 Hz), 4.8 (1 H, br. s.), 4.7 (1 H, br. s.), 3.2 - 3.3 (4 H, m), 2.6 (1 H, d, *J*=12.8 Hz), 2.5 - 2.6 (1 H, m), 2.3 - 2.4 (1 H, m), 2.2 (1 H, dd, *J*=16.0, 5.3 Hz), 1.9 - 2.0 (1 H, m), 1.7 - 1.8 (3 H, m), 1.7 (3 H, br. s.), 1.6 - 1.7 (4 H, m), 1.5 (4 H, d, *J*=7.3 Hz),

1.4 - 1.5 (2 H, m), 1.4 (8 H, dd, *J*=7.0, 5.2 Hz), 1.3 (2 H, br. s.), 1.1 - 1.2 (1 H, m), 1.1 (3 H, br. s.), 1.1 (6 H, br. s.), 1.0 (3 H, d, *J*=1.5 Hz), 1.0 (3 H, br. s.), 0.9 (3 H, br. s.).

Example 8

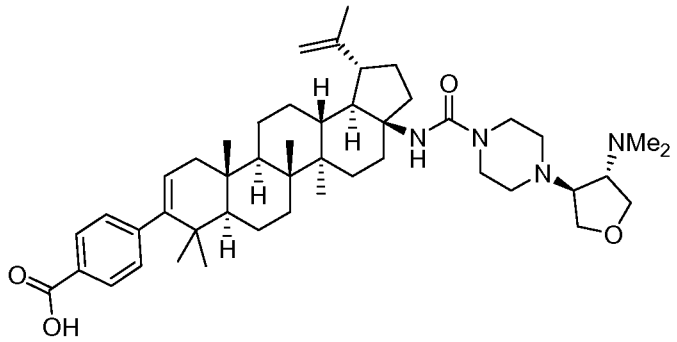
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(1-(piperidin-1-ylmethyl)cyclopropyl)ureido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimethylamino)ethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 1-(piperidin-1-ylmethyl)cyclopropanamine, 2 HCl was used instead of *N,N*-dimethylethylenediamine in Step 1. LCMS: m/e 710.6 $(M+H)^+$, 2.00 min (method 6). ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.9 (2 H, d, *J*=7.9 Hz), 7.2 (2 H, d, *J*=7.9 Hz), 5.3 (1 H, d, *J*=4.9 Hz), 4.8 (1 H, s), 4.7 (1 H, s), 3.5 - 3.7 (2 H, m), 3.3 (1 H, s), 3.2 - 3.3 (2 H, m), 3.0 (2 H, ddd, *J*=12.0, 8.5, 3.7 Hz), 2.6 (1 H, d, *J*=13.4 Hz), 2.6 (1 H, td, *J*=10.9, 5.0 Hz), 2.4 (1 H, dd, *J*=11.9, 8.2 Hz), 2.2 (1 H, dd, *J*=17.1, 6.4 Hz), 1.9 - 2.1 (3 H, m), 1.7 - 1.9 (5 H, m), 1.7 (3 H, s), 1.7 - 1.7 (1 H, m), 1.5 - 1.7 (8 H, m), 1.3 - 1.5 (6 H, m), 1.2 - 1.2 (1 H, m), 1.1 (1 H, d, *J*=4.0 Hz), 1.1 (3 H, s), 1.1 (6 H, br. s.), 1.0 (3 H, s), 1.0 (3 H, s), 0.9 - 0.9 (2 H, m).

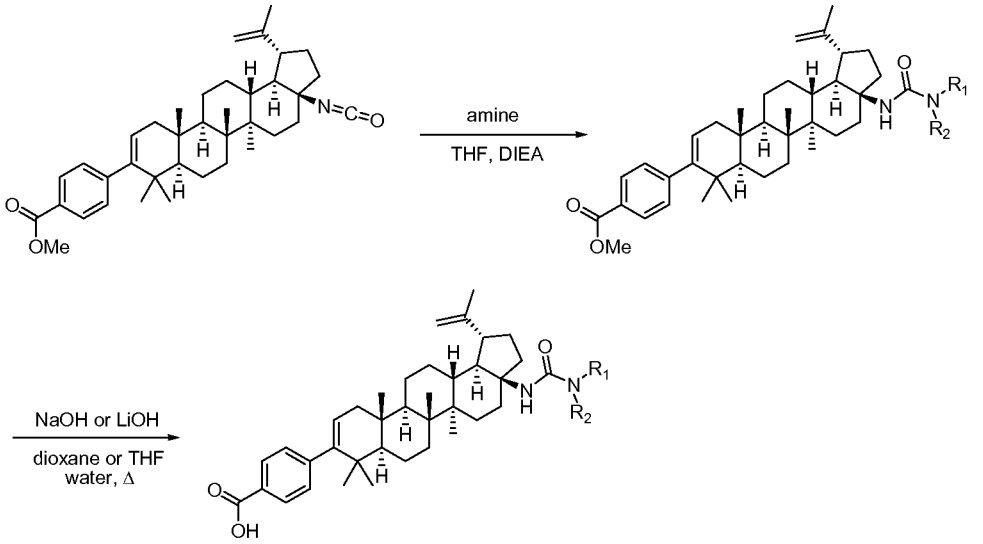
Example 9

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-((3S,4S)-4-(dimethylamino)tetrahydrofuran-3-yl)piperazine-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared in 20% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimethylamino)ethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except (3S,4S)-N,N-dimethyl-4-(piperazin-1-yl)tetrahydrofuran-3-amine was used instead of *N,N*-dimethylethylenediamine in Step 1. LCMS: m/e 755.6 $(M+H)^+$, 1.85 min (method 6). ^{1}H NMR (500MHz , *METHANOL-d_4*) δ = 7.93 (d, *J* = 8.2 Hz, 2 H), 7.23 (d, *J* = 8.2 Hz, 2 H), 5.31 (d, *J* = 6.1 Hz, 1 H), 4.78 (s, 1 H), 4.64 (br. s., 1 H), 4.09 (d, *J* = 3.4 Hz, 1 H), 4.05 (d, *J* = 4.9 Hz, 2 H), 4.02 (td, *J* = 3.5, 6.8 Hz, 1 H), 3.96 (td, *J* = 5.1, 10.1 Hz, 1 H), 3.73 (d, *J* = 5.2 Hz, 1 H), 3.56 - 3.41 (m, 4 H), 2.96 (s, 6 H), 2.87 - 2.66 (m, 5 H), 2.59 (d, *J* = 13.1 Hz, 1 H), 2.45 (dd, *J* = 8.7, 11.7 Hz, 1 H), 2.16 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.97 - 1.90 (m, 1 H), 1.90 - 1.82 (m, 1 H), 1.82 - 1.74 (m, 2 H), 1.73 (s, 3 H), 1.66 - 1.54 (m, 3 H), 1.51 (d, *J* = 12.5 Hz, 4 H), 1.45 - 1.26 (m, 6 H), 1.23 - 1.15 (m, 2 H), 1.13 (s, 3 H), 1.10 (d, *J* = 13.4 Hz, 2 H), 1.06 (s, 3 H), 1.04 (s, 3 H), 0.97 (s, 3 H), 0.95 (s, 3 H).

General Procedure for C-17 Urea Formation:



Step 1: General procedure for the preparation of C-17 urea methyl esters.

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate in THF (approximately 0.1 M) was added Hunig's base (3-9 equiv.) and the amine (3 equiv.). The mixture was stirred at rt for 2-72 h. The reaction mixture was concentrated and redissolved in a mixture of THF and methanol and often a couple drops of water were added. The mixture was filtered and purified by reverse phase preparative HPLC.

Step 2: General Procedures for hydrolysis of the benzoic ester using NaOH or $LiOH \cdot H_2O$.

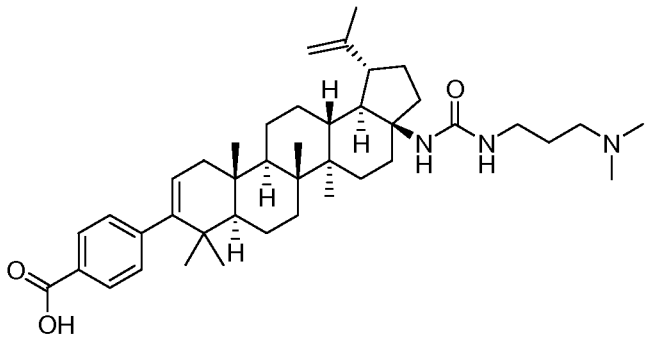
The C-17 urea formed in Step 1 above was dissolved in either 1,4-dioxane or THF to give approximately a 0.1M solution. Aqueous 1N NaOH (4 eq.) was added to the mixture and it was heated to 50-85 °C. After heating for 2-48 h, the mixture was cooled to rt. The crude mixture was purified by reverse phase preparative HPLC.

Alternatively, the ester hydrolysis can be carried out as follows: The C-17 urea formed in Step 1 above was dissolved in either 1,4-dioxane or THF to give approximately a 0.1M solution. To the solution was added water (ratio 4:1 or 5:1

organic 1,4-dioxane or THF: water) followed by $LiOH \cdot H_2O$ (5-12 equiv.). The mixture was heated to 50-85 °C. After heating for as little as 60 seconds to as long as 24 h, the mixture was cooled to rt. The crude mixture was purified by reverse phase preparative HPLC.

Example 10

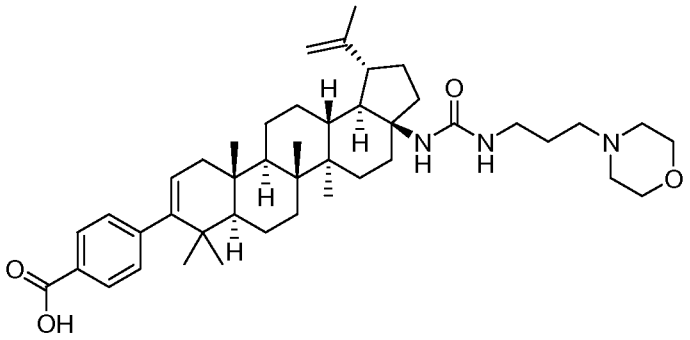
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(3-(dimethylamino)propyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *N1,N1*-dimethylpropane-1,3-diamine as the reactant amine. The mono-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (60 mg, 32.7% yield). LCMS: m/z 658 ($M+H^+$), retention time 1.86 min (method 2). ^1H NMR (500 MHz, *MeOD*) δ ppm 0.97 (s, 3 H), 0.99 (s, 3 H), 1.07 (s, 6 H), 1.11 - 1.13 (m, 1 H), 1.15 (s, 3 H), 1.17 - 1.22 (m, 1 H), 1.28 - 1.48 (m, 5 H), 1.48 - 1.64 (m, 6 H), 1.64 - 1.83 (m, 7 H), 1.83 - 2.01 (m, 4 H), 2.18 (dd, *J*=17.09, 6.41 Hz, 1 H), 2.37 (dd, *J*=12.21, 8.24 Hz, 1 H), 2.58 - 2.68 (m, 2 H), 2.90 (s, 6 H), 3.13 (td, *J*=7.02, 1.83 Hz, 2 H), 3.25 (td, *J*=6.49, 0.76 Hz, 1 H), 4.66 (s, 1 H), 4.78 (d, *J*=1.53 Hz, 1 H), 5.33 (dd, *J*=6.10, 1.22 Hz, 1 H), 7.25 (m, *J*=8.24 Hz, 2 H), 7.95 (m, *J*=8.24 Hz, 2 H).

Example 11

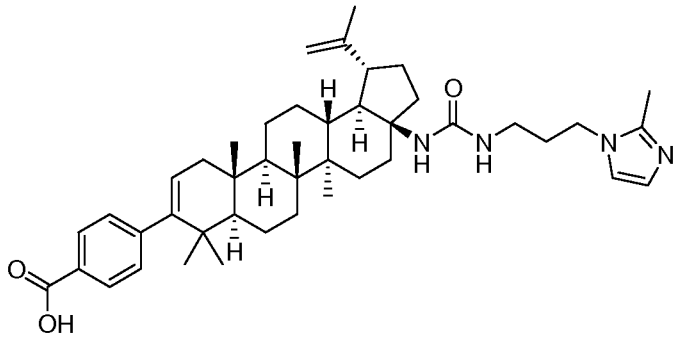
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(3-morpholinopropyl)ureido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 3-morpholinopropan-1-amine as the reactant amine. The mono-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (85 mg, 43% yield). LCMS: m/z 700 ($M+H^+$), retention time 1.89 min (method 2). ^1H NMR (500 MHz, *MeOD*) δ ppm 0.97 (s, 3 H), 0.99 (s, 3 H), 1.07 (s, 6 H), 1.11 - 1.13 (m, 1 H), 1.15 (s, 3 H), 1.17 - 1.21 (m, 1 H), 1.28 - 1.47 (m, 5 H), 1.50 - 1.63 (m, 6 H), 1.64 - 1.72 (m, 1 H), 1.74 (br. s., 1 H), 1.75 (s, 3 H), 1.76 - 1.83 (m, 2 H), 1.87 (td, *J*=12.21, 3.36 Hz, 1 H), 1.91 - 1.99 (m, 3 H), 2.18 (dd, *J*=17.09, 6.41 Hz, 1 H), 2.35 (dd, *J*=12.05, 8.09 Hz, 1 H), 2.58 - 2.67 (m, 2 H), 3.11 - 3.20 (m, 4 H), 3.25 - 3.31 (m, 2 H), 3.45 (t, *J*=12.97 Hz, 2 H), 3.81 (t, *J*=12.51 Hz, 2 H), 4.11 (d, *J*=12.82 Hz, 2 H), 4.66 (s, 1 H), 4.78 (s, 1 H), 5.33 (dd, *J*=6.10, 1.83 Hz, 1 H), 7.24 (m, *J*=8.55 Hz, 2 H), 7.95 (m, *J*=8.55 Hz, 2 H).

Example 12

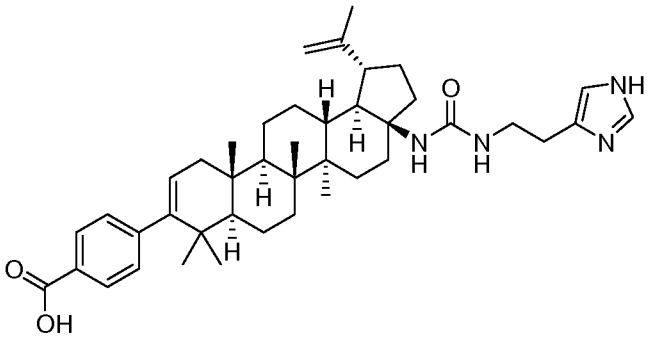
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(3-(2-methyl-1H-imidazol-1-yl)propyl)ureido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 3-(2-methyl-1H-imidazol-1-yl)propan-1-amine dihydrochloride as the reactant amine. The mono-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (40 mg, 21% yield). LCMS: m/z 709 ($M+H^+$), retention time 1.83 min (method 2). ^{1}H NMR (500 MHz, *MeOD*) δ ppm 0.97 (s, 3 H), 0.99 (s, 3 H), 1.07 (s, 6 H), 1.12 (d, *J*=13.43 Hz, 1 H), 1.15 (s, 3 H), 1.17 - 1.22 (m, 1 H), 1.27 - 1.46 (m, 5 H), 1.47 - 1.64 (m, 6 H), 1.66 - 1.82 (m, 7 H), 1.83 - 1.98 (m, 2 H), 2.04 (quin, *J*=6.94 Hz, 2 H), 2.18 (dd, *J*=17.09, 6.41 Hz, 1 H), 2.38 (dd, *J*=12.36, 8.09 Hz, 1 H), 2.58 - 2.65 (m, 2 H), 2.66 (s, 3 H), 3.18 (t, *J*=6.71 Hz, 2 H), 4.18 (t, *J*=7.17 Hz, 2 H), 4.66 (s, 1 H), 4.78 (d, *J*=1.83 Hz, 1 H), 5.33 (dd, *J*=6.26, 1.68 Hz, 1 H), 7.24 (m, *J*=8.55 Hz, 2 H), 7.47 (d, *J*=1.83 Hz, 1 H), 7.59 (d, *J*=2.14 Hz, 1 H), 7.95 (m, *J*=8.24 Hz, 2 H).

Example 13

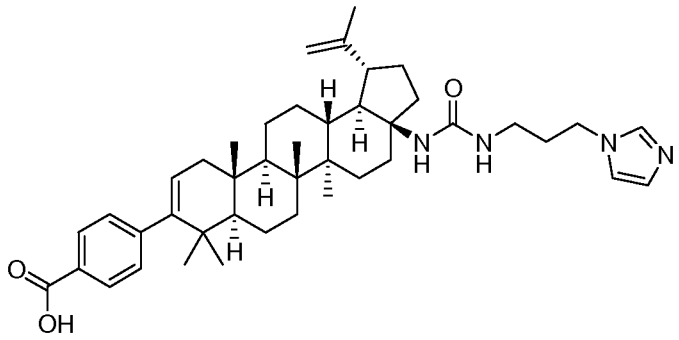
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(1H-imidazol-4-yl)ethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using histamine as the reactant amine. The mono-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (23 mg, 11% yield). LCMS: m/z 667 ($M+H^+$), retention time 1.79 min (method 2). ^{1}H NMR (500 MHz, *MeOD*) δ ppm 0.97 (s, 3 H), 0.99 (s, 3 H), 1.05 (s, 3 H), 1.06 (s, 3 H), 1.07 - 1.11 (m, 1 H), 1.12 (s, 3 H), 1.13 - 1.20 (m, 1 H), 1.26 - 1.45 (m, 5 H), 1.49 - 1.68 (m, 7 H), 1.71 (d, *J*=11.60 Hz, 1 H), 1.74 (s, 3 H), 1.75 - 1.94 (m, 4 H), 2.17 (dd, *J*=17.09, 6.41 Hz, 1 H), 2.31 (dd, *J*=12.36, 8.09 Hz, 1 H), 2.54 - 2.64 (m, 2 H), 2.90 (t, *J*=6.71 Hz, 2 H), 3.45 (t, *J*=6.87 Hz, 2 H), 4.65 (s, 1 H), 4.76 (d, *J*=1.83 Hz, 1 H), 5.33 (dd, *J*=6.10, 1.83 Hz, 1 H), 7.24 (d, *J*=8.24 Hz, 2 H), 7.34 (s, 1 H), 7.94 (d, *J*=8.24 Hz, 2 H), 8.84 (d, *J*=1.22 Hz, 1 H).

Example 14

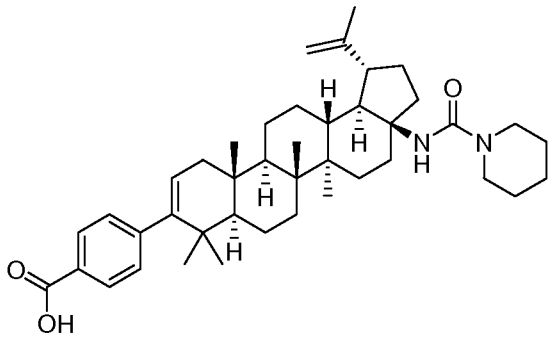
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(3-(1H-imidazol-1-yl)propyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 3-(1H-imidazol-1-yl)propan-1-amine as the reactant amine. The mono-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (109 mg, 53% yield). LCMS: m/z 681 ($M+H^+$), retention time 1.82 min (method 2). ^1H NMR (500 MHz, *MeOD*) δ ppm 0.97 (s, 3 H), 0.99 (s, 3 H), 1.06 (s, 6 H), 1.09 - 1.14 (m, 1 H), 1.15 (s, 3 H), 1.17 - 1.21 (m, 1 H), 1.27 - 1.46 (m, 5 H), 1.47 - 1.63 (m, 6 H), 1.64 - 1.73 (m, 2 H), 1.75 (s, 3 H), 1.76 - 1.82 (m, 2 H), 1.83 - 2.00 (m, 2 H), 2.07 (qd, *J*=7.07, 6.87 Hz, 2 H), 2.18 (dd, *J*=17.09, 6.41 Hz, 1 H), 2.39 (dd, *J*=12.36, 8.09 Hz, 1 H), 2.58 - 2.68 (m, 2 H), 3.11 - 3.23 (m, 2 H), 4.31 (t, *J*=6.87 Hz, 2 H), 4.66 (s, 1 H), 4.78 (d, *J*=1.83 Hz, 1 H), 5.33 (dd, *J*=6.10, 1.83 Hz, 1 H), 7.24 (m, *J*=8.54 Hz, 2 H), 7.60 (t, *J*=1.53 Hz, 1 H), 7.71 (t, *J*=1.68 Hz, 1 H), 7.94 (m, *J*=8.54 Hz, 2 H), 9.00 (s, 1 H).

Example 15

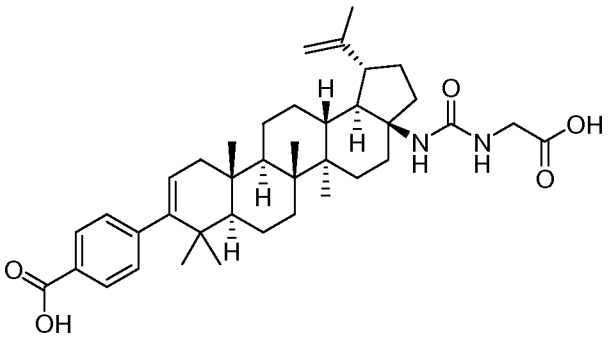
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(piperidine-1-carboxamido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using piperidine as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (10 mg, 6% yield). LCMS: m/z 641 ($M+H^+$), retention time 2.67 min (method 2). ^{1}H NMR (500 MHz, *MeOD*) δ ppm 0.97 (s, 3 H), 0.99 (s, 3 H), 1.07 (s, 3 H), 1.08 (s, 3 H), 1.12 (dt, *J*=13.81, 3.17 Hz, 1 H), 1.16 (s, 3 H), 1.17 - 1.22 (m, 1 H), 1.28 - 1.47 (m, 5 H), 1.48 - 1.65 (m, 11 H), 1.65 - 1.70 (m, 2 H), 1.71 - 1.90 (m, 7 H), 1.91 - 2.02 (m, 1 H), 2.14 - 2.21 (m, 1 H), 2.49 (dd, *J*=12.36, 8.09 Hz, 1 H), 2.59 - 2.71 (m, 2 H), 3.35 - 3.48 (m, 4 H), 4.63 - 4.67 (m, 1 H), 4.80 (d, *J*=1.83 Hz, 1 H), 5.33 (dd, *J*=6.10, 1.83 Hz, 1 H), 7.25 (m, *J*=8.24 Hz, 2 H), 7.94 (m, *J*=8.24 Hz, 2 H).

Example 16

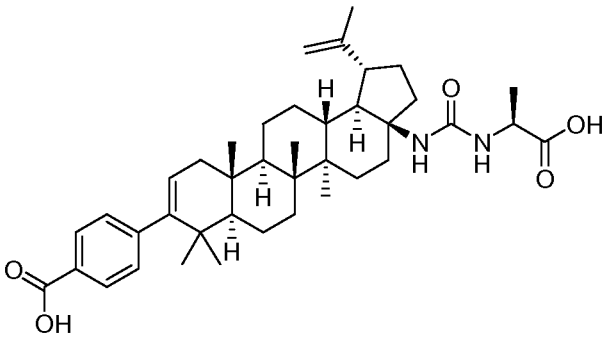
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(carboxymethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using glycine methyl ester hydrochloride as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (59 mg, 45% yield). LCMS: m/z 631 ($M+H^+$), retention time 2.17 min (method 2). 1H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (s, 3 H), 0.95 (s, 3 H), 1.02 (s, 6 H), 1.04 - 1.11 (m, 2 H), 1.12 (s, 3 H), 1.23 - 1.41 (m, 5 H), 1.42 - 1.61 (m, 6 H), 1.65 (t, *J*=11.60 Hz, 1 H), 1.68 - 1.79 (m, 6 H), 1.85 (td, *J*=12.21, 3.36 Hz, 1 H), 1.92 - 2.05 (m, 1 H), 2.13 (dd, *J*=17.09, 6.41 Hz, 1 H), 2.36 (dd, *J*=12.36, 8.09 Hz, 1 H), 2.55 - 2.66 (m, 2 H), 3.80 - 3.95 (m, 2 H), 4.58 - 4.64 (m, 1 H), 4.74 (d, *J*=1.83 Hz, 2 H), 5.29 (dd, *J*=6.26, 1.68 Hz, 1 H), 7.19 - 7.23 (m, 2 H), 7.91 - 7.95 (m, 2 H).

Example 17

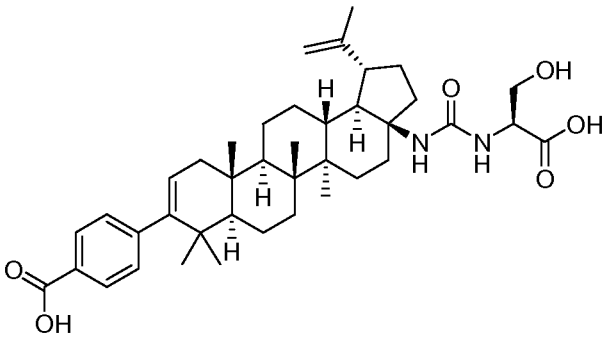
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-((S)-1-carboxyethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using L-alanine methyl ester hydrochloride as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (74 mg, 54% yield). LCMS: m/z 645 ($M+H^+$), retention time 2.26 min (method 2). ^1H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.93 (br. s., 3 H), 0.94 (br. s., 3 H), 0.99 (s, 6 H), 1.02 - 1.09 (m, 2 H), 1.10 (s, 3 H), 1.19 - 1.35 (m, 5 H), 1.37 (d, *J*=7.32 Hz, 3 H), 1.39 - 1.57 (m, 6 H), 1.63 (t, *J*=11.60 Hz, 1 H), 1.66 - 1.76 (m, 6 H), 1.76 - 1.85 (m, 1 H), 1.88 - 1.99 (m, 1 H), 2.11 (dd, *J*=17.09, 6.41 Hz, 1 H), 2.35 (dd, *J*=12.36, 8.09 Hz, 1 H), 2.50 - 2.61 (m, 2 H), 4.28 (q, *J*=7.02 Hz, 1 H), 4.61 (br. s., 1 H), 4.72 (br. s., 1 H), 5.26 - 5.31 (m, 1 H), 7.20 (d, *J*=8.24 Hz, 2 H), 7.92 (d, *J*=8.55 Hz, 2 H).

Example 18

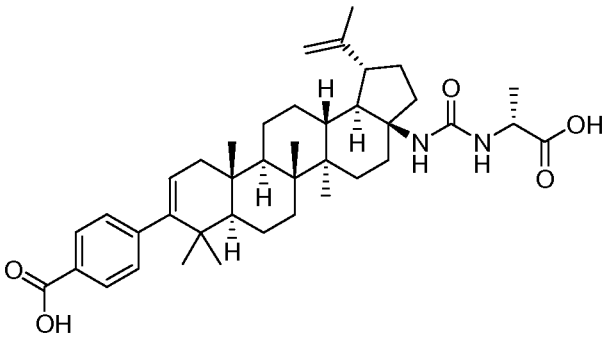
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-((S)-1-carboxy-2-hydroxyethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using L-serine methyl ester hydrochloride as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (70 mg, 48% yield). LCMS: m/z 661 ($M+H^+$), retention time 2.19 min (method 2). ^1H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.93 (br. s., 3 H), 0.93 (s, 3 H), 0.99 (br. s., 3 H), 1.00 (s, 3 H), 1.03 - 1.09 (m, 2 H), 1.11 (s, 3 H), 1.21 - 1.41 (m, 5 H), 1.41 - 1.57 (m, 6 H), 1.64 (t, *J*=11.60 Hz, 1 H), 1.67 - 1.77 (m, 6 H), 1.84 (td, *J*=12.21, 3.36 Hz, 1 H), 1.88 - 1.99 (m, 1 H), 2.11 (dd, *J*=17.09, 6.41 Hz, 1 H), 2.35 (dd, *J*=12.21, 8.24 Hz, 1 H), 2.54 - 2.63 (m, 2 H), 3.80 (dd, *J*=10.99, 3.66 Hz, 1 H), 3.93 (dd, *J*=10.99, 4.27 Hz, 1 H), 4.37 (t, *J*=3.97 Hz, 1 H), 4.61 (br. s., 1 H), 4.72 (d, *J*=1.53 Hz, 1 H), 5.28 (dd, *J*=6.26, 1.68 Hz, 1 H), 7.20 (m, *J*=8.54 Hz, 2 H), 7.92 (m, *J*=8.24 Hz, 2 H).

Example 19

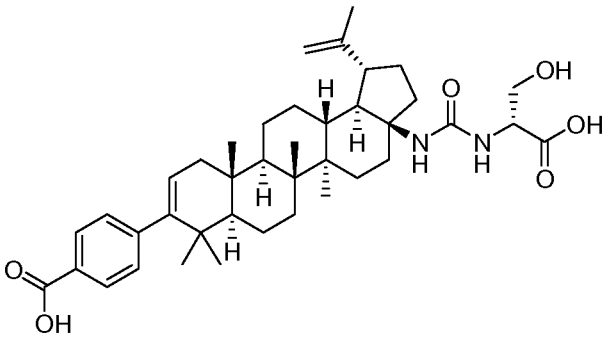
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-((R)-1-carboxyethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *D*-alanine methyl ester hydrochloride as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (68 mg, 50% yield). LCMS: m/z 645 ($M+H^+$), retention time 2.23 min (method 2). ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.93 (br. s., 3 H), 0.94 (br. s., 3 H), 1.00 (s, 6 H), 1.03 - 1.14 (m, 5 H), 1.20 - 1.36 (m, 5 H), 1.37 (d, *J*=7.02 Hz, 3 H), 1.40 - 1.58 (m, 6 H), 1.58 - 1.68 (m, 2 H), 1.68 - 1.75 (m, 5 H), 1.75 - 1.83 (m, 1 H), 1.92 - 2.03 (m, 1 H), 2.11 (dd, *J*=17.09, 6.41 Hz, 1 H), 2.34 (dd, *J*=12.21, 8.24 Hz, 1 H), 2.51 - 2.60 (m, 2 H), 4.27 (q, *J*=7.32 Hz, 1 H), 4.60 (br. s., 2 H), 4.72 (d, *J*=1.53 Hz, 1 H), 5.28 (dd, *J*=6.10, 1.53 Hz, 1 H), 7.20 (m, *J*=8.55 Hz, 2 H), 7.92 (m, *J*=8.24 Hz, 2 H).

Example 20

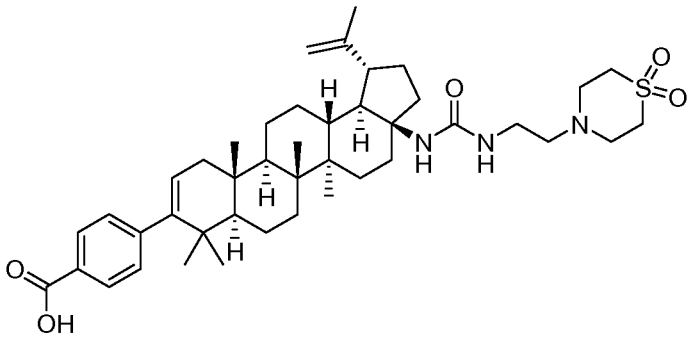
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-((R)-1-carboxy-2-hydroxyethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *D*-serine methyl ester hydrochloride as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (51 mg, 34% yield). LCMS: m/z 661 ($M+H^+$), retention time 2.11 min (method 2). ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.92 (br. s., 6 H), 0.98 (br. s., 6 H), 1.02 - 1.14 (m, 5 H), 1.17 - 1.38 (m, 5 H), 1.39 - 1.58 (m, 6 H), 1.58 - 1.75 (m, 7 H), 1.76 - 1.86 (m, 1 H), 1.90 - 2.04 (m, 1 H), 2.04 - 2.13 (m, 1 H), 2.36 (t, *J*=9.77 Hz, 1 H), 2.56 (d, *J*=12.51 Hz, 2 H), 3.81 (d, *J*=10.99 Hz, 1 H), 3.94 (d, *J*=10.99 Hz, 1 H), 4.35 (d, *J*=2.44 Hz, 1 H), 4.60 (br. s., 1 H), 4.71 (br. s., 1 H), 5.28 (br. s., 1 H), 7.19 (m, *J*=7.32 Hz, 2 H), 7.92 (m, *J*=7.63 Hz, 2 H).

Example 21

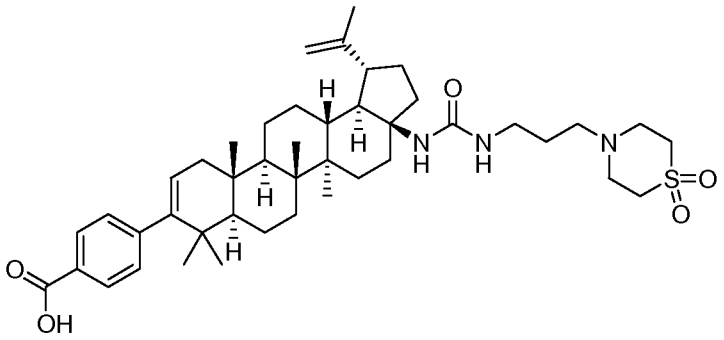
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)carbamoyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 4-(2-aminoethyl)thiomorpholine 1,1-dioxide as the reactant amine. The mono-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (121 mg, 74% yield). LCMS: m/z 734 ($M+H^+$), retention time 2.49 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (s, 3 H), 0.95 (s, 3 H), 1.02 (br. s., 3 H), 1.03 (br. s., 3 H), 1.10 (s, 3 H), 1.11 - 1.17 (m, 2 H), 1.21 - 1.60 (m, 11 H), 1.63 - 1.82 (m, 8 H), 1.86 - 2.00 (m, 1 H), 2.13 (dd, *J*=17.24, 6.26 Hz, 1 H), 2.35 (dd, *J*=12.05, 8.39 Hz, 1 H), 2.52 - 2.63 (m, 2 H), 3.20 (br. s., 2 H), 3.39 - 3.52 (m, 6 H), 3.69 (br. s., 4 H), 4.63 (s, 1 H), 4.75 (d, *J*=1.22 Hz, 1 H), 5.29 (d, *J*=4.58 Hz, 1 H), 7.21 (m, *J*=8.24 Hz, 2 H), 7.93 (m, *J*=8.24 Hz, 2 H).

Example 22

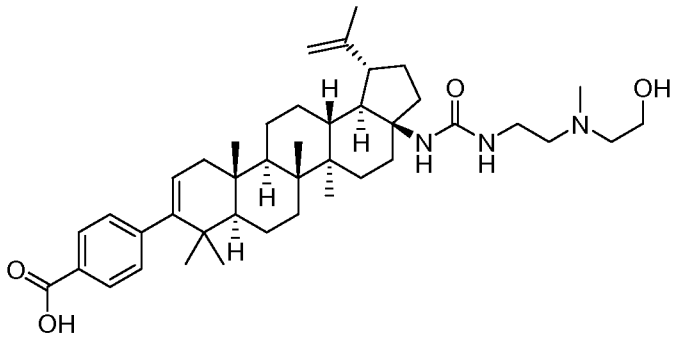
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((3-(1,1-dioxido-4-thiomorpholinyl)propyl)carbamoyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 4-(3-aminopropyl)thiomorpholine 1,1-dioxide as the reactant amine. The mono-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (115 mg, 59% yield). LCMS: m/z 748 ($M+H^+$), retention time 2.44 min (method 11). 1H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.95 (s, 3 H), 0.96 (s, 3 H), 1.02 (br. s., 3 H), 1.03 (br. s., 3 H), 1.11 (s, 3 H), 1.12 - 1.18 (m, 2 H), 1.24 - 1.44 (m, 5 H), 1.44 - 1.60 (m, 6 H), 1.63 - 1.80 (m, 8 H), 1.85 - 1.99 (m, 3 H), 2.14 (dd, *J*=17.09, 6.41 Hz, 1 H), 2.32 (dd, *J*=12.05, 8.09 Hz, 1 H), 2.52 - 2.63 (m, 2 H), 3.14 (t, *J*=7.02 Hz, 2 H), 3.19 - 3.30 (m, 2 H), 3.50 (d, *J*=4.58 Hz, 4 H), 3.65 (d, *J*=5.19 Hz, 4 H), 4.63 (s, 1 H), 4.75 (s, 1 H), 5.27 - 5.32 (m, 1 H), 7.21 (m, *J*=8.24 Hz, 2 H), 7.93 (m, *J*=8.24 Hz, 2 H).

Example 23

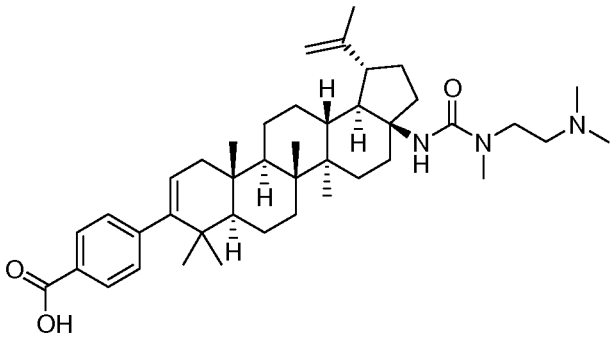
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-((2-hydroxyethyl)(methyl)amino)ethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 2-((2-aminoethyl)(methyl)amino)ethanol as the reactant amine. The mono-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (43 mg, 69% yield). LCMS: m/z 674 ($M+H^+$), retention time 2.41 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.93 (br. s., 3 H), 0.94 (br. s., 3 H), 1.00 (br. s., 3 H), 1.00 (br. s., 3 H), 1.08 (s, 3 H), 1.08 - 1.15 (m, 2 H), 1.22 - 1.39 (m, 5 H), 1.40 - 1.56 (m, 6 H), 1.59 - 1.79 (m, 8 H), 1.85 - 1.99 (m, 1 H), 2.11 (dd, *J*=17.09, 6.41 Hz, 1 H), 2.35 (br. s., 1 H), 2.48 - 2.61 (m, 2 H), 2.96 (s, 3 H), 3.09 - 3.61 (m, 6 H), 3.87 (t, *J*=5.19 Hz, 2 H), 4.61 (br. s., 1 H), 4.73 (br. s., 1 H), 5.24 - 5.31 (m, 1 H), 7.20 (d, *J*=8.24 Hz, 2 H), 7.92 (d, *J*=8.24 Hz, 2 H).

Example 24

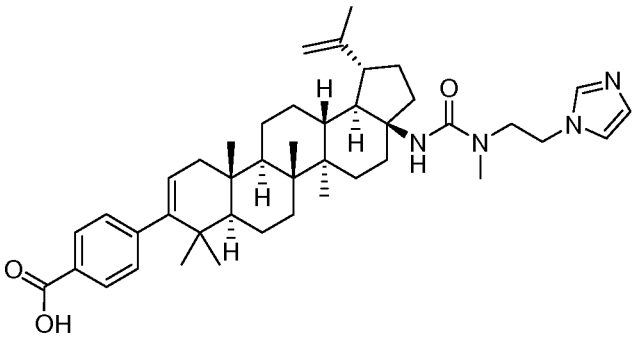
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimethylamino)ethyl)-3-methylureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *N1,N1,N2*-trimethylethane-1,2-diamine as the reactant amine. The mono-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (34 mg, 57% yield). LCMS: m/z 658 ($M+H^+$), retention time 2.41 min (method 11). ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.93 (br. s., 3 H), 0.94 (br. s., 3 H), 1.00 (s, 3 H), 1.03 (s, 3 H), 1.10 (s, 3 H), 1.10 - 1.20 (m, 2 H), 1.20 - 1.28 (m, 1 H), 1.31 - 1.42 (m, 4 H), 1.44 - 1.58 (m, 7 H), 1.62 - 1.80 (m, 7 H), 1.88 - 2.01 (m, 1 H), 2.12 (dd, *J*=17.09, 6.10 Hz, 1 H), 2.41 - 2.56 (m, 3 H), 2.92 (s, 6 H), 3.03 (s, 3 H), 3.18 - 3.31 (m, 2 H), 3.51 (ddd, *J*=15.11, 5.95, 5.80 Hz, 1 H), 3.73 - 3.83 (m, 1 H), 4.54 (s, 1 H), 4.64 (br. s., 1 H), 4.75 (s, 1 H), 5.25 - 5.31 (m, 1 H), 7.20 (d, *J*=8.24 Hz, 2 H), 7.92 (d, *J*=8.24 Hz, 2 H).

Example 25

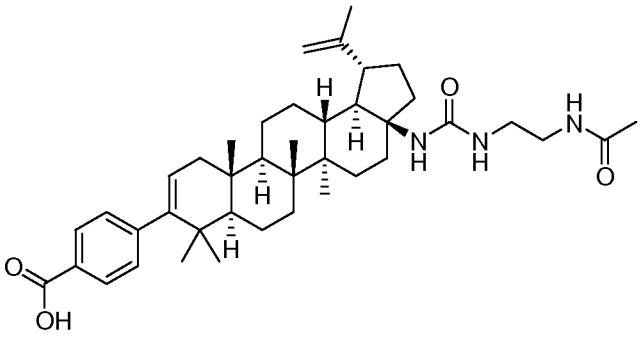
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(1H-imidazol-1-yl)ethyl)-3-methylureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 2-(1H-imidazol-1-yl)-N-methylethanamine, 2 HCl as the reactant amine. The mono-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (35 mg, 56% yield). LCMS: m/z 681 ($M+H^+$), retention time 2.39 min (method 11). ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (br. s., 3 H), 0.94 (br. s., 3 H), 1.00 (s, 3 H), 1.02 (s, 3 H), 1.09 (s, 3 H), 1.09 - 1.19 (m, 2 H), 1.23 - 1.42 (m, 5 H), 1.43 - 1.54 (m, 6 H), 1.54 - 1.60 (m, 1 H), 1.61 - 1.76 (m, 7 H), 1.80 - 1.94 (m, 1 H), 2.12 (dd, *J*=17.24, 6.26 Hz, 1 H), 2.29 (dd, *J*=12.67, 8.09 Hz, 1 H), 2.35 - 2.51 (m, 2 H), 3.01 (s, 3 H), 3.65 (dt, *J*=14.57, 5.84 Hz, 1 H), 3.79 - 3.89 (m, 1 H), 4.33 - 4.43 (m, 2 H), 4.64 (br. s., 1 H), 4.74 (br. s., 1 H), 5.25 - 5.31 (m, 1 H), 7.20 (d, *J*=8.55 Hz, 2 H), 7.41 (t, *J*=1.53 Hz, 1 H), 7.51 (t, *J*=1.68 Hz, 1 H), 7.92 (d, *J*=8.24 Hz, 2 H), 8.88 (d, *J*=1.22 Hz, 1 H).

Example 26

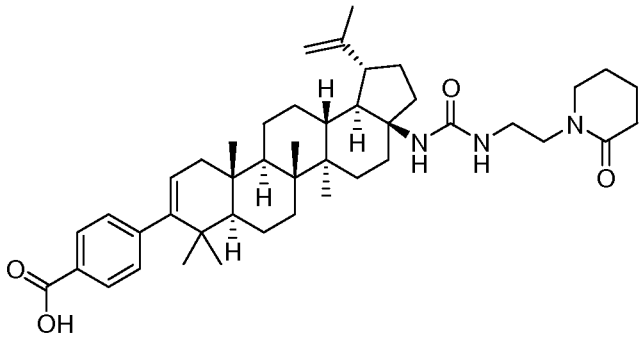
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-acetamidoethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *N*-(2-aminoethyl)acetamide as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (24 mg, 48% yield). LCMS: m/z 658 ($M+H^+$), retention time 2.73 min (method 11). ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.93 (br. s., 3 H), 0.94 (br. s., 3 H), 1.00 (br. s., 3 H), 1.00 (br. s., 3 H), 1.04 - 1.15 (m, 5 H), 1.21 - 1.41 (m, 6 H), 1.41 - 1.58 (m, 6 H), 1.58 - 1.67 (m, 2 H), 1.70 (s, 3 H), 1.70 - 1.82 (m, 3 H), 1.86 - 1.94 (m, 1 H), 1.96 (s, 3 H), 2.11 (dd, *J*=17.40, 6.41 Hz, 1 H), 2.34 (dd, *J*=12.05, 8.09 Hz, 1 H), 2.49 - 2.61 (m, 2 H), 3.19 - 3.27 (m, 4 H), 4.61 (br. s., 1 H), 4.72 (s, 1 H), 5.25 - 5.31 (m, 1 H), 7.20 (d, *J*=8.55 Hz, 2 H), 7.92 (d, *J*=8.24 Hz, 2 H).

Example 27

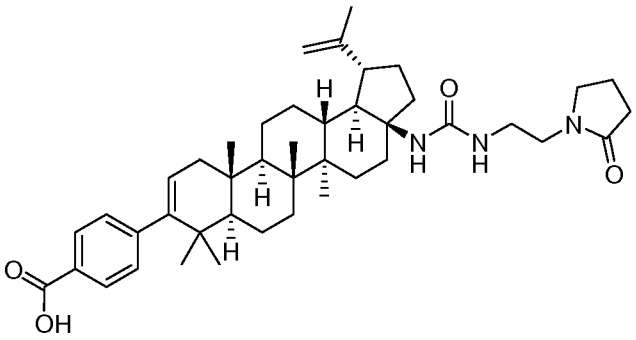
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(2-(2-oxopiperidin-1-yl)ethyl)ureido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 1-(2-aminoethyl)piperidin-2-one hydrobromide as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (37 mg, 68% yield). LCMS: m/z 698 ($M+H^+$), retention time 2.83 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.93 (br. s., 3 H), 0.94 (br. s., 3 H), 1.00 (s, 6 H), 1.04 - 1.14 (m, 5 H), 1.21 - 1.41 (m, 5 H), 1.41 - 1.58 (m, 6 H), 1.58 - 1.67 (m, 2 H), 1.70 (s, 3 H), 1.70 - 1.85 (m, 7 H), 1.86 - 1.97 (m, 1 H), 2.11 (dd, *J*=17.09, 6.10 Hz, 1 H), 2.29 - 2.39 (m, 3 H), 2.50 - 2.61 (m, 2 H), 3.30 - 3.32 (m, 1 H), 3.40 (t, *J*=5.34 Hz, 2 H), 3.45 (t, *J*=5.95 Hz, 2 H), 4.61 (br. s., 1 H), 4.72 (br. s., 1 H), 5.25 - 5.31 (m, 1 H), 7.20 (d, *J*=8.24 Hz, 2 H), 7.92 (d, *J*=8.24 Hz, 2 H).

Example 28

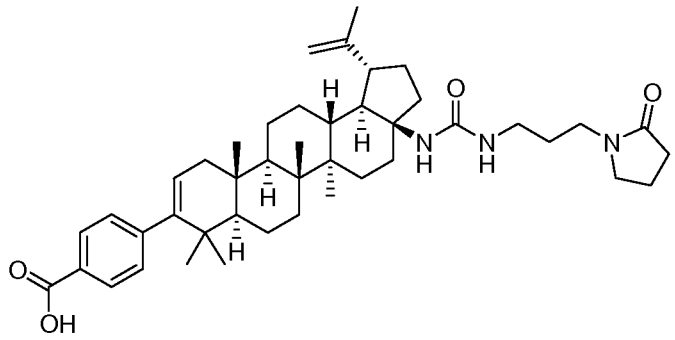
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(2-(2-oxopyrrolidin-1-yl)ethyl)ureido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 1-(2-aminoethyl)pyrrolidin-2-one oxalic acid salt as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (37 mg, 67% yield). LCMS: m/z 684 ($M+H^+$), retention time 2.78 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.93 (s, 3 H), 0.94 (s, 3 H), 1.00 (s, 6 H), 1.04 - 1.15 (m, 5 H), 1.21 - 1.41 (m, 6 H), 1.41 - 1.59 (m, 6 H), 1.59 - 1.67 (m, 2 H), 1.67 - 1.81 (m, 6 H), 1.86 - 1.97 (m, 1 H), 2.00 - 2.08 (m, 2 H), 2.11 (dd, *J*=17.09, 6.41 Hz, 1 H), 2.33 (dd, *J*=12.36, 8.09 Hz, 1 H), 2.38 (t, *J*=8.09 Hz, 2 H), 2.50 - 2.60 (m, 2 H), 3.28 - 3.32 (m, 2 H), 3.53 (t, *J*=7.32 Hz, 2 H), 4.61 (s, 1 H), 4.72 (d, *J*=1.53 Hz, 1 H), 5.28 (dd, *J*=5.95, 1.68 Hz, 1 H), 7.20 (m, *J*=8.54 Hz, 2 H), 7.92 (m, *J*=8.24 Hz, 2 H).

Example 29

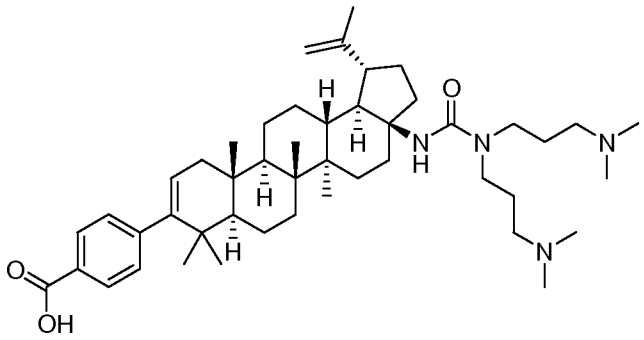
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(3-(2-oxopyrrolidin-1-yl)propyl)ureido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 1-(3-aminopropyl)pyrrolidin-2-one as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (38 mg, 69% yield). LCMS: m/z 698 ($M+H^+$), retention time 2.79 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.93 (br. s., 3 H), 0.94 (br. s., 3 H), 1.00 (br. s., 3 H), 1.00 (s, 3 H), 1.04 - 1.16 (m, 5 H), 1.21 - 1.41 (m, 5 H), 1.41 - 1.59 (m, 6 H), 1.59 - 1.76 (m, 9 H), 1.80 (td, *J*=12.21, 3.05 Hz, 1 H), 1.88 - 2.00 (m, 1 H), 2.03 - 2.16 (m, 3 H), 2.36 (dd, *J*=12.21, 8.24 Hz, 1 H), 2.42 (t, *J*=8.09 Hz, 2 H), 2.51 - 2.64 (m, 2 H), 3.09 (t, *J*=6.56 Hz, 2 H), 3.25 - 3.38 (m, 2 H), 3.47 (t, *J*=7.17 Hz, 2 H), 4.61 (s, 1 H), 4.73 (d, *J*=1.53 Hz, 1 H), 5.25 - 5.32 (m, 1 H), 7.20 (m, *J*=8.24 Hz, 2 H), 7.92 (m, *J*=8.24 Hz, 2 H).

Example 30

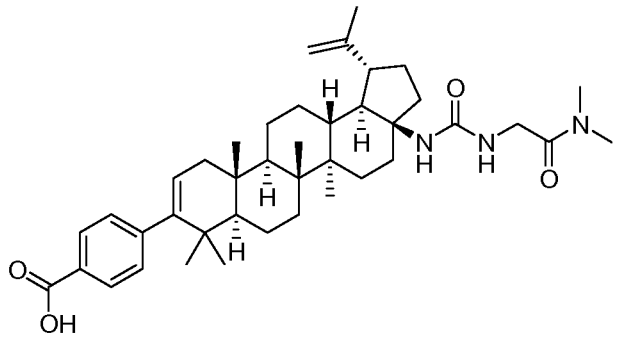
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3,3-bis(3-(dimethylamino)propyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *N1*-(3-(dimethylamino)propyl)-*N3,N3*-dimethylpropane-1,3-diamine as the reactant amine. The bis-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (15 mg, 20% yield). LCMS: m/z 743 ($M+H^+$), retention time 2.27 min (method 11). ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (s, 3 H), 0.94 (s, 3 H), 1.00 (s, 3 H), 1.05 (s, 3 H), 1.09 (s, 3 H), 1.11 - 1.19 (m, 2 H), 1.26 (d, *J*=6.71 Hz, 1 H), 1.30 - 1.44 (m, 3 H), 1.44 - 1.62 (m, 8 H), 1.63 - 1.81 (m, 7 H), 1.83 - 1.95 (m, 1 H), 2.02 (br. s., 4 H), 2.13 (dd, *J*=17.09, 6.41 Hz, 1 H), 2.41 (dd, *J*=12.51, 8.24 Hz, 1 H), 2.51 (td, *J*=10.91, 5.04 Hz, 1 H), 2.59 (d, *J*=13.43 Hz, 1 H), 2.89 (s, 12 H), 3.13 (t, *J*=7.02 Hz, 4 H), 3.34 - 3.43 (m, 4 H), 4.76 (s, 1 H), 5.26 - 5.33 (m, 1 H), 7.20 (m, *J*=8.55 Hz, 2 H), 7.92 (m, *J*=8.24 Hz, 2 H).

Example 31

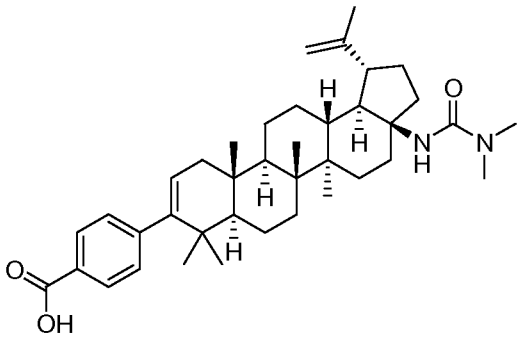
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimethylamino)-2-oxoethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 2-amino-*N,N*-dimethylacetamide as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (7 mg, 14% yield). LCMS: m/z 658 ($M+H^+$), retention time 2.77 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.93 (s, 3 H), 0.94 (s, 3 H), 1.01 (s, 6 H), 1.05 - 1.16 (m, 5 H), 1.21 - 1.41 (m, 6 H), 1.41 - 1.57 (m, 6 H), 1.60 - 1.78 (m, 7 H), 1.84 (td, *J*=12.28, 3.51 Hz, 1 H), 1.91 - 2.01 (m, 1 H), 2.12 (dd, *J*=17.09, 6.41 Hz, 1 H), 2.36 (dd, *J*=12.21, 7.93 Hz, 1 H), 2.55 - 2.64 (m, 2 H), 2.98 (s, 3 H), 3.03 (s, 3 H), 3.89 - 4.07 (m, 2 H), 4.61 (d, *J*=1.22 Hz, 1 H), 4.73 (d, *J*=1.83 Hz, 1 H), 5.29 (dd, *J*=6.10, 1.83 Hz, 1 H), 7.20 (d, *J*=8.54 Hz, 2 H), 7.92 (d, *J*=8.24 Hz, 2 H).

Example 32

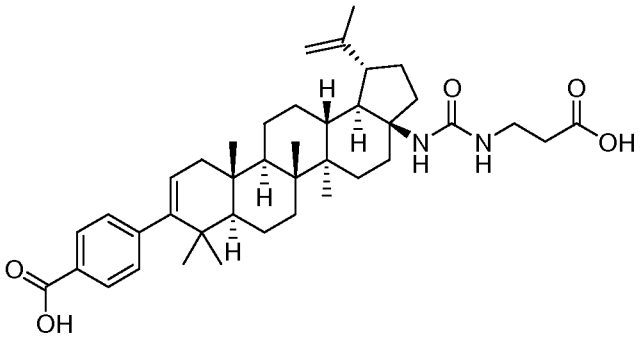
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3,3-dimethylureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was formed as a byproduct during the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimethylamino)-2-oxoethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid. Hydrolysis of the penultimate methyl ester by the general procedure as described and purification by reverse phase preparative HPLC gave a white solid (13 mg, 29% yield). LCMS: m/z 601 ($M+H^+$), retention time 2.90 min (method 11). ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (s, 3 H), 0.94 (s, 3 H), 1.00 (s, 3 H), 1.03 (s, 3 H), 1.10 (s, 3 H), 1.11 - 1.19 (m, 2 H), 1.24 - 1.44 (m, 6 H), 1.45 - 1.60 (m, 7 H), 1.61 - 1.66 (m, 1 H), 1.69 (d, *J*=5.49 Hz, 2 H), 1.71 (s, 3 H), 1.72 - 1.78 (m, 2 H), 1.91 - 2.01 (m, 1 H), 2.12 (dd, *J*=17.09, 6.41 Hz, 1 H), 2.42 - 2.52 (m, 2 H), 2.56 (dt, *J*=13.20, 3.32 Hz, 1 H), 2.95 (s, 6 H), 4.63 (d, *J*=1.53 Hz, 1 H), 4.74 (d, *J*=1.83 Hz, 1 H), 5.29 (dd, *J*=6.26, 1.68 Hz, 1 H), 7.20 (m, *J*=8.24 Hz, 2 H), 7.92 (m, *J*=8.24 Hz, 2 H).

Example 33

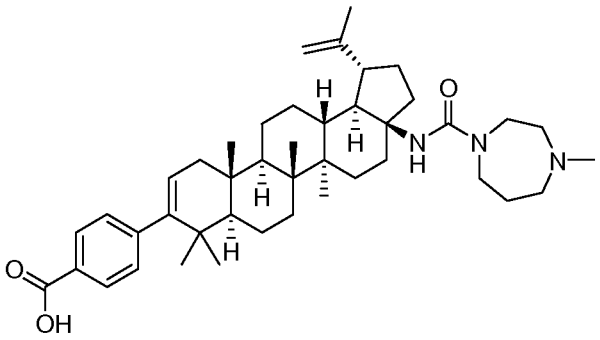
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-carboxyethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using methyl-3-aminopropanoate HCl as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (33 mg, 67% yield). LCMS: m/z 645 ($M+H^+$), retention time 2.69 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.93 (br. s., 3 H), 0.94 (s, 3 H), 1.00 (s, 6 H), 1.03 - 1.14 (m, 5 H), 1.21 - 1.40 (m, 5 H), 1.40 - 1.58 (m, 6 H), 1.58 - 1.67 (m, 2 H), 1.67 - 1.75 (m, 5 H), 1.75 - 1.83 (m, 1 H), 1.87 - 1.98 (m, 1 H), 2.11 (dd, *J*=17.09, 6.41 Hz, 1 H), 2.34 (dd, *J*=12.05, 8.09 Hz, 1 H), 2.49 (t, *J*=6.26 Hz, 2 H), 2.51 - 2.63 (m, 2 H), 3.37 (td, *J*=6.33, 3.81 Hz, 2 H), 4.60 (s, 1 H), 4.72 (d, *J*=1.83 Hz, 1 H), 5.28 (dd, *J*=6.10, 1.53 Hz, 1 H), 7.20 (m, *J*=8.54 Hz, 2 H), 7.92 (m, *J*=8.24 Hz, 2 H).

Example 34

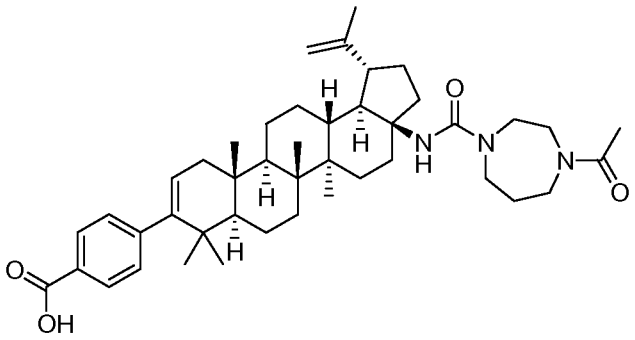
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(4-methyl-1,4-diazepane-1-carboxamido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 1-methyl-1,4-diazepane as the reactant amine. The mono-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (30 mg, 48% yield). LCMS: m/z 670 ($M+H^+$), retention time 2.41 min (method 11). ^1H NMR (400 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (s, 6 H), 1.00 (s, 3 H), 1.04 (s, 3 H), 1.09 (s, 3 H), 1.10 - 1.22 (m, 3 H), 1.22 - 1.45 (m, 5 H), 1.45 - 1.64 (m, 8 H), 1.64 - 1.81 (m, 7 H), 1.87 - 2.01 (m, 1 H), 2.12 (dd, *J*=17.19, 6.40 Hz, 1 H), 2.33 (br. s., 2 H), 2.40 - 2.53 (m, 2 H), 2.58 (d, *J*=13.30 Hz, 1 H), 2.92 (s, 3 H), 3.54 (br. s., 2 H), 4.64 (s, 1 H), 4.75 (d, *J*=1.00 Hz, 1 H), 5.26 - 5.33 (m, 1 H), 7.20 (m, *J*=8.28 Hz, 2 H), 7.92 (m, *J*=8.28 Hz, 2 H).

Example 35

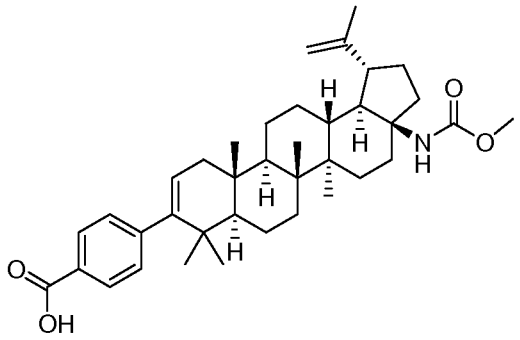
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-acetyl-1,4-diazepane-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 1-[1,4-diazepan1-yl]ethanone as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (27 mg, 48% yield). LCMS: m/z 698 ($M+H^+$), retention time 2.74 min (method 11). ^1H NMR (400 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (br. s., 3 H), 0.94 (br. s., 3 H), 1.01 (s, 3 H), 1.03 (s, 3 H), 1.09 (s, 3 H), 1.10 - 1.19 (m, 2 H), 1.21 - 1.66 (m, 14 H), 1.67 - 1.78 (m, 6 H), 1.85 - 2.02 (m, 3 H), 2.11 (s, 2 H), 2.12 - 2.17 (m, 2 H), 2.34 - 2.50 (m, 2 H), 2.54 - 2.64 (m, 1 H), 3.41 - 3.48 (m, 2 H), 3.50 - 3.64 (m, 5 H), 4.63 (br. s., 1 H), 4.75 (d, *J*=9.16 Hz, 1 H), 5.29 (d, *J*=4.58 Hz, 1 H), 7.20 (d, *J*=8.24 Hz, 2 H), 7.92 (d, *J*=8.24 Hz, 2 H).

Example 36

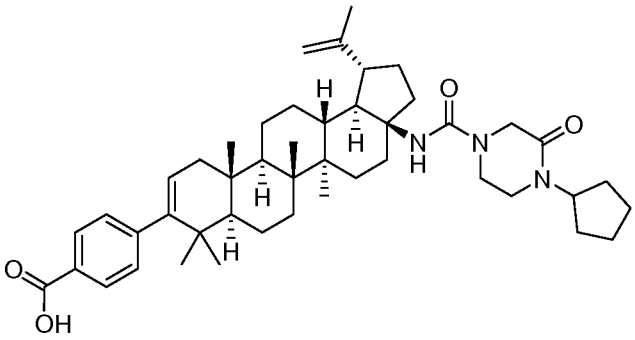
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(methoxycarbonylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was formed as a byproduct during the urea formation step in the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-acetyl-1,4-diazepane-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid. Hydrolysis of the penultimate methyl ester by the general procedure as described and purification by reverse phase preparative HPLC gave a white solid (6 mg, 13% yield). LCMS: m/z 588 ($M+H^+$), retention time 3.07 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.93 (s, 3 H), 0.94 (s, 3 H), 1.00 (s, 3 H), 1.01 (s, 3 H), 1.09 (s, 3 H), 1.09 - 1.16 (m, 2 H), 1.23 - 1.27 (m, 1 H), 1.28 - 1.44 (m, 5 H), 1.45 - 1.57 (m, 6 H), 1.59 - 1.77 (m, 9 H), 1.88 - 2.00 (m, 1 H), 2.12 (dd, *J*=17.09, 6.41 Hz, 1 H), 2.28 - 2.39 (m, 1 H), 2.45 - 2.58 (m, 2 H), 3.62 (br. s., 3 H), 4.62 (d, *J*=1.53 Hz, 1 H), 4.74 (d, *J*=1.83 Hz, 1 H), 5.29 (dd, *J*=6.26, 1.68 Hz, 1 H), 7.20 (d, *J*=8.24 Hz, 2 H), 7.92 (d, *J*=8.24 Hz, 2 H).

Example 37

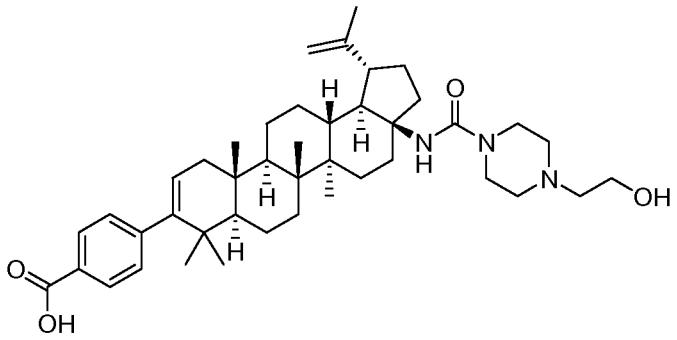
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-cyclopentyl-3-oxopiperazine-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 1-cyclopentylpiperazin-2-one, HCl, 0.5 H_2O as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (18 mg, 28% yield). LCMS: m/z 724 ($M+H^+$), retention time 2.97 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.93 (br. s., 3 H), 0.94 (br. s., 3 H), 1.00 (s, 3 H), 1.03 (s, 3 H), 1.09 (s, 3 H), 1.11 - 1.19 (m, 2 H), 1.24 (d, *J*=8.85 Hz, 1 H), 1.30 - 1.42 (m, 4 H), 1.43 - 1.60 (m, 10 H), 1.62 - 1.67 (m, 2 H), 1.67 - 1.80 (m, 9 H), 1.82 - 1.90 (m, 2 H), 1.90 - 2.00 (m, 1 H), 2.12 (dd, *J*=17.09, 6.41 Hz, 1 H), 2.40 - 2.60 (m, 3 H), 3.35 - 3.41 (m, 2 H), 3.53 - 3.68 (m, 2 H), 3.94 - 4.04 (m, 1 H), 4.04 - 4.13 (m, 1 H), 4.63 (br. s., 1 H), 4.75 (s, 1 H), 4.90 (quin, *J*=8.47 Hz, 1 H), 5.25 - 5.31 (m, 1 H), 5.34 - 5.38 (m, 1 H), 7.20 (d, *J*=8.24 Hz, 2 H), 7.92 (d, *J*=8.24 Hz, 2 H).

Example 38

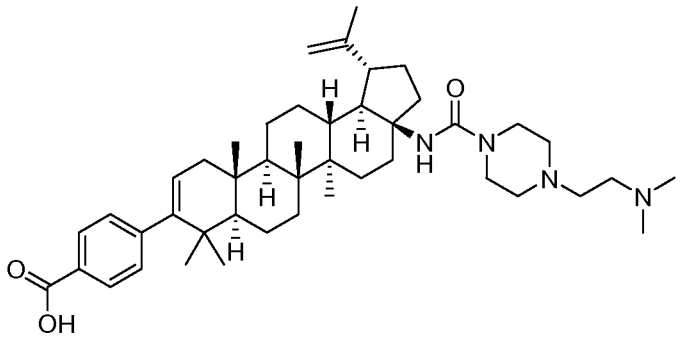
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-(2-hydroxyethyl)piperazine-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 2-(piperazin-1-yl)ethanol as the reactant amine. The mono-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (12 mg, 18% yield). LCMS: m/z 686 ($M+H^+$), retention time 2.41 min (method 11). 1H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (s, 3 H), 0.94 (s, 3 H), 1.00 (s, 3 H), 1.04 (s, 3 H), 1.08 (s, 3 H), 1.09 - 1.19 (m, 2 H), 1.24 - 1.28 (m, 1 H), 1.32 - 1.43 (m, 4 H), 1.44 - 1.59 (m, 7 H), 1.67 - 1.80 (m, 7 H), 1.86 - 1.98 (m, 1 H), 2.12 (dd, *J*=17.24, 6.26 Hz, 1 H), 2.42 (dd, *J*=12.36, 8.09 Hz, 1 H), 2.53 - 2.65 (m, 2 H), 3.23 - 3.29 (m, 3 H), 3.92 (dd, *J*=5.95, 4.43 Hz, 2 H), 4.75 (d, *J*=1.53 Hz, 1 H), 5.29 (dd, *J*=6.10, 1.83 Hz, 1 H), 7.20 (m, *J*=8.24 Hz, 2 H), 7.92 (m, *J*=8.54 Hz, 2 H).

Example 39

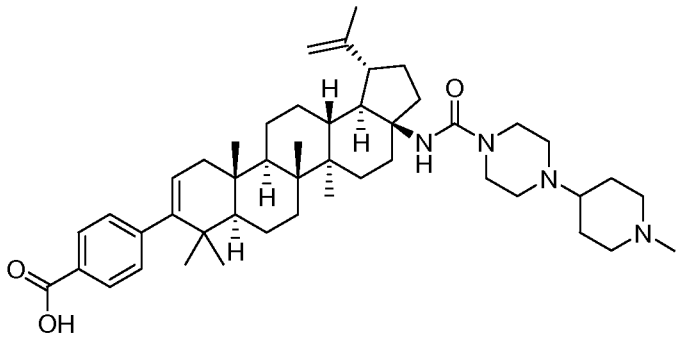
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-(2-(dimethylamino)ethyl)piperazine-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *N,N*-dimethyl-2-(piperazin-1-yl)ethanamine as the reactant amine. The bis-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (15 mg, 19% yield). LCMS: m/z 713 ($M+H^+$), retention time 2.44 min (method 11). 1H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (s, 3 H), 0.94 (s, 3 H), 1.00 (s, 3 H), 1.03 (s, 3 H), 1.08 (s, 3 H), 1.09 - 1.20 (m, 2 H), 1.24 - 1.44 (m, 7 H), 1.44 - 1.62 (m, 7 H), 1.64 - 1.79 (m, 7 H), 1.88 - 2.00 (m, 1 H), 2.12 (dd, *J*=17.09, 6.41 Hz, 1 H), 2.44 (dd, *J*=12.21, 8.24 Hz, 1 H), 2.51 (dt, *J*=10.15, 5.15 Hz, 1 H), 2.57 (d, *J*=13.12 Hz, 1 H), 2.73 (br. s., 4 H), 2.87 - 2.99 (m, 8 H), 3.39 - 3.55 (m, 4 H), 4.75 (s, 1 H), 5.29 (d, *J*=4.58 Hz, 1 H), 7.20 (m, *J*=8.24 Hz, 2 H), 7.92 (m, *J*=8.24 Hz, 2 H).

Example 40

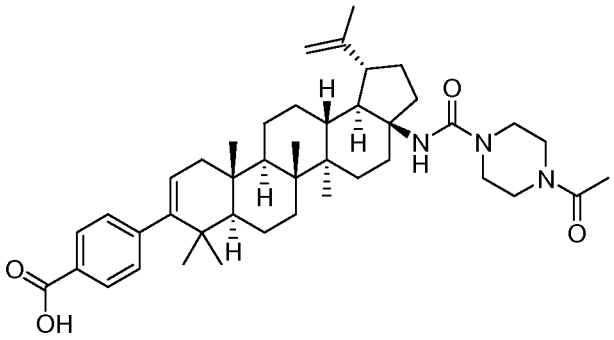
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(4-(1-methylpiperidin-4-yl)piperazine-1-carboxamido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 1-(1-methylpiperidin-4-yl)piperazine as the reactant amine. The bis-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (48 mg, 61% yield). LCMS: m/z 739 ($M+H^+$), retention time 2.41 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.93 (s, 3 H), 0.94 (s, 3 H), 1.00 (s, 3 H), 1.03 (s, 3 H), 1.08 (s, 3 H), 1.09 - 1.19 (m, 2 H), 1.23 - 1.28 (m, 1 H), 1.29 - 1.44 (m, 4 H), 1.44 - 1.64 (m, 9 H), 1.65 - 1.79 (m, 7 H), 1.87 - 1.99 (m, 1 H), 1.99 - 2.08 (m, 2 H), 2.12 (dd, *J*=17.09, 6.41 Hz, 1 H), 2.40 - 2.60 (m, 3 H), 2.77 - 2.93 (m, 5 H), 3.03 - 3.13 (m, 1 H), 3.35 (br. s., 4 H), 3.47 (br. s., 4 H), 3.99 - 4.15 (m, 2 H), 4.63 (s, 1 H), 4.75 (d, *J*=1.22 Hz, 1 H), 5.29 (dd, *J*=6.10, 1.53 Hz, 1 H), 7.20 (m, *J*=8.54 Hz, 2 H), 7.92 (m, *J*=8.24 Hz, 2 H).

Example 41

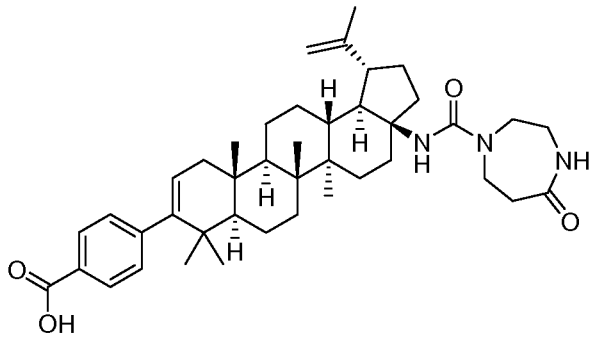
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-acetylpiperazine-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 1-(piperazin-1-yl)ethanone as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (6 mg, 11% yield). LCMS: m/z 684 ($M+H^+$), retention time 2.81 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (br. s., 3 H), 0.94 (s, 3 H), 1.01 (s, 3 H), 1.04 (s, 3 H), 1.09 (s, 3 H), 1.10 - 1.20 (m, 2 H), 1.24 - 1.28 (m, 2 H), 1.29 - 1.45 (m, 4 H), 1.45 - 1.62 (m, 7 H), 1.64 - 1.79 (m, 7 H), 1.89 - 2.00 (m, 1 H), 2.08 - 2.16 (m, 4 H), 2.46 (dd, *J*=12.36, 8.09 Hz, 1 H), 2.52 (td, *J*=10.60, 5.34 Hz, 1 H), 2.58 (ddd, *J*=13.35, 3.36, 3.13 Hz, 1 H), 3.35 - 3.48 (m, 3 H), 3.49 - 3.60 (m, 3 H), 3.60 - 3.73 (m, 2 H), 4.75 (d, *J*=1.53 Hz, 1 H), 5.29 (dd, *J*=6.10, 1.53 Hz, 1 H), 7.20 (m, *J*=8.54 Hz, 2 H), 7.92 (m, *J*=8.54 Hz, 2 H).

Example 42

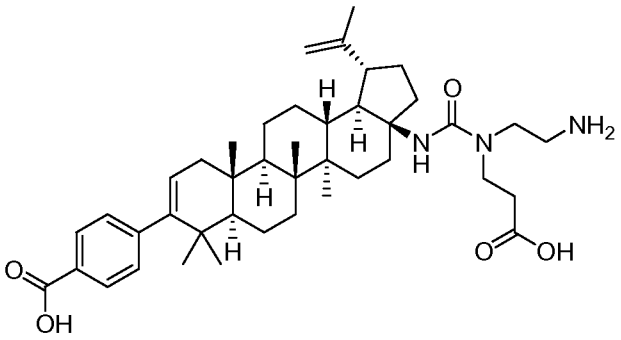
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(5-oxo-1,4-diazepane-1-carboxamido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 1,4-diazepan-5-one as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (26 mg, 46% yield). LCMS: m/z 670 ($M+H^+$), retention time 2.70 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (s, 3 H), 0.94 (s, 3 H), 1.01 (s, 3 H), 1.04 (s, 3 H), 1.09 (s, 3 H), 1.10 - 1.19 (m, 2 H), 1.26 (dd, *J*=7.17, 3.20 Hz, 1 H), 1.31 - 1.43 (m, 5 H), 1.45 - 1.54 (m, 6 H), 1.55 - 1.60 (m, 2 H), 1.63 - 1.80 (m, 7 H), 1.88 - 1.99 (m, 1 H), 2.13 (dd, *J*=16.94, 6.26 Hz, 1 H), 2.44 - 2.53 (m, 2 H), 2.60 (ddd, *J*=13.50, 2.82, 2.59 Hz, 1 H), 2.68 (t, *J*=5.19 Hz, 2 H), 3.49 - 3.68 (m, 4 H), 4.57 (s, 1 H), 4.75 (d, *J*=1.53 Hz, 1 H), 5.29 (dd, *J*=6.10, 1.53 Hz, 1 H), 7.20 (d, *J*=8.54 Hz, 2 H), 7.92 (d, *J*=8.54 Hz, 2 H).

Example 43

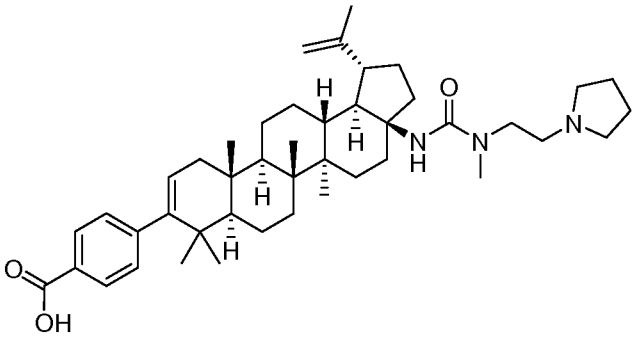
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-aminoethyl)-3-(2-carboxyethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was formed as a byproduct during the ester hydrolysis step in the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(5-oxo-1,4-diazepane-1-carboxamido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid. Purification by reverse phase preparative HPLC gave a white solid (10 mg, 15% yield) mono-TFA salt. LCMS: m/z 688 ($M+H^+$), retention time 2.40 min (method 11). ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (s, 6 H), 1.01 (s, 3 H), 1.04 (s, 3 H), 1.07 - 1.17 (m, 5 H), 1.23 - 1.42 (m, 7 H), 1.44 - 1.62 (m, 7 H), 1.67 - 1.81 (m, 6 H), 1.84 - 2.00 (m, 2 H), 2.13 (dd, *J*=17.39, 6.41 Hz, 1 H), 2.38 (dd, *J*=11.90, 7.93 Hz, 1 H), 2.51 - 2.58 (m, 1 H), 2.59 - 2.66 (m, 1 H), 2.66 - 2.73 (m, 1 H), 2.77 (td, *J*=10.83, 4.58 Hz, 1 H), 2.99 - 3.10 (m, 2 H), 3.36 - 3.46 (m, 3 H), 3.76 (ddd, *J*=15.56, 9.31, 3.81 Hz, 1 H), 4.76 (d, *J*=1.83 Hz, 1 H), 5.29 (dd, *J*=6.10, 1.53 Hz, 1 H), 7.20 (m, *J*=8.24 Hz, 2 H), 7.92 (m, *J*=8.24 Hz, 2 H).

Example 44

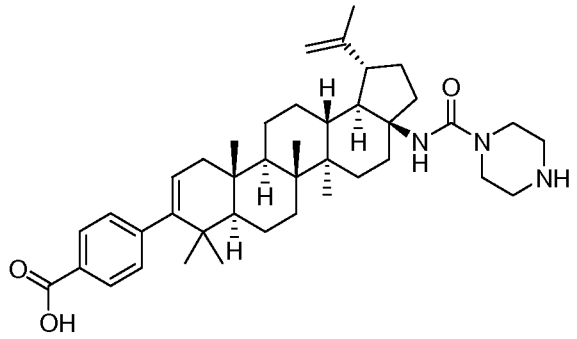
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-methyl-3-(2-(pyrrolidin-1-yl)ethyl)ureido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *N*-methyl-2-(pyrrolidin-1-yl)ethanamine as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (34 mg, 54% yield) mono-TFA salt. LCMS: m/z 684 ($M+H^+$), retention time 2.41 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (br. s., 3 H), 0.94 (br. s., 3 H), 1.00 (s, 3 H), 1.04 (s, 3 H), 1.10 (s, 3 H), 1.10 - 1.21 (m, 2 H), 1.26 (dd, *J*=10.68, 2.75 Hz, 1 H), 1.32 - 1.43 (m, 4 H), 1.45 - 1.59 (m, 7 H), 1.62 - 1.81 (m, 8 H), 1.87 - 2.00 (m, 1 H), 2.08 (br. s., 4 H), 2.12 (dd, *J*=17.09, 6.41 Hz, 1 H), 2.41 - 2.57 (m, 3 H), 3.03 (s, 3 H), 3.06 (br. s., 2 H), 3.25 - 3.39 (m, 2 H), 3.52 (dt, *J*=14.65, 6.26 Hz, 1 H), 3.63 - 3.83 (m, 3 H), 4.64 (br. s., 1 H), 4.75 (s, 1 H), 5.26 - 5.32 (m, 1 H), 7.20 (d, *J*=7.93 Hz, 2 H), 7.92 (d, *J*=8.24 Hz, 2 H).

Example 45

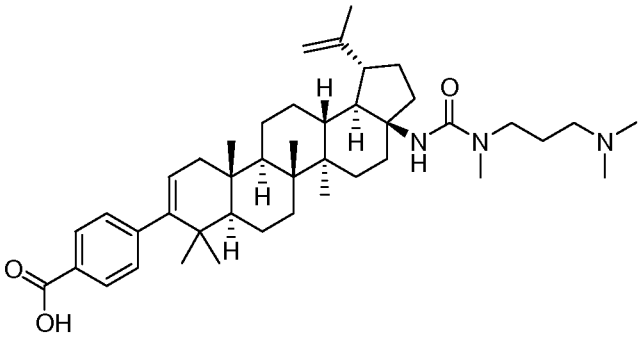
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(piperazine-1-carboxamido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 1-(piperazin-1-yl)ethanone as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (5 mg, 8% yield) mono-TFA salt. LCMS: m/z 642 ($M+H^+$), retention time 2.42 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (s, 3 H), 0.94 (s, 3 H), 1.00 (s, 3 H), 1.04 (s, 3 H), 1.08 (s, 3 H), 1.09 - 1.19 (m, 2 H), 1.26 (dd, *J*=8.09, 2.29 Hz, 1 H), 1.29 - 1.44 (m, 4 H), 1.44 - 1.51 (m, 4 H), 1.51 - 1.62 (m, 3 H), 1.67 - 1.80 (m, 7 H), 1.87 - 1.97 (m, 1 H), 2.12 (dd, *J*=17.09, 6.41 Hz, 1 H), 2.43 (dd, *J*=12.36, 8.09 Hz, 1 H), 2.53 - 2.63 (m, 2 H), 3.13 - 3.27 (m, 4 H), 3.55 - 3.68 (m, 4 H), 4.75 (d, *J*=1.53 Hz, 1 H), 4.95 (s, 1 H), 5.29 (dd, *J*=6.10, 1.53 Hz, 1 H), 7.20 (d, *J*=8.54 Hz, 2 H), 7.92 (d, *J*=8.24 Hz, 2 H).

Example 46

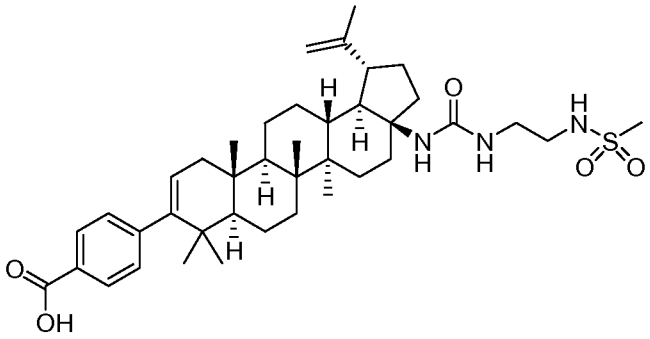
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(3-(dimethylamino)propyl)-3-methylureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *N1,N1,N3*-trimethylpropane-1,3-diamine as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (21 mg, 31% yield) mono-TFA salt. LCMS: m/z 672 ($M+H^+$), retention time 1.86 min (method 2). ^1H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (s, 3 H) 0.94 (s, 3 H) 1.01 (s, 3 H) 1.05 (s, 3 H) 1.07 - 1.20 (m, 5 H) 1.24 - 1.29 (m, 2 H) 1.33 - 1.39 (m, 2 H) 1.40 - 1.59 (m, 9 H) 1.62 - 1.80 (m, 7 H) 1.88 - 2.02 (m, 3 H) 2.13 (dd, *J*=17.09, 6.41 Hz, 1 H) 2.43 (dd, *J*=12.51, 8.24 Hz, 1 H) 2.46 - 2.55 (m, 2 H) 2.87 (s, 6 H) 2.98 - 3.10 (m, 5 H) 3.34 - 3.49 (m, 2 H) 4.76 (d, *J*=1.22 Hz, 1 H) 5.29 (dd, *J*=6.10, 1.83 Hz, 1 H) 7.20 (m, *J*=8.24 Hz, 2 H) 7.92 (m, *J*=8.24 Hz, 2 H).

Example 47

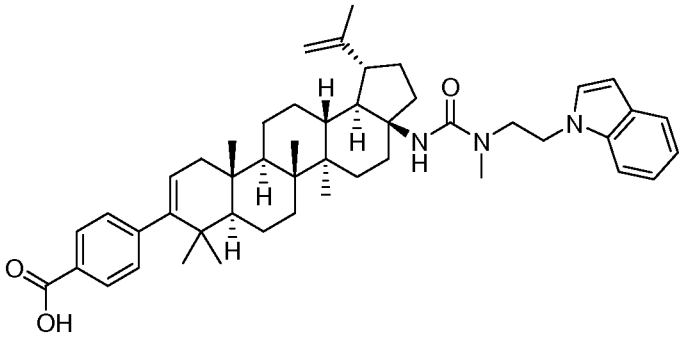
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(2-(methylsulfonamido)ethyl)ureido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *N*-(2-aminoethyl)methanesulfonamide hydrochloride as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (28 mg, 51% yield). LCMS: m/z 694 ($M+H^+$), retention time 2.17 min (method 2). ^1H NMR (400 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.93 (br. s., 3 H) 0.94 (s, 3 H) 1.00 (s, 6 H) 1.04 - 1.16 (m, 5 H) 1.23 - 1.43 (m, 6 H) 1.45 - 1.56 (m, 5 H) 1.59 - 1.83 (m, 8 H) 1.87 - 2.00 (m, 1 H) 2.11 (dd, *J*=17.19, 6.40 Hz, 1 H) 2.36 (dd, *J*=12.05, 8.28 Hz, 1 H) 2.49 - 2.63 (m, 2 H) 2.95 (s, 3 H) 3.09 - 3.17 (m, 2 H) 3.20 - 3.30 (m, 2 H) 4.61 (s, 1 H) 4.72 (d, *J*=1.76 Hz, 1 H) 5.29 (dd, *J*=6.02, 1.51 Hz, 1 H) 7.20 (m, *J*=8.28 Hz, 2 H) 7.92 (m, *J*=8.28 Hz, 2 H).

Example 48

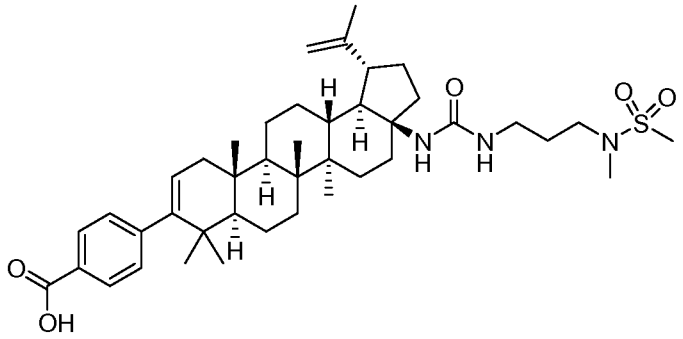
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(1H-indol-1-yl)ethyl)-3-methylureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 2-(1H-indol-1-yl)-*N*-methylethanamine as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (30 mg, 39% yield) mono-TFA salt. LCMS: m/z 730 ($M+H^+$), retention time 2.73 min (method 2). ^1H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (br. s., 3 H) 0.94 (br. s., 3 H) 0.95 (br. s., 3 H) 0.97 (s, 3 H) 0.99 (s, 3 H) 1.01 - 1.12 (m, 2 H) 1.21 - 1.29 (m, 3 H) 1.32 - 1.37 (m, 2 H) 1.38 - 1.53 (m, 7 H) 1.54 - 1.73 (m, 7 H) 1.79 - 1.92 (m, 1 H) 2.09 (dd, *J*=17.09, 6.41 Hz, 1 H) 2.19 (td, *J*=10.61, 4.43 Hz, 1 H) 2.42 (s, 3 H) 2.48 - 2.57 (m, 2 H) 3.60 (ddd, *J*=14.50, 5.49, 5.34 Hz, 1 H) 3.71 (ddd, *J*=14.65, 5.65, 5.34 Hz, 1 H) 4.28 - 4.39 (m, 2 H) 4.60 (br. s., 1 H) 4.69 (s, 1 H) 5.27 (d, *J*=6.10 Hz, 1 H) 6.51 (d, *J*=3.05 Hz, 1 H) 7.05 - 7.12 (m, 2 H) 7.15 - 7.22 (m, 3 H) 7.38 (d, *J*=8.24 Hz, 1 H) 7.61 (d, *J*=7.93 Hz, 1 H) 7.92 (d, *J*=8.24 Hz, 2 H).

Example 49

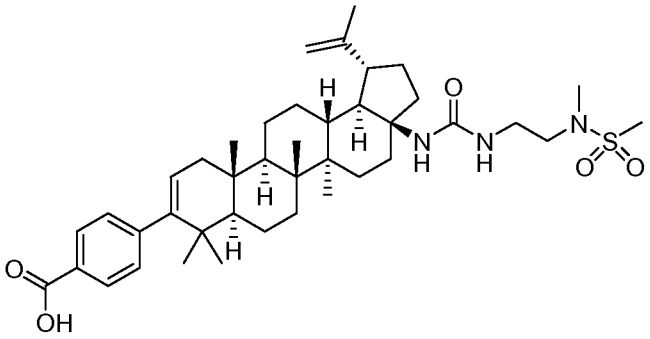
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(3-(*N*-methylmethylsulfonamido)propyl)ureido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *N*-(3-aminopropyl)-*N*-methylmethanesulfonamide as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (36 mg, 62% yield). LCMS: m/z 730 ($M+H^+$), retention time 2.25 min (method 2). ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.93 (s, 3 H) 0.94 (s, 3 H) 1.00 (s, 6 H) 1.05 - 1.15 (m, 5 H) 1.21 - 1.41 (m, 5 H) 1.41 - 1.59 (m, 6 H) 1.62 - 1.81 (m, 10 H) 1.88 - 1.99 (m, 1 H) 2.11 (dd, *J*=17.09, 6.41 Hz, 1 H) 2.35 (dd, *J*=12.36, 8.09 Hz, 1 H) 2.50 - 2.63 (m, 2 H) 2.85 (s, 3 H) 2.86 (s, 3 H) 3.12 - 3.23 (m, 4 H) 4.61 (s, 1 H) 4.72 (d, *J*=1.53 Hz, 1 H) 5.25 - 5.32 (m, 1 H) 7.20 (m, *J*=8.24 Hz, 2 H) 7.92 (m, *J*=8.24 Hz, 2 H).

Example 50

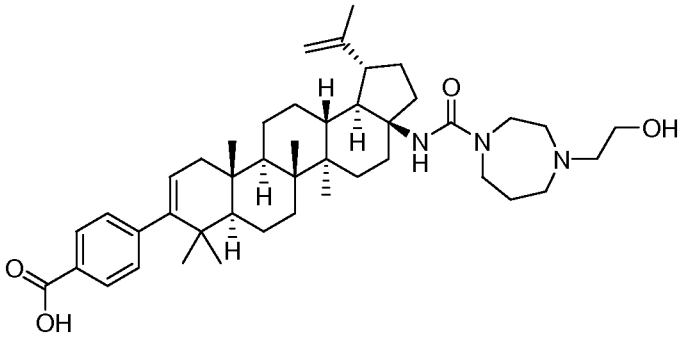
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(2-(N-methylmethylsulfonamido)ethyl)ureido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *N*-(2-aminoethyl)-*N*-methylmethanesulfonamide as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (37 mg, 65% yield). LCMS: m/z 708 ($M+H^+$), retention time 2.25 min (method 2). ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.93 (br. s., 3 H) 0.94 (s, 3 H) 1.00 (s, 6 H) 1.04 - 1.15 (m, 5 H) 1.21 - 1.41 (m, 5 H) 1.41 - 1.58 (m, 6 H) 1.59 - 1.75 (m, 7 H) 1.75 - 1.83 (m, 1 H) 1.88 - 2.00 (m, 1 H) 2.11 (dd, *J*=17.09, 6.41 Hz, 1 H) 2.36 (dd, *J*=12.36, 8.09 Hz, 1 H) 2.51 - 2.64 (m, 2 H) 2.86 (s, 3 H) 2.91 (s, 3 H) 3.18 - 3.25 (m, 2 H) 3.31 (t, *J*=5.49 Hz, 2 H) 4.61 (s, 1 H) 4.72 (d, *J*=1.53 Hz, 1 H) 5.28 (dd, *J*=6.26, 1.68 Hz, 1 H) 7.20 (d, *J*=8.54 Hz, 2 H) 7.92 (d, *J*=8.24 Hz, 2 H).

Example 51

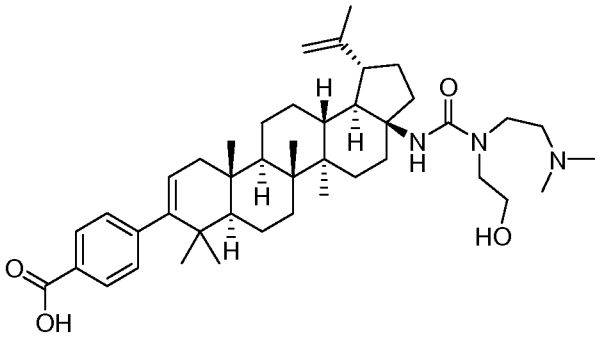
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-(2-hydroxyethyl)-1,4-diazepane-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 2-(1,4-diazepan-1-yl)ethanol as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (49 mg, 72% yield) mono-TFA salt. LCMS: m/z 700 ($M+H^+$), retention time 1.77 min (method 2). ^1H NMR (400 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (s, 3 H) 0.94 (s, 3 H) 1.00 (s, 3 H) 1.04 (s, 3 H) 1.09 (s, 3 H) 1.10 - 1.18 (m, 2 H) 1.18 - 1.64 (m, 13 H) 1.64 - 1.82 (m, 7 H) 1.85 - 2.01 (m, 1 H) 2.12 (dd, *J*=17.19, 6.40 Hz, 1 H) 2.29 - 2.41 (m, 2 H) 2.41 - 2.53 (m, 2 H) 2.58 (d, *J*=13.30 Hz, 1 H) 3.25 - 3.32 (m, 2 H) 3.35 - 3.63 (m, 6 H) 3.69 - 4.00 (m, 4 H) 4.64 (br. s., 1 H) 4.75 (s, 1 H) 5.29 (d, *J*=4.77 Hz, 1 H) 7.19 (m, 2 H) 7.91 (m, 2 H).

Example 52

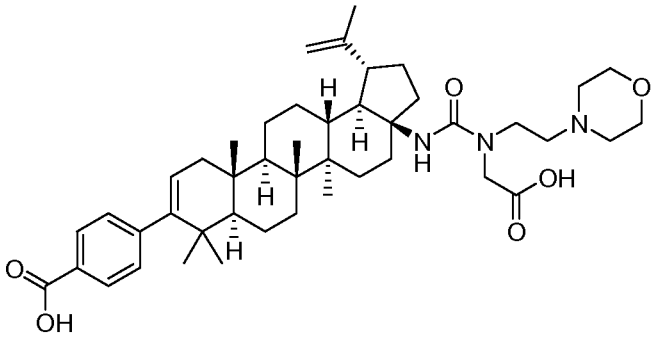
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimethylamino)ethyl)-3-(2-hydroxyethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 2-(2-(dimethylamino)ethylamino)ethanol as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (35 mg, 51% yield) mono-TFA salt. LCMS: m/z 688 ($M+H^+$), retention time 1.79 min (method 2). ^1H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.93 (br. s., 3 H) 0.94 (br. s., 3 H) 1.01 (br. s., 3 H) 1.02 (br. s., 3 H) 1.06 - 1.18 (m, 5 H) 1.20 - 1.66 (m, 12 H) 1.66 - 1.81 (m, 7 H) 1.81 - 2.01 (m, 2 H) 2.12 (dd, *J*=17.09, 6.41 Hz, 1 H) 2.37 (dd, *J*=12.05, 8.09 Hz, 1 H) 2.46 - 2.61 (m, 2 H) 2.93 (s, 6 H) 3.21 - 3.31 (m, 2 H) 3.48 - 3.61 (m, 3 H) 3.72 - 3.79 (m, 2 H) 4.61 (br. s., 1 H) 4.74 (br. s., 1 H) 5.23 - 5.35 (m, 1 H) 7.20 (d, *J*=8.24 Hz, 2 H) 7.92 (d, *J*=8.24 Hz, 2 H).

Example 53

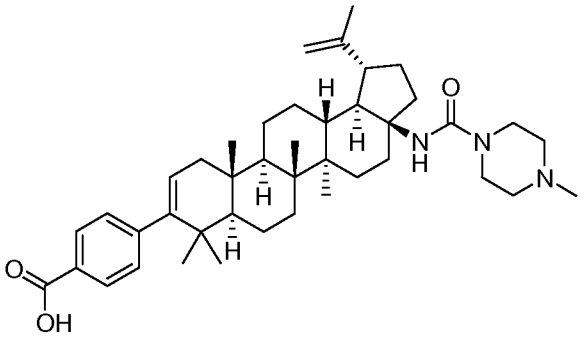
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(carboxymethyl)-3-(2-morpholinoethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using ethyl 2-(2-morpholinoethylamino)acetate as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (5 mg, 6% yield) mono-TFA salt. LCMS: m/z 744 ($M+H^+$), retention time 1.81 min (method 2). ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (br. s., 3 H) 0.94 (s, 3 H) 1.01 (s, 3 H) 1.02 (s, 3 H) 1.10 (d, *J*=2.44 Hz, 1 H) 1.11 - 1.16 (m, 4 H) 1.19 - 1.64 (m, 12 H) 1.64 - 1.80 (m, 7 H) 1.87 - 1.98 (m, 1 H) 2.13 (dd, *J*=17.09, 6.41 Hz, 1 H) 2.35 (dd, *J*=12.51, 8.24 Hz, 1 H) 2.47 - 2.59 (m, 2 H) 3.23 - 3.30 (m, 2 H) 3.37 (s, 3 H) 3.58 (td, *J*=10.38, 4.88 Hz, 1 H) 3.70 - 4.03 (m, 6 H) 4.72 (s, 1 H) 4.78 (d, *J*=1.53 Hz, 1 H) 5.29 (dd, *J*=6.10, 1.53 Hz, 1 H) 7.20 (m, *J*=8.24 Hz, 2 H) 7.92 (m, *J*=8.24 Hz, 2 H).

Example 54

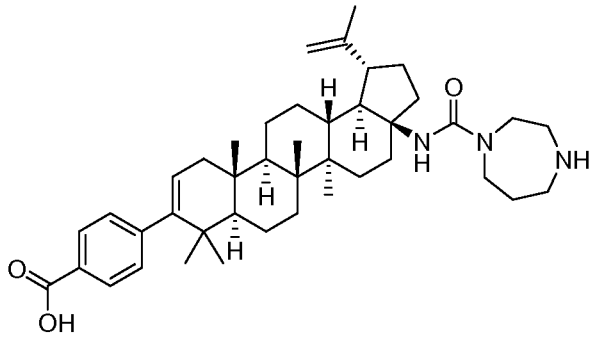
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(4-methylpiperazine-1-carboxamido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 1-methylpiperazine as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (49 mg, 75% yield) mono-TFA salt. LCMS: m/z 656 ($M+H^+$), retention time 2.44 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (br. s., 3 H) 0.94 (s, 3 H) 1.00 (s, 3 H) 1.03 (s, 3 H) 1.05 - 1.19 (m, 5 H) 1.23 - 1.28 (m, 1 H) 1.31 - 1.42 (m, 4 H) 1.44 - 1.59 (m, 7 H) 1.64 - 1.81 (m, 7 H) 1.86 - 1.98 (m, 1 H) 2.12 (dd, *J*=17.24, 6.26 Hz, 1 H) 2.42 (dd, *J*=12.36, 8.39 Hz, 1 H) 2.51 - 2.65 (m, 2 H) 2.90 (s, 3 H) 3.34 (br. s., 4 H) 3.96 (br. s., 2 H) 4.64 (br. s., 1 H) 4.75 (d, *J*=1.22 Hz, 1 H) 5.29 (dd, *J*=6.26, 1.68 Hz, 1 H) 7.20 (m, *J*=8.24 Hz, 2 H) 7.92 (m, *J*=8.55 Hz, 2 H).

Example 55

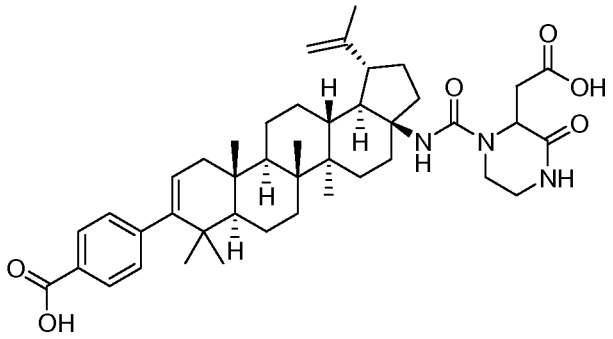
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(1,4-diazepane-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using homopiperazine as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (33 mg, 53% yield) mono-TFA salt. LCMS: m/z 656 ($M+H^+$), retention time 2.43 min (method 11). ^1H NMR (400 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (s, 6 H) 1.00 (s, 3 H) 1.04 (s, 3 H) 1.09 (s, 3 H) 1.10 - 1.22 (m, 2 H) 1.24 - 1.30 (m, 1 H) 1.34 - 1.59 (m, 11 H) 1.64 - 1.82 (m, 7 H) 1.86 - 2.01 (m, 1 H) 2.12 (dd, *J*=17.07, 6.27 Hz, 1 H) 2.18 - 2.29 (m, 2 H) 2.42 - 2.53 (m, 2 H) 2.59 (d, *J*=13.30 Hz, 1 H) 3.20 - 3.31 (m, 4 H) 3.48 - 3.62 (m, 2 H) 3.76 (t, *J*=4.27 Hz, 2 H) 4.47 (s, 1 H) 4.64 (s, 1 H) 4.75 (s, 1 H) 5.29 (d, *J*=4.77 Hz, 1 H) 7.20 (m, *J*=8.03 Hz, 2 H) 7.92 (m, *J*=8.03 Hz, 2 H).

Example 56

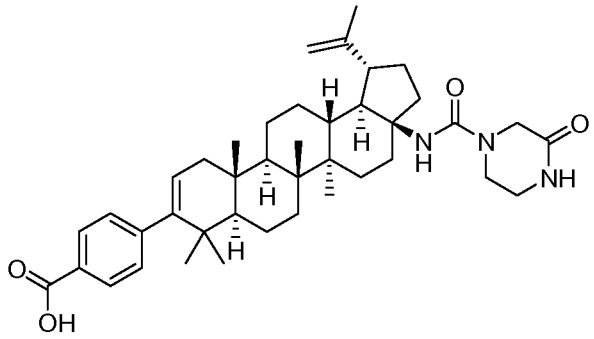
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(carboxymethyl)-3-oxopiperazine-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using ethyl 2-(3-oxopiperazin-2-yl)acetate as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (38 mg, 64% yield). LCMS: m/z 714 ($M+H^+$), retention time 2.66 min (method 11). This material is a diastereomeric mixture in a ratio of approximately 1:1. ^{1}H NMR (400 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.91 - 0.97 (m, 6 H) 0.97 - 1.04 (m, 6 H) 1.05 - 1.17 (m, 5 H) 1.19 - 1.64 (m, 13 H) 1.65 - 1.80 (m, 7 H) 1.80 - 2.08 (m, 3 H) 2.12 (dt, *J*=17.07, 6.02 Hz, 1 H) 2.23 (dd, *J*=12.30, 8.28 Hz, 0.5 H) 2.34 - 2.44 (m, 0.5 H) 2.58 (d, *J*=13.30 Hz, 0.5 H) 2.65 - 2.76 (m, 1 H) 2.80 - 2.96 (m, 2 H) 2.97 - 3.13 (m, 2 H) 3.14 - 3.24 (m, 1 H) 3.50 - 3.64 (m, 1.5 H) 3.94 - 4.03 (m, 0.5 H) 4.07 (dd, *J*=13.80, 2.76 Hz, 0.5 H) 4.70 - 4.80 (m, 2 H) 5.25 - 5.32 (m, 1 H) 7.19 (d, *J*=8.03 Hz, 2 H) 7.92 (d, 2 H).

Example 57

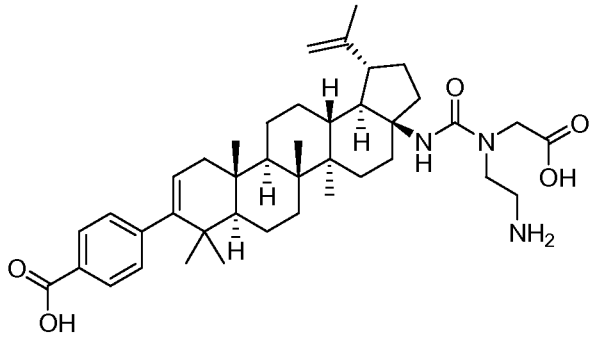
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-oxopiperazine-1-carboxamido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using piperazin-2-one as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (7 mg, 12% yield). LCMS: m/z 656 ($M+H^+$), retention time 2.71 min (method 11). ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (s, 3 H) 0.94 (s, 3 H) 1.00 (s, 3 H) 1.03 (s, 3 H) 1.10 (s, 3 H) 1.10 - 1.20 (m, 2 H) 1.25 (d, *J*=10.07 Hz, 1 H) 1.29 - 1.44 (m, 4 H) 1.44 - 1.63 (m, 7 H) 1.65 - 1.80 (m, 7 H) 1.89 - 2.00 (m, 1 H) 2.13 (dd, *J*=17.09, 6.41 Hz, 1 H) 2.46 (dd, *J*=12.51, 8.24 Hz, 1 H) 2.49 - 2.61 (m, 2 H) 3.36 - 3.45 (m, 2 H) 3.54 - 3.67 (m, 2 H) 3.91 - 4.02 (m, 1 H) 4.02 - 4.13 (m, 1 H) 4.64 (d, *J*=1.22 Hz, 1 H) 4.76 (d, *J*=1.22 Hz, 1 H) 5.29 (dd, *J*=6.26, 1.68 Hz, 1 H) 7.20 (d, *J*=8.24 Hz, 2 H) 7.92 (d, *J*=8.55 Hz, 2 H).

Example 58

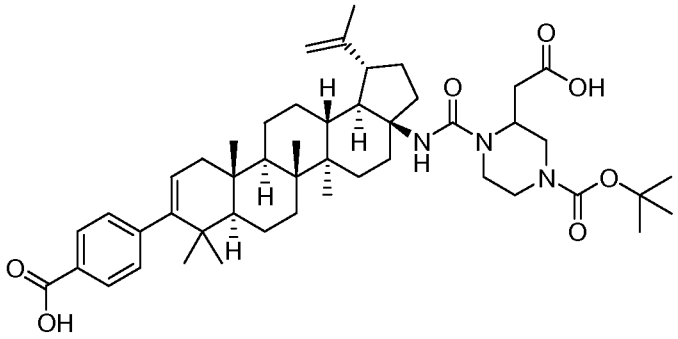
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-aminoethyl)-3-(carboxymethyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was formed as a byproduct during the ester hydrolysis step in the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-oxopiperazine-1-carboxamido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid. Purification by reverse phase preparative HPLC gave a white solid (22 mg, 33% yield) mono-TFA salt. LCMS: m/z 674 ($M+H^+$), retention time 2.41 min (method 11). ^1H NMR (400 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (s, 3 H) 0.94 (s, 3 H) 1.01 (s, 3 H) 1.02 (s, 3 H) 1.07 - 1.18 (m, 5 H) 1.20 - 1.59 (m, 12 H) 1.60 - 1.79 (m, 8 H) 1.86 - 2.01 (m, 1 H) 2.12 (dd, *J*=17.07, 6.27 Hz, 1 H) 2.37 - 2.51 (m, 2 H) 2.51 - 2.60 (m, 1 H) 3.05 - 3.18 (m, 2 H) 3.47 (ddd, *J*=15.37, 5.46, 5.27 Hz, 1 H) 3.70 - 3.82 (m, 1 H) 3.93 - 4.06 (m, 2 H) 4.62 (s, 1 H) 4.75 (d, *J*=1.51 Hz, 1 H) 5.29 (dd, *J*=6.02, 1.51 Hz, 1 H) 7.20 (m, *J*=8.28 Hz, 2 H) 7.92 (m, *J*=8.28 Hz, 2 H).

Example 59

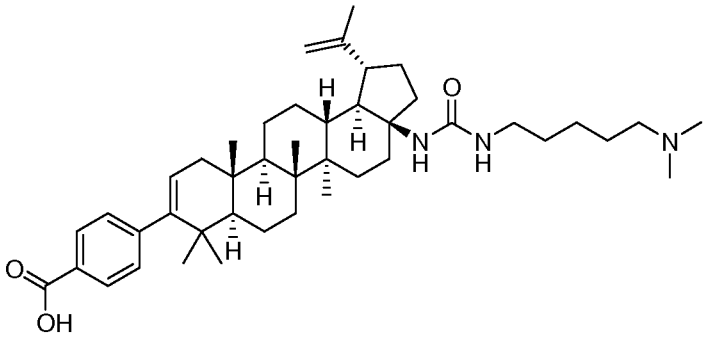
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-(*tert*-butoxycarbonyl)-2-(carboxymethyl)piperazine-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *tert*-butyl 3-(2-methoxy-2-oxoethyl)piperazine-1-carboxylate as the reactant amine. The product was isolated after reverse phase preparative HPLC purification as a white solid (39 mg, 63% yield). LCMS: m/z 800 ($M+H^+$), retention time 2.94 min (method 11). This material is a diastereomeric mixture in a ratio of approximately 2:1. ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 1H NMR (500 MHz, MeOD) δ ppm 0.89 - 0.97 (m, 6 H) 0.97 - 1.05 (m, 6 H) 1.05 - 1.18 (m, 5 H) 1.25 (d, *J*=3.36 Hz, 1 H) 1.29 - 1.44 (m, 5 H) 1.48 (d, *J*=5.80 Hz, 13 H) 1.51 - 1.62 (m, 3 H) 1.65 - 1.80 (m, 7 H) 1.81 - 2.00 (m, 2 H) 2.12 (ddd, *J*=17.09, 6.10, 3.66 Hz, 1 H) 2.27 - 2.42 (m, 1 H) 2.57 (dd, *J*=17.24, 4.12 Hz, 1 H) 2.63 (dd, *J*=12.82, 9.77 Hz, 2 H) 2.75 (br. s., 0.5 H) 2.88 (d, *J*=7.02 Hz, 1.5 H) 2.95 - 3.04 (m, 1 H) 3.09 (br. s., 0.5 H) 3.80 (d, *J*=11.60 Hz, 0.5 H) 3.91 (d, *J*=12.21 Hz, 0.5 H) 4.03 (d, *J*=10.38 Hz, 1 H) 5.29 (dd, *J*=4.27, 2.14 Hz, 1 H) 7.20 (dd, *J*=8.24, 2.44 Hz, 2 H) 7.92 (d, *J*=7.32 Hz, 2 H).

Example 60

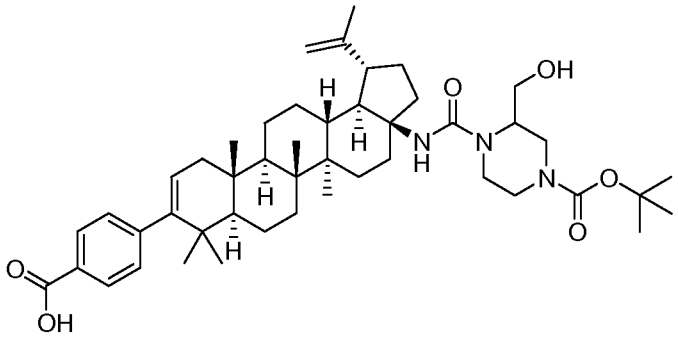
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(5-(dimethylamino)pentyl)ureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *N1,N1*-dimethylpentane-1,5-diamine as the reactant amine. The mono-TFA salt product was isolated after reverse phase preparative HPLC purification as a white solid (21 mg, 57% yield). LCMS: m/z 686 ($M+H^+$), retention time 2.44 min (method 11). ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.93 (br. s., 3 H) 0.94 (s, 3 H) 1.00 (br. s., 3 H) 1.01 (br. s., 3 H) 1.04 - 1.16 (m, 5 H) 1.23 - 1.26 (m, 1 H) 1.28 - 1.44 (m, 7 H) 1.44 - 1.59 (m, 7 H) 1.59 - 1.67 (m, 2 H) 1.67 - 1.84 (m, 8 H) 1.86 - 1.98 (m, 1 H) 2.12 (dd, *J*=17.40, 6.41 Hz, 1 H) 2.34 (dd, *J*=12.21, 8.24 Hz, 1 H) 2.50 - 2.63 (m, 2 H) 2.86 (s, 6 H) 3.03 - 3.17 (m, 4 H) 4.61 (s, 1 H) 4.72 (d, *J*=1.53 Hz, 1 H) 5.24 - 5.32 (m, 1 H) 7.20 (m, *J*=8.24 Hz, 2 H) 7.92 (m, *J*=8.24 Hz, 2 H).

Example 61

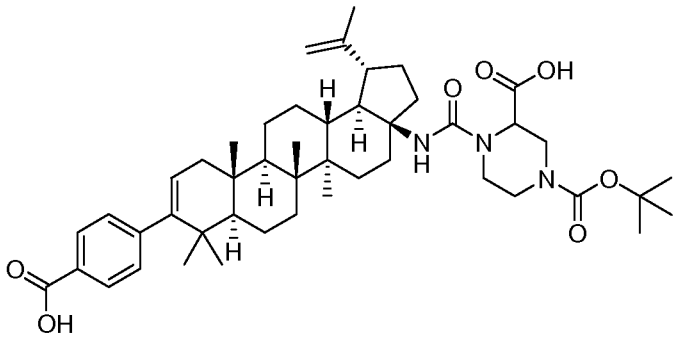
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-(*tert*-butoxycarbonyl)-2-(hydroxymethyl)piperazine-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using *tert*-butyl 3-(hydroxymethyl)piperazine-1-carboxylate as the reactant amine. The product was isolated as a mixture of two diastereomers after reverse phase preparative HPLC purification as a white solid (68 mg, 60% yield). LCMS: m/z 772 ($M+H^+$), retention time 2.91 and 2.99 min (method 11). This material is a diastereomeric mixture in a ratio of approximately 5:4. ^{1}H NMR (400 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.89 - 0.98 (m, 6 H) 0.98 - 1.04 (m, 6 H) 1.05 - 1.18 (m, 5 H) 1.20 - 1.44 (m, 6 H) 1.47 (d, *J*=2.26 Hz, 9 H) 1.48 - 1.61 (m, 6 H) 1.62 - 1.77 (m, 7 H) 1.80 - 2.01 (m, 2 H) 2.12 (dd, *J*=16.81, 6.02 Hz, 1 H) 2.32 - 2.42 (m, 1 H) 2.46 - 2.56 (m, 1 H) 2.60 (dd, *J*=13.30, 2.51 Hz, 1 H) 2.98 - 3.15 (m, 2 H) 3.21 (ddd, *J*=18.63, 13.87, 4.64 Hz, 1 H) 3.61 - 3.69 (m, 1 H) 3.71 - 3.91 (m, 4 H) 3.94 - 4.06 (m, 1 H) 4.61 (d, *J*=8.78 Hz, 1 H) 4.74 (dd, *J*=10.79, 1.25 Hz, 1 H) 5.24 - 5.33 (m, 1 H) 7.20 (dd, *J*=8.41, 1.88 Hz, 2 H) 7.86 - 7.92 (m, 1 H) 7.93 (s, 1 H).

Example 62

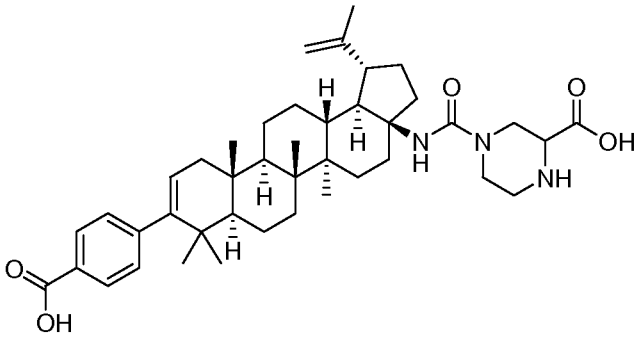
Preparation of 4-(*tert*-butoxycarbonyl)-1-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-carboxyphenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-ylcarbamoyl)piperazine-2-carboxylic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 1-*tert*-butyl 3-methyl piperazine-1,3-dicarboxylate as the reactant amine. The product was isolated as a mixture of two diastereomers after reverse phase preparative HPLC purification as a white solid (76 mg, 62% yield). LCMS: m/z 786 ($M+H^+$), retention time 2.84 min (method 11). This material is a diastereomeric mixture in a ratio of approximately 1:1. ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.93 (br. s., 3 H) 0.94 (br. s., 3 H) 1.01 (s, 3 H) 1.02 (s, 3 H) 1.04 - 1.18 (m, 5 H) 1.19 - 1.43 (m, 6 H) 1.46 (d, *J*=2.75 Hz, 9 H) 1.47 - 1.61 (m, 6 H) 1.61 - 1.80 (m, 8 H) 1.91 - 2.05 (m, 1 H) 2.12 (dd, *J*=17.09, 6.41 Hz, 1 H) 2.43 (dd, *J*=12.21, 8.24 Hz, 1 H) 2.46 - 2.53 (m, 1 H) 2.53 - 2.62 (m, 1 H) 2.98 (br. s., 1 H) 3.17 (d, *J*=9.77 Hz, 1 H) 3.35 - 3.44 (m, 1 H) 3.50 (d, *J*=9.77 Hz, 1 H) 4.09 (br. s., 1 H) 4.60 (d, *J*=13.73 Hz, 1 H) 4.63 (br. s., 1 H) 4.68 (br. s., 1 H) 4.75 (br. s., 1 H) 5.29 (d, *J*=4.58 Hz, 1 H) 7.20 (d, *J*=8.24 Hz, 2 H) 7.92 (d, *J*=8.24 Hz, 2 H).

Example 63

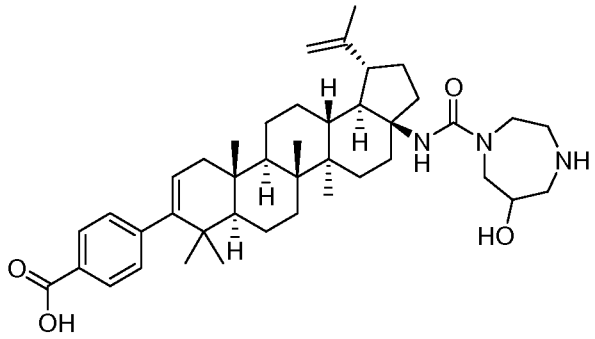
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-carboxyphenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-ylcarbamoyl)piperazine-2-carboxylic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using methyl piperazine-2-carboxylate as the reactant amine. The product was isolated as a mixture of two diastereomers after reverse phase preparative HPLC purification as a white solid (75 mg, 41% yield) mono-TFA salt. LCMS: m/z 686 ($M+H^+$), retention time 2.46 min (method 11). This material is a diastereomeric mixture in a ratio of approximately 1:1. ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.93 (br. s., 3 H) 0.93 (br. s., 3 H) 0.99 (s, 3 H) 1.02 (s, 3 H) 1.05 - 1.18 (m, 5 H) 1.25 (d, *J*=7.63 Hz, 1 H) 1.28 - 1.42 (m, 4 H) 1.42 - 1.52 (m, 5 H) 1.52 - 1.64 (m, 2 H) 1.65 - 1.84 (m, 7 H) 1.87 - 1.99 (m, 1 H) 2.11 (dd, *J*=17.09, 6.41 Hz, 1 H) 2.41 (td, *J*=11.90, 8.85 Hz, 1 H) 2.55 (dd, *J*=13.43, 2.75 Hz, 1 H) 2.63 (tt, *J*=10.72, 5.46 Hz, 1 H) 3.07 - 3.18 (m, 0.5 H) 3.19 - 3.27 (m, 0.5 H) 3.34 - 3.51 (m, 2 H) 3.57 - 3.71 (m, 1 H) 3.71 - 3.83 (m, 1 H) 3.98 - 4.05 (m, 0.5 H) 4.07 - 4.16 (m, 1 H) 4.16 - 4.25 (m, 0.5 H) 4.63 (s, 1 H) 4.76 (br. s., 1 H) 5.28 (d, *J*=4.88 Hz, 1 H) 7.19 (m, *J*=8.24 Hz, 2 H) 7.92 (m, *J*=8.24 Hz, 2 H).

Example 64

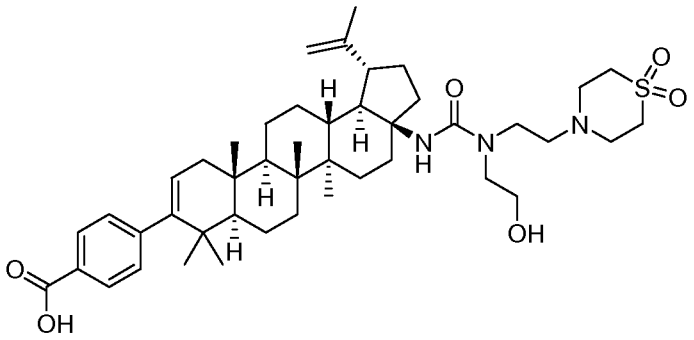
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(6-hydroxy-1,4-diazepane-1-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the general procedures described above for the C-17 urea formation and subsequent ester hydrolysis using 1,4-diazepan-6-ol dihydrobromide as the reactant amine. The product was isolated as a mixture of two diastereomers after reverse phase preparative HPLC purification as a white solid (30 mg, 35% yield) mono-TFA salt. LCMS: m/z 672 ($M+H^+$), retention time 2.42 min (method 11). This material is a diastereomeric mixture in a ratio of approximately 1:1. ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.89 - 0.96 (m, 6 H) 0.97 - 1.05 (m, 6 H) 1.05 - 1.17 (m, 5 H) 1.22 - 1.42 (m, 6 H) 1.42 - 1.60 (m, 7 H) 1.64 - 1.80 (m, 7 H) 1.82 - 2.02 (m, 2 H) 2.12 (dd, *J*=17.09, 6.10 Hz, 1 H) 2.49 - 2.65 (m, 2 H) 3.12 - 3.32 (m, 4 H) 3.36 - 3.44 (m, 1 H) 3.45 - 3.53 (m, 1 H) 3.78 (d, *J*=15.56 Hz, 0.5 H) 3.95 (d, *J*=15.56 Hz, 0.5 H) 4.25 - 4.44 (m, 2 H) 4.62 (d, *J*=8.85 Hz, 1 H) 4.71 (br. s., 0.5 H) 4.75 (br. s., 0.5 H) 5.29 (d, *J*=6.10 Hz, 1 H) 5.69 (s, 0.5 H) 5.74 (s, 0.5 H) 7.20 (dd, *J*=8.24, 1.53 Hz, 2 H) 7.92 (d, *J*=7.93 Hz, 2 H).

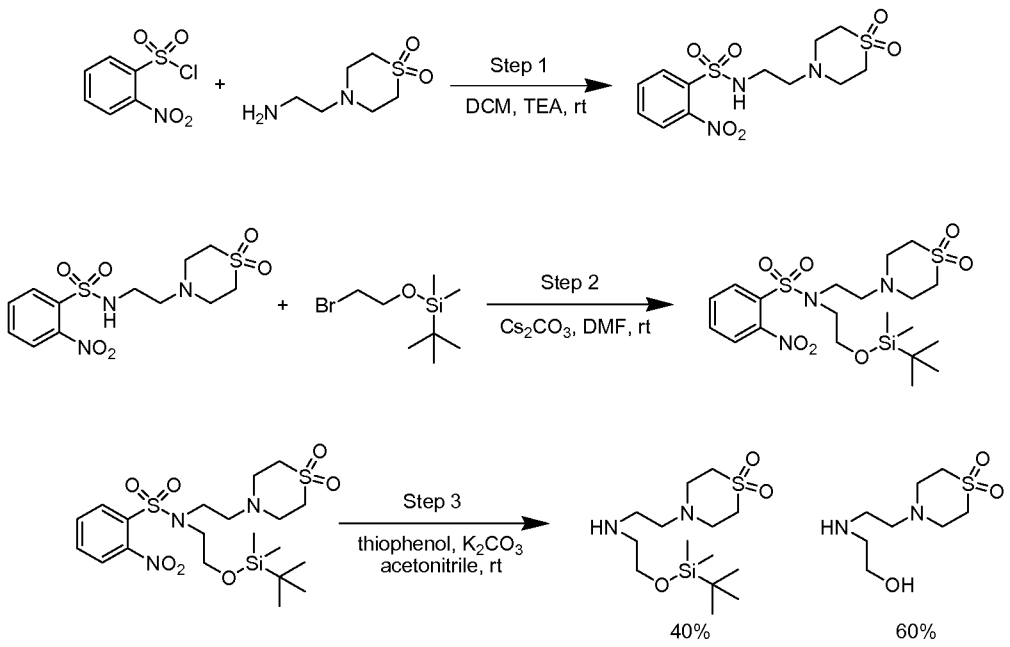
Example 65

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)(2-hydroxyethyl)carbamoyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

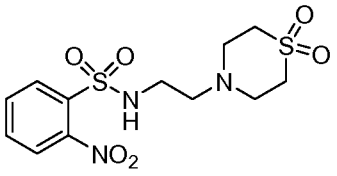


The title compound was prepared following the general procedures described for the C-17 urea formation and subsequent ester hydrolysis using the mixture of 2-((*tert*-butyl(dimethyl)silyl)oxy)-*N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)ethanamine and 2-((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)ethanol acquired in Step 3 below as the reactant amine. The urea formation step gave the desilylated material directly as the major product of the reaction, so no desilylation step was necessary. After ester hydrolysis, the mono-TFA salt product was isolated by reverse phase preparative HPLC purification as a white solid (96 mg, 57% yield). LCMS: m/z 778 ($M+H^+$), retention time 2.43 min (method 11). ^{1}H NMR (400 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (br. s., 3 H) 0.94 (s, 3 H) 1.01 (br. s., 3 H) 1.02 (s, 3 H) 1.06 - 1.16 (m, 5 H) 1.20 - 1.45 (m, 6 H) 1.45 - 1.64 (m, 6 H) 1.64 - 1.79 (m, 6 H) 1.81 - 2.00 (m, 2 H) 2.12 (dd, *J*=17.07, 6.27 Hz, 1 H) 2.38 (dd, *J*=11.80, 8.03 Hz, 1 H) 2.48 - 2.63 (m, 2 H) 3.16 (br. s., 2 H) 3.30 (br. s., 1 H) 3.37 (br. s., 4 H) 3.43 - 3.58 (m, 3 H) 3.60 (br. s., 4 H) 3.76 (br. s., 2 H) 4.61 (d, *J*=1.51 Hz, 1 H) 4.73 (d, *J*=1.25 Hz, 1 H) 5.29 (d, *J*=4.77 Hz, 1 H) 7.20 (m, *J*=8.28 Hz, 2 H) 7.92 (m, *J*=8.28 Hz, 2 H).

Synthesis of amine used in preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)(2-hydroxyethyl)carbamoyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid:



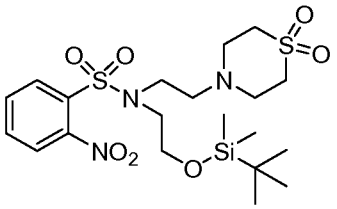
Step 1. Preparation of *N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-2-nitrobenzenesulfonamide.



A mixture of 4-(2-aminoethyl)thiomorpholine 1,1-dioxide (2.00 g, 11.2 mmol) and triethylamine (1.42 g, 14.0 mmol) in DCM (100 mL) was cooled in an ice bath and treated slowly with 2-nitrobenzene-1-sulfonyl chloride (2.49 g, 11.2 mmol). The mixture was removed from the ice bath and stirred at rt for 18 h. The resulting mixture was washed with water (2 x 50 mL) and the combined aqueous washes were

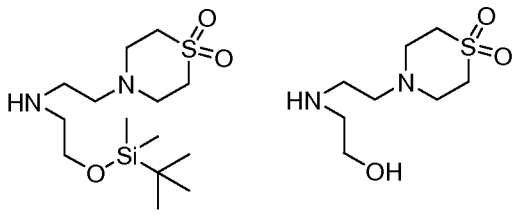
extracted with DCM (50 mL). The organic phases were combined, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to a yellow solid. Purification by silica gel chromatography (linear gradient 100% DCM to 100:1 DCM:MeOH) gave the title compound as a pale yellow solid (3.47 g, 85% yield). LCMS: m/z 364 ($M+H^+$), retention time 0.98 min (method 11). ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 2.71 (t, *J*=5.49 Hz, 2 H) 2.96 (br. s., 4 H) 3.05 (br. s., 4 H) 3.20 (q, *J*=5.49 Hz, 2 H) 5.93 (br. s., 1 H) 7.73 - 7.84 (m, 2 H) 7.84 - 7.93 (m, 1 H) 8.11 - 8.23 (m, 1 H).

Step 2. Preparation of *N*-(2-((*tert*-butyl(dimethyl)silyl)oxy)ethyl)-*N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-2-nitrobenzenesulfonamide.



N-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-2-nitrobenzenesulfonamide (0.400 g, 1.10 mmol) was combined with cesium carbonate (0.538 g, 1.65 mmol) in DMF (5 mL). The slurry was stirred at rt for 30 min, then to it was added (2-bromoethoxy)(*tert*-butyl)dimethylsilane (0.527 g, 2.20 mmol). The resulting mixture was stirred at rt for 18 h. Dilution with ethyl acetate (60 mL) and water (40 mL) followed by shaking gave a separation of phases. The organic phase was isolated, washed with water (2 x 30 mL) and brine (25 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to a residue. Purification by silica gel chromatography (gradient 100% DCM to 100:1 DCM:MeOH) gave the title compound as a yellow solid (0.560 g, 98% yield). LCMS: m/z 522 ($M+H^+$), retention time 2.22 min (method 11). ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 0.01 (s, 6 H) 0.86 (s, 9 H) 2.75 (t, *J*=5.95 Hz, 2 H) 3.05 (s, 8 H) 3.44 (t, *J*=5.49 Hz, 2 H) 3.57 (t, *J*=6.41 Hz, 2 H) 3.70 (t, *J*=5.49 Hz, 2 H) 7.63 - 7.78 (m, 3 H) 8.02 - 8.11 (m, 1 H).

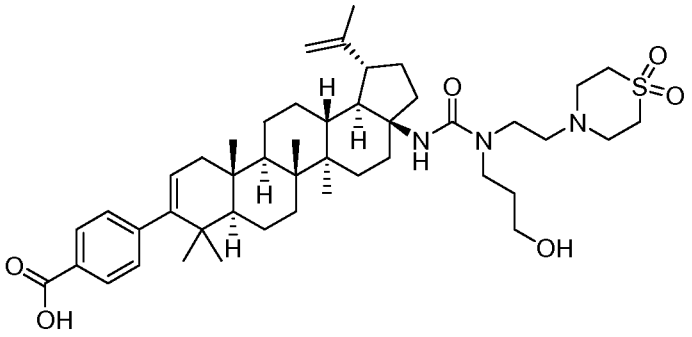
Step 3. Preparation of a mixture of 2-((*tert*-butyl(dimethyl)silyl)oxy)-*N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)ethanamine and 2-((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)ethanol



N-(2-((*tert*-butyl(dimethyl)silyl)oxy)ethyl)-*N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-2-nitrobenzenesulfonamide (0.550 g, 1.05 mmol) and thiophenol (0.348 g, 3.16 mmol) were combined in dry acetonitrile (10 mL). Potassium carbonate (0.583 g, 4.22 mmol) was added and the mixture was stirred at rt for 18 h. The mixture was diluted with ethyl acetate and filtered to remove unwanted solids. The crude filtrate was concentrated in vacuo, redissolved in methanol, and loaded onto a strong cation exchange resin cartridge to capture the desired product. Undesired materials were eluted from the cartridge with methanol, and then the desired material was released from the resin by elution with 2M ammonia in methanol. Concentration in vacuo gave a yellow oil (0.300 g, 85% yield). ^{1}H NMR revealed that the material collected was a roughly 2:3 mixture of desired product and desilylated desired material. No further purification was performed and the mixture was carried forward to the next step.

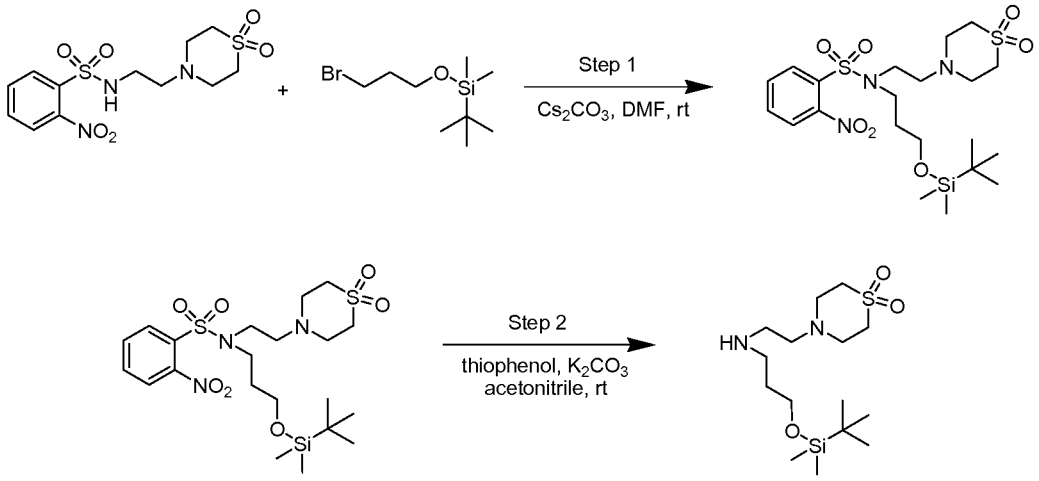
Example 66

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)(3-hydroxypropyl)carbamoyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

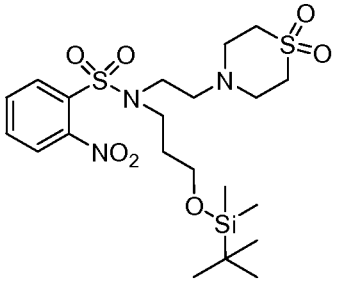


The title compound was prepared following the general procedures described for the C-17 urea formation and subsequent ester hydrolysis using 3-((*tert*-butyl(dimethyl)silyl)oxy)-*N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-1-propanamine as the reactant amine (prepared as described below). The urea formation step gave the desilylated material directly as the major product of the reaction, so no desilylation step was necessary. After ester hydrolysis, the mono-TFA salt product was isolated by reverse phase preparative HPLC purification as a white solid (86 mg, 53% yield). LCMS: m/z 792 ($M+H^+$), retention time 2.45 min (method 11). ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.93 (br. s., 3 H) 0.94 (br. s., 3 H) 1.00 (s, 3 H) 1.02 (s, 3 H) 1.07 - 1.17 (m, 5 H) 1.25 (d, *J*=7.02 Hz, 1 H) 1.28 - 1.45 (m, 5 H) 1.45 - 1.65 (m, 7 H) 1.65 - 1.75 (m, 6 H) 1.75 - 1.85 (m, 2 H) 1.85 - 1.99 (m, 2 H) 2.12 (dd, *J*=17.09, 6.41 Hz, 1 H) 2.41 (dd, *J*=12.05, 8.09 Hz, 1 H) 2.58 (d, *J*=13.43 Hz, 1 H) 2.66 (td, *J*=10.91, 4.73 Hz, 1 H) 3.09 (br. s., 2 H) 3.39 - 3.52 (m, 2 H) 3.54 (br. s., 4 H) 3.55 - 3.63 (m, 2 H) 3.67 (ddd, *J*=10.76, 5.26, 5.04 Hz, 1 H) 4.62 (s, 1 H) 4.75 (s, 1 H) 5.29 (d, *J*=4.58 Hz, 1 H) 7.20 (m, *J*=8.24 Hz, 2 H) 7.92 (m, *J*=8.24 Hz, 2 H).

Synthesis of amine used in preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)(3-hydroxypropyl)carbamoyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid:



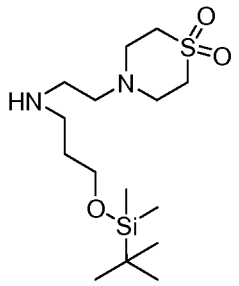
Step 1. Preparation of *N*-(3-((*tert*-butyl(dimethyl)silyl)oxy)propyl)-*N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-2-nitrobenzenesulfonamide.



N-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-2-nitrobenzenesulfonamide (0.400 g, 1.10 mmol) was combined with cesium carbonate (0.538 g, 1.65 mmol) in DMF (5 mL). The slurry was stirred at rt for 30 min, then to it was added (3-bromopropoxy)(*tert*-butyl)dimethylsilane (0.558 g, 2.20 mmol). The resulting mixture was stirred at rt for 18 h. LCMS indicated incomplete conversion, so additional (3-bromopropoxy)(*tert*-butyl)dimethylsilane (0.558 g, 2.20 mmol) and cesium carbonate (0.538 g, 1.65 mmol) were added and the mixture was heated to 70 °C for 1 h. Dilution with ethyl acetate (60 mL) and water (40 mL) followed by shaking gave a separation of phases. The organic phase was isolated, washed with water (2 x 30 mL) and brine (25 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to a residue. Purification by silica gel chromatography (gradient 100% DCM to 100:1 DCM:MeOH) gave the title compound as a sticky yellow material, partially crystalline (0.548 g, 93% yield). LCMS: m/z 536 ($M+H^+$), retention time 2.26 min (method 11). ^1H NMR (400 MHz,

CHLOROFORM-*d*) δ ppm 0.02 (s, 6 H) 0.87 (s, 9 H) 1.63 - 1.75 (m, 2 H) 2.72 (t, *J*=6.40 Hz, 2 H) 3.07 (s, 8 H) 3.32 - 3.40 (m, 2 H) 3.47 (t, *J*=6.40 Hz, 2 H) 3.56 (t, *J*=5.90 Hz, 2 H) 7.63 - 7.76 (m, 3 H) 8.08 (dd, *J*=7.53, 1.76 Hz, 1 H).

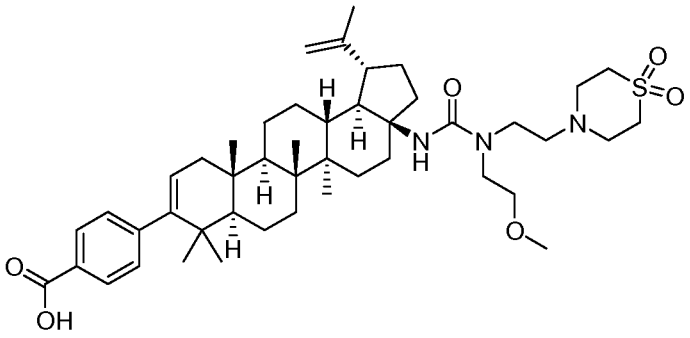
Step 2. Preparation of 3-((*tert*-butyl(dimethyl)silyl)oxy)-*N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-1-propanamine.



N-(3-((*tert*-butyl(dimethyl)silyl)oxy)propyl)-*N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-2-nitrobenzenesulfonamide (0.540 g, 1.01 mmol) and thiophenol (0.333 g, 3.02 mmol) were combined in dry acetonitrile (10 mL). Potassium carbonate (0.557 g, 4.03 mmol) was added and the mixture was stirred at rt for 18 h. The mixture was diluted with ethyl acetate and filtered to remove unwanted solids. The crude filtrate was concentrated in vacuo, redissolved in methanol, and loaded onto a strong cation exchange resin cartridge to capture the desired product. Undesired materials were eluted from the cartridge with methanol, and then the desired material was released from the resin by elution with 2M ammonia in methanol. Concentration in vacuo gave the title compound as a yellow oil (0.294 g, 83% yield). No further purification was performed and the mixture was carried forward to the next step. LCMS: m/z 351 ($M+H^+$), ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.06 (s, 6 H) 0.90 (s, 9 H) 1.75 (quin, *J*=6.46 Hz, 2 H) 2.69 - 2.72 (m, 2 H) 2.72 - 2.80 (m, 4 H) 3.00 - 3.11 (m, 8 H) 3.70 (t, *J*=6.02 Hz, 2 H).

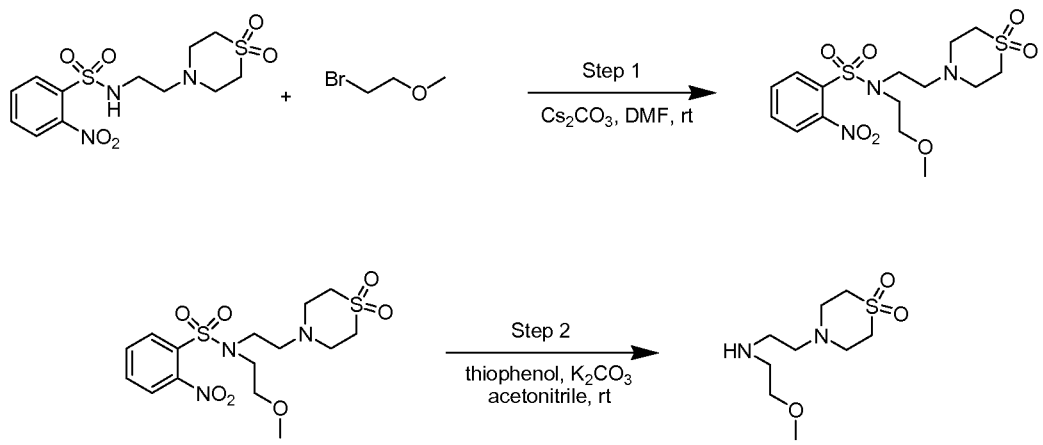
Example 67

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)(2-methoxyethyl)carbamoyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

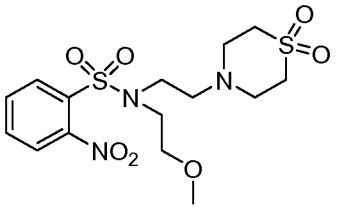


The title compound was prepared following the general procedures described for the C-17 urea formation and subsequent ester hydrolysis using 2-(1,1-dioxido-4-thiomorpholinyl)-*N*-(2-methoxyethyl)ethanamine (prepared as described below) as the reactant amine. After ester hydrolysis, the mono-TFA salt product was isolated by reverse phase preparative HPLC purification as a white solid (89 mg, 57% yield). LCMS: m/z 792 ($M+H^+$), retention time 2.48 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (br. s., 3 H) 0.95 (s, 3 H) 1.01 (s, 3 H) 1.02 (s, 3 H) 1.06 - 1.17 (m, 5 H) 1.24 - 1.29 (m, 1 H) 1.30 - 1.42 (m, 4 H) 1.44 - 1.55 (m, 6 H) 1.55 - 1.65 (m, 2 H) 1.65 - 1.77 (m, 6 H) 1.82 (td, *J*=12.13, 3.20 Hz, 1 H) 1.86 - 1.98 (m, 1 H) 2.13 (dd, *J*=17.09, 6.41 Hz, 1 H) 2.38 (dd, *J*=12.36, 8.09 Hz, 1 H) 2.47 (td, *J*=10.99, 5.19 Hz, 1 H) 2.51 - 2.61 (m, 1 H) 3.03 - 3.19 (m, 2 H) 3.34 - 3.44 (m, 5 H) 3.51 (s, 3 H) 3.52 - 3.69 (m, 8 H) 4.64 (s, 1 H) 4.73 (s, 1 H) 5.29 (d, *J*=4.58 Hz, 1 H) 7.20 (m, *J*=8.24 Hz, 2 H) 7.92 (m, *J*=8.24 Hz, 2 H).

Synthesis of amine used in preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)(2-methoxyethyl)carbamoyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid:



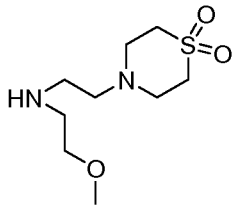
Step 1. Preparation of *N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-*N*-(2-methoxyethyl)-2-nitrobenzenesulfonamide.



N-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-2-nitrobenzenesulfonamide (0.400 g, 1.10 mmol) was combined with cesium carbonate (0.538 g, 1.65 mmol) in DMF (5 mL). The slurry was stirred at rt for 30 min, then to it was added 1-bromo-2-methoxyethane (0.306 g, 2.20 mmol). The resulting mixture was stirred at rt for 72 h. LCMS indicated incomplete conversion, so additional 1-bromo-2-methoxyethane (0.306 g, 2.20 mmol) and cesium carbonate (0.538 g, 1.65 mmol) were added and the mixture was heated to 70°C for 1 h. Dilution with ethyl acetate (60 mL) and water (40 mL) followed by shaking gave a separation of phases. The organic phase was isolated, washed with water (2 x 30 mL) and brine (25 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to a residue. Purification by silica gel chromatography (gradient 100% DCM to 60:1 DCM:MeOH) gave the title compound as a yellow oil (0.486 g, 105% yield). LCMS: m/z 422 ($M+H^+$), retention time 1.35 min (method 11). ^1H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 2.72 (t, *J*=6.41 Hz, 2 H) 3.01 (s, 8 H) 3.21 (s, 3 H) 3.39 - 3.52 (m, 6 H) 7.62 - 7.66 (m, 1 H)

7.66 - 7.74 (m, *J*=7.48, 7.32, 7.32, 7.32, 1.68 Hz, 2 H) 8.01 (dd, *J*=7.78, 1.68 Hz, 1 H).

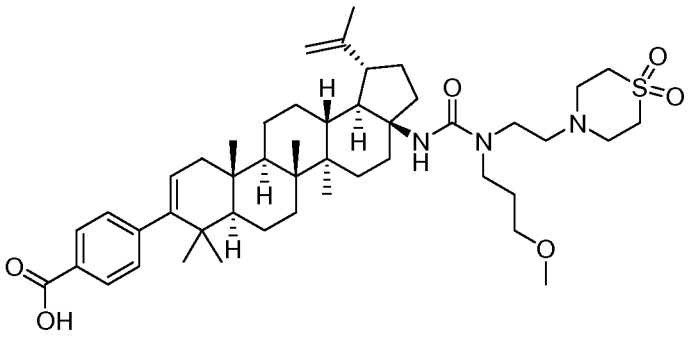
Step 2. Preparation of 2-(1,1-dioxido-4-thiomorpholinyl)-*N*-(2-methoxyethyl)ethanamine.



N-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-*N*-(2-methoxyethyl)-2-nitrobenzenesulfonamide (0.470 g, 1.12 mmol) and thiophenol (0.369 g, 3.35 mmol) were combined in dry acetonitrile (10 mL). Potassium carbonate (0.616 g, 4.46 mmol) was added and the mixture was stirred at rt for 18 h. The mixture was diluted with ethyl acetate and filtered to remove unwanted solids. The crude filtrate was concentrated in vacuo, redissolved in methanol, and loaded onto a strong cation exchange resin cartridge to capture the desired product. Undesired materials were eluted from the cartridge with methanol, and then the desired material was released from the resin by elution with 2M ammonia in methanol. Concentration in vacuo gave the title compound as a yellow solid (0.222 g, 84% yield). No further purification was performed and the mixture was carried forward to the next step. LCMS: m/z 237 ($M+H^+$), ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 2.15 (br. s., 1 H) 2.66 - 2.71 (m, 2 H) 2.71 - 2.77 (m, 2 H) 2.82 (t, *J*=5.04 Hz, 2 H) 2.97 - 3.05 (m, 4 H) 3.05 - 3.10 (m, 4 H) 3.37 (s, 3 H) 3.51 (t, *J*=5.04 Hz, 2 H).

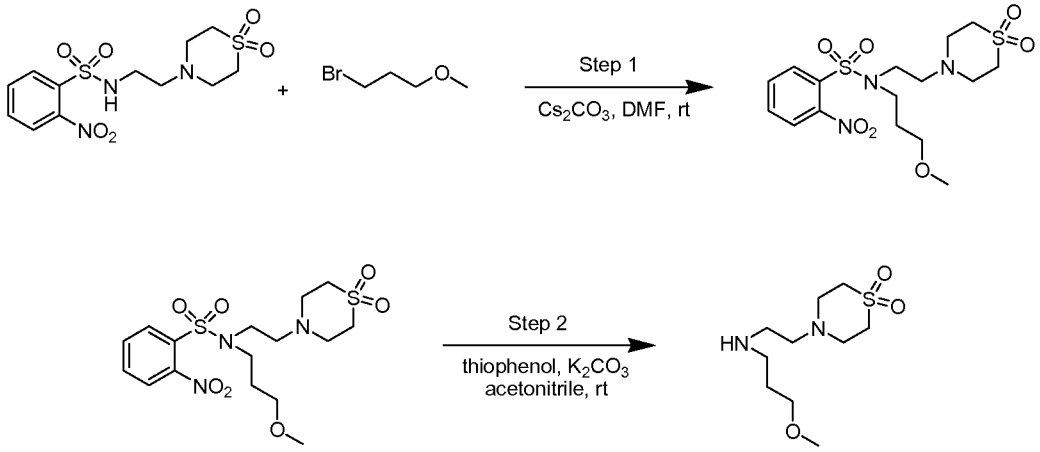
Example 68

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)(3-methoxypropyl)carbamoyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

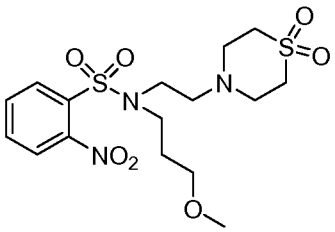


The title compound was prepared following the general procedures described for the C-17 urea formation and subsequent ester hydrolysis using *N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-3-methoxy-1-propanamine (prepared as described below) as the reactant amine. After ester hydrolysis, the mono-TFA salt product was isolated by reverse phase preparative HPLC purification as a white solid (132 mg, 82% yield). LCMS: m/z 806 ($M+H^+$), retention time 2.52 min (method 11). ^1H NMR (400 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (br. s., 3 H) 0.95 (s, 3 H) 1.01 (s, 3 H) 1.03 (s, 3 H) 1.10 (s, 3 H) 1.11 - 1.21 (m, 2 H) 1.21 - 1.42 (m, 5 H) 1.43 - 1.65 (m, 8 H) 1.65 - 1.77 (m, 6 H) 1.77 - 1.98 (m, 5 H) 2.12 (dd, *J*=17.07, 6.27 Hz, 1 H) 2.40 (dd, *J*=12.17, 8.16 Hz, 1 H) 2.55 - 2.67 (m, 2 H) 3.01 (t, *J*=6.15 Hz, 2 H) 3.29 (d, *J*=5.02 Hz, 4 H) 3.34 - 3.42 (m, 1 H) 3.42 - 3.59 (m, 11 H) 4.74 (d, *J*=1.51 Hz, 1 H) 5.24 - 5.34 (m, 1 H) 7.20 (m, *J*=8.28 Hz, 2 H) 7.92 (m, *J*=8.28 Hz, 2 H).

Synthesis of amine used in preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)(3-methoxypropyl)carbamoyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid:

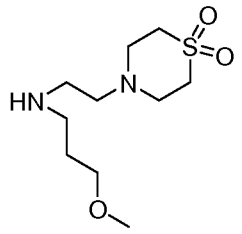


Step 1. Preparation of *N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-*N*-(3-methoxypropyl)-2-nitrobenzenesulfonamide.



N-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-2-nitrobenzenesulfonamide (0.400 g, 1.10 mmol) was combined with cesium carbonate (0.538 g, 1.65 mmol) in DMF (5 mL). The slurry was stirred at rt for 30 min, then to it was added 1-bromo-3-methoxypropane (0.337 g, 2.20 mmol). The resulting mixture was stirred at rt for 72 h. LCMS indicated incomplete conversion, so additional 1-bromo-3-methoxypropane (0.337 g, 2.20 mmol) and cesium carbonate (0.538 g, 1.65 mmol) were added and the mixture was heated to 70 °C for 1 hour. Dilution with ethyl acetate (60 mL) and water (40 mL) followed by shaking gave a separation of phases. The organic phase was isolated, washed with water (2 x 30 mL) and brine (25 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to a residue. Purification by silica gel chromatography (gradient 100% DCM to 60:1 DCM:MeOH) gave the title compound as a yellow oil (0.522 g, 109% yield). LCMS: m/z 436 ($M+H^+$), retention time 1.50 min (method 11). ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 1.68 - 1.77 (m, 2 H) 2.67 (t, *J*=6.26 Hz, 2 H) 3.02 (br. s., 8 H) 3.16 (s, 3 H) 3.27 (t, *J*=5.80 Hz, 2 H) 3.31 - 3.37 (m, 2 H) 3.41 (t, *J*=6.26 Hz, 2 H) 7.61 - 7.65 (m, 1 H) 7.66 - 7.74 (m, 2 H) 7.99 - 8.03 (m, 1 H).

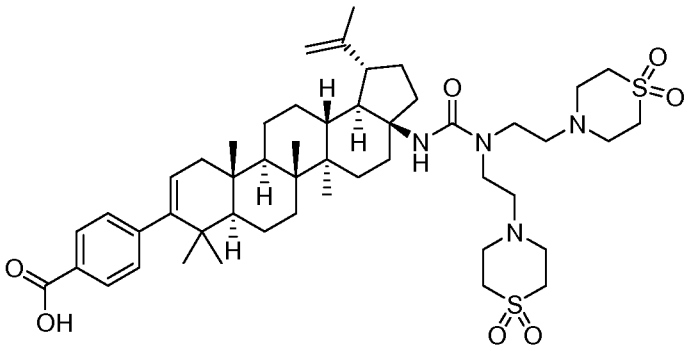
Step 2. Preparation of *N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-3-methoxy-1-propanamine.



N-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-*N*-(3-methoxypropyl)-2-nitrobenzenesulfonamide (0.510 g, 1.17 mmol) and thiophenol (0.387 g, 3.51 mmol) were combined in dry acetonitrile (10 mL). Potassium carbonate (0.647 g, 4.68 mmol) was added and the mixture was stirred at rt for 18 h. The mixture was diluted with ethyl acetate and filtered to remove unwanted solids. The crude filtrate was concentrated in vacuo, redissolved in methanol, and loaded onto a strong cation exchange resin cartridge to capture the desired product. Undesired materials were eluted from the cartridge with methanol, and then the desired material was released from the resin by elution with 2M ammonia in methanol. Concentration in vacuo gave a yellow oil (0.255 g, 87% yield). No further purification was performed and the mixture was carried forward to the next step. LCMS: m/z 251 ($M+H^+$), ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.77 (quin, *J*=6.53 Hz, 2 H) 2.13 (br. s., 2 H) 2.62 - 2.68 (m, 2 H) 2.68 - 2.75 (m, 4 H) 2.93 - 3.11 (m, 8 H) 3.32 (s, 3 H) 3.44 (t, *J*=6.15 Hz, 2 H).

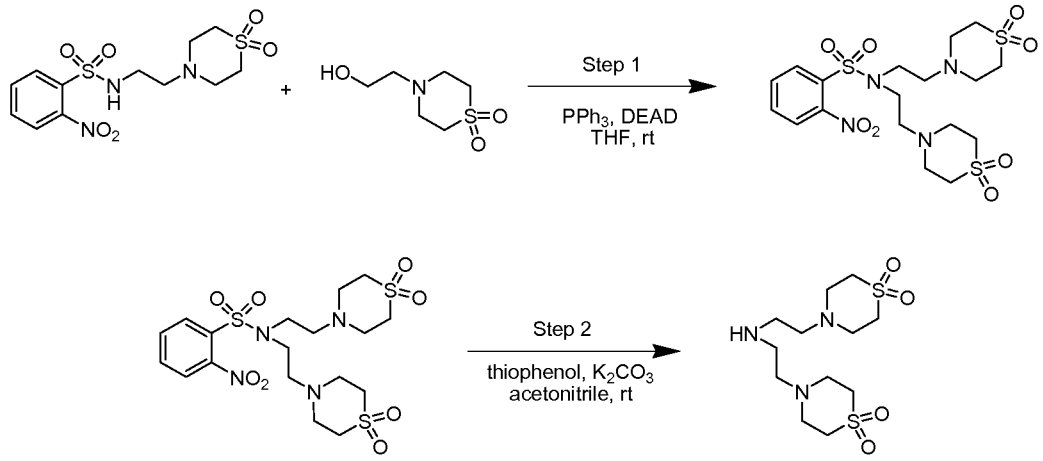
Example 69

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((bis(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)carbamoyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

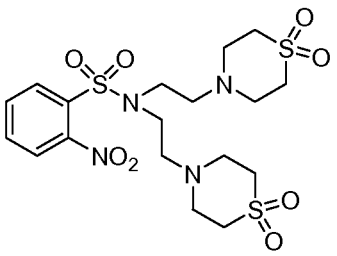


The title compound was prepared following the general procedures described for the C-17 urea formation and subsequent ester hydrolysis using 2-(1,1-dioxido-4-thiomorpholinyl)-N-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)ethanamine (prepared as described below) as the reactant amine. After ester hydrolysis, the bis-TFA salt product was isolated by reverse phase preparative HPLC purification as a slightly yellow solid (109 mg, 64% yield). LCMS: m/z 895 ($M+H^+$), retention time 2.42 min (method 11). ^1H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (br. s., 3 H) 0.95 (br. s., 3 H) 1.01 (s, 3 H) 1.04 (s, 3 H) 1.12 (s, 3 H) 1.13 - 1.22 (m, 2 H) 1.23 - 1.32 (m, 2 H) 1.33 - 1.43 (m, 2 H) 1.43 - 1.63 (m, 8 H) 1.64 - 1.81 (m, 7 H) 1.84 - 1.96 (m, 1 H) 2.13 (dd, *J*=17.24, 6.26 Hz, 1 H) 2.38 (td, *J*=10.61, 5.04 Hz, 1 H) 2.47 (dd, *J*=12.51, 8.24 Hz, 1 H) 2.50 - 2.59 (m, 1 H) 3.01 (br. s., 4 H) 3.26 (br. s., 8 H) 3.35 - 3.50 (m, 10 H) 3.50 - 3.62 (m, 2 H) 4.67 (s, 1 H) 4.80 (s, 1 H) 5.29 (dd, *J*=6.10, 1.53 Hz, 1 H) 7.20 (d, *J*=8.24 Hz, 2 H) 7.92 (d, *J*=8.55 Hz, 2 H).

Synthesis of amine used in preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((bis(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)carbamoyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid:

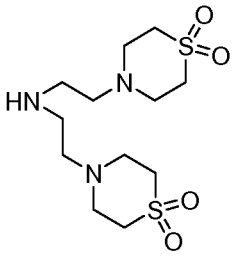


Step 1. Preparation of *N,N*-bis(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-2-nitrobenzenesulfonamide.



N-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-2-nitrobenzenesulfonamide (0.500 g, 1.38 mmol) was combined with 4-(2-hydroxyethyl)thiomorpholine 1,1-dioxide (0.296 g, 1.65 mmol) in THF (10 mL). To this mixture was added triphenylphosphine (0.541 g, 2.06 mmol) and diethyl azodicarboxylate (0.359 g, 2.06 mmol). The resulting mixture was stirred at rt for 72 h. The mixture was concentrated in vacuo, then redissolved in acetonitrile. Purification by reverse phase preparative HPLC gave the title compound as a pale yellow solid (0.863 g, 83% yield) bis-TFA salt. LCMS: m/z 525 ($M+H^+$), retention time 1.25 min (method 11). ^{1}H NMR (500 MHz, MeOD) δ ppm 2.85 (t, *J*=6.71 Hz, 4 H) 3.14 (d, *J*=5.49 Hz, 8 H) 3.18 (d, *J*=5.80 Hz, 8 H) 3.51 (t, *J*=6.71 Hz, 4 H) 7.71 - 7.75 (m, 1 H) 7.75 - 7.84 (m, 2 H) 8.05 (d, *J*=7.63 Hz, 1 H).

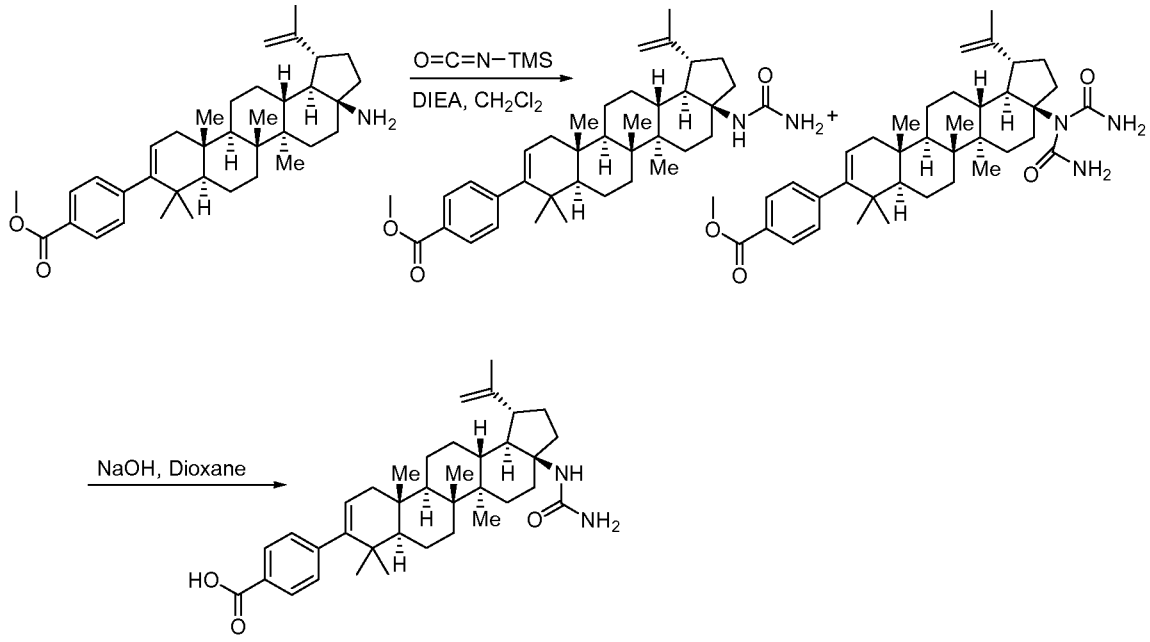
Step 2. Preparation of 2-(1,1-dioxido-4-thiomorpholinyl)-*N*-(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)ethanamine.



N,N-bis(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)-2-nitrobenzenesulfonamide (0.85 g, 1.13 mmol) and thiophenol (0.373 g, 3.39 mmol) were combined in dry acetonitrile (10 mL). Potassium carbonate (0.936 g, 6.78 mmol) was added and the mixture was stirred at rt for 18h. The mixture was diluted with ethyl acetate and filtered to remove unwanted solids. The crude filtrate was concentrated in vacuo, redissolved in methanol, and loaded onto a strong cation exchange resin cartridge to capture the desired product. Undesired materials were eluted from the cartridge with methanol, and then the desired material was released from the resin by elution with 2M ammonia in methanol. Concentration in vacuo gave a sticky yellow oil (0.381 g, 100% yield). No further purification was performed and the mixture was carried forward to the next step.

Example 69-1

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-ureido-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid and 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(1-carbamoylureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



example 69-1

Step 1. To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (50 mg, 0.092 mmol) in DCM (1 mL) was added diisopropylethylamine (0.016 mL, 0.092 mmol) and isocyanatotrimethylsilane (15.89 mg, 0.138 mmol) .The resulting mixture was stirred at rt for 48 hours. LC-MS showed desired product at M+1=587.48 (2.87 min, method 13) and a side product M+1=630.48 (2.97 min, method 13). The volatiles were removed in vacuo. The crude products were obtained as yellow oil and were used in next step as is.

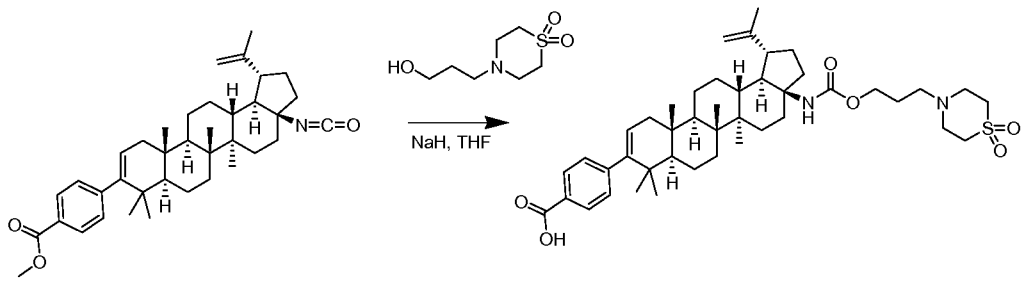
Step 2. 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-ureido-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, step 2. The product was isolated as white solid (15 mg, 28%). **Example 69-1:** LCMS: m/e 573.45 $(M+H)^+$, 2.67 min (method 13). ^{1}H NMR (400MHz, METHANOL-d_4) δ 7.94 (d, *J*=8.5 Hz, 2H), 7.24 (d, *J*=8.5

Hz, 2H), 5.32 (dd, *J*=6.1, 1.6 Hz, 1H), 4.78 (d, *J*=1.8 Hz, 1H), 4.67 - 4.63 (m, 1H), 2.69 - 2.59 (m, 2H), 2.40 (dd, *J*=12.2, 8.2 Hz, 1H), 2.17 (dd, *J*=17.2, 6.4 Hz, 1H), 2.04 - 1.84 (m, 2H), 1.74 (s, 3H), 1.82 - 1.67 (m, 3H), 1.63 - 1.48 (m, 6H), 1.46 - 1.26 (m, 6H), 1.16 (s, 3H), 1.22 - 1.08 (m, 2H), 1.06 (s, 3H), 1.06 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H).

Section 2. Carbamates

Example 70

Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[[3-(1,1-dioxido-4-thiomorpholinyl)propoxy]carbonyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl].

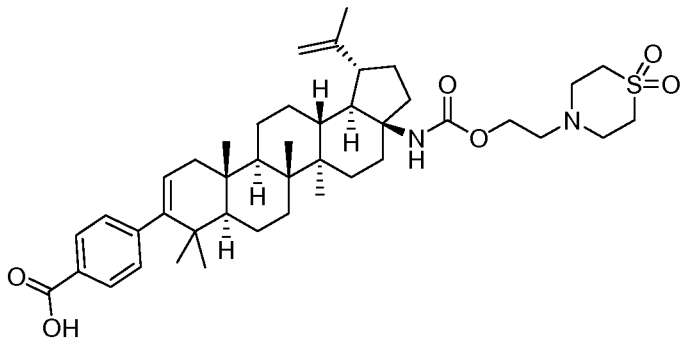


To a cloudy solution of 4-(3-hydroxypropyl)thiomorpholine 1,1-dioxide (407 mg, 2.106 mmol) in tetrahydrofuran (5 mL) was added sodium hydride (84 mg, 2.106 mmol). The resulting white slurry was stirred at rt. After 40 min, the resulting paste was diluted with tetrahydrofuran (5 mL) and was treated with methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (200 mg, 0.351 mmol) in one portion. The resulting white slurry was stirred at rt overnight. After 16 h, the reaction was poured into 0.1N HCl (20 mL) and extracted with 2 x 50 mL EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to give a white foam product. The crude material was dissolved in 2

mL THF, filtered and purified by reverse phase preparative HPLC using HPLC method 1 to give the mono-TFA salt of the title compound (123.1 mg, 0.143 mmol, 40.6% yield) as white solid. LCMS: m/e 749.5 $(M+H)^+$, 2.10 min (method 6). ^1H NMR (500MHz , 1:1 *MeOD:CDCl$_3$*) δ = 7.92 (d, *J* = 8.5 Hz, 2 H), 7.20 (d, *J* = 8.5 Hz, 2 H), 5.29 (dd, *J* = 1.8, 6.1 Hz, 1 H), 4.75 (d, *J* = 1.5 Hz, 1 H), 4.63 (d, *J* = 1.2 Hz, 1 H), 4.09 (t, *J* = 5.8 Hz, 2 H), 3.42 (br. s., 3 H), 2.98 (t, *J* = 7.0 Hz, 2 H), 2.57 (dt, *J* = 5.3, 10.9 Hz, 1 H), 2.51 (d, *J* = 12.8 Hz, 1 H), 2.35 - 2.28 (m, 1 H), 2.12 (dd, *J* = 6.4, 17.1 Hz, 1 H), 2.02 - 1.88 (m, 3 H), 1.82 - 1.65 (m, 7 H), 1.65 - 1.45 (m, 6 H), 1.45 - 1.19 (m, 6 H), 1.15 - 1.10 (m, 2 H), 1.09 (s, 3 H), 1.02 (s, 3 H), 1.01 (s, 3 H), 0.95 (s, 3 H), 0.94 (s, 3 H). ^{13}C NMR (*1:1 MeOD:CDCl$_3$*) δ ppm 15.2, 16.5, 17.2, 19.9, 20.7, 21.8, 22.3, 26.2, 26.5, 28.2, 29.9, 30.2, 30.5, 34.5, 37.2, 38.4, 38.6, 41.6, 42.7, 43.0, 48.2, 50.1, 50.5, 50.6, 51.9, 53.9, 54.6, 62.4, 64.9, 78.8, 111.0, 124.9, 129.3, 129.7, 131.0, 147.4, 149.8, 150.4, 156.3, 170.1.

Example 71

Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[[2-(1,1-dioxido-4-thiomorpholinyl)ethoxy]carbonyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl].

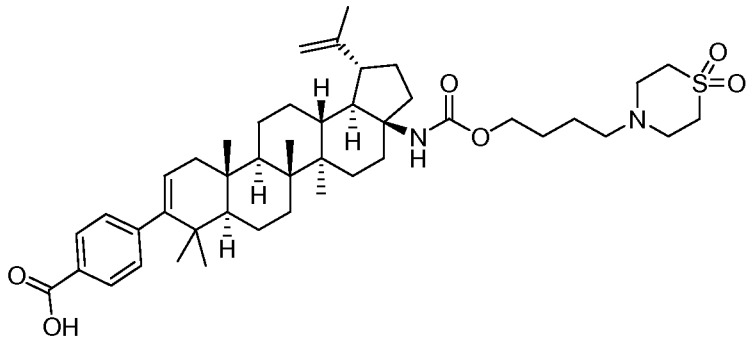


The title compound was prepared in 24% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[[3-(1,1-dioxido-4-

thiomorpholinyl)propoxy]carbonyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl], except 4-(2-hydroxyethyl)thiomorpholine 1,1-dioxide was used instead of 4-(3-hydroxypropyl)thiomorpholine 1,1-dioxide. LCMS: m/e 735.3 $(M+H)^+$, 2.63 min (method 6). ^{1}H NMR (500MHz , *METHANOL-d4*) δ = 7.95 (d, *J* = 8.5 Hz, 2 H), 7.25 (d, *J* = 8.5 Hz, 2 H), 5.33 (dd, *J* = 1.7, 6.3 Hz, 1 H), 4.79 (d, *J* = 1.8 Hz, 1 H), 4.66 (s, 1 H), 4.38 - 4.28 (m, 1 H), 4.27 - 4.19 (m, 1 H), 3.56 - 3.43 (m, 3 H), 3.31 (br. s., 2 H), 3.17 (br. s., 2 H), 2.71 (dt, *J* = 5.3, 11.1 Hz, 1 H), 2.57 (d, *J* = 13.4 Hz, 1 H), 2.33 (dd, *J* = 8.4, 12.1 Hz, 1 H), 2.18 (dd, *J* = 6.4, 17.1 Hz, 1 H), 2.00 - 1.89 (m, 2 H), 1.84 - 1.76 (m, 2 H), 1.75 (s, 3 H), 1.73 (d, *J* = 4.3 Hz, 1 H), 1.71 - 1.64 (m, 1 H), 1.62 - 1.56 (m, 2 H), 1.56 - 1.48 (m, 4 H), 1.47 - 1.35 (m, 4 H), 1.31 (dt, *J* = 4.0, 9.3 Hz, 2 H), 1.15 (s, 3 H), 1.12 (d, *J* = 3.1 Hz, 1 H), 1.07 (s, 6 H), 0.99 (s, 3 H), 0.97 (s, 3 H).

Example 72

Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[[4-(1,1-dioxido-4-thiomorpholinyl)butoxy]carbonyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl].



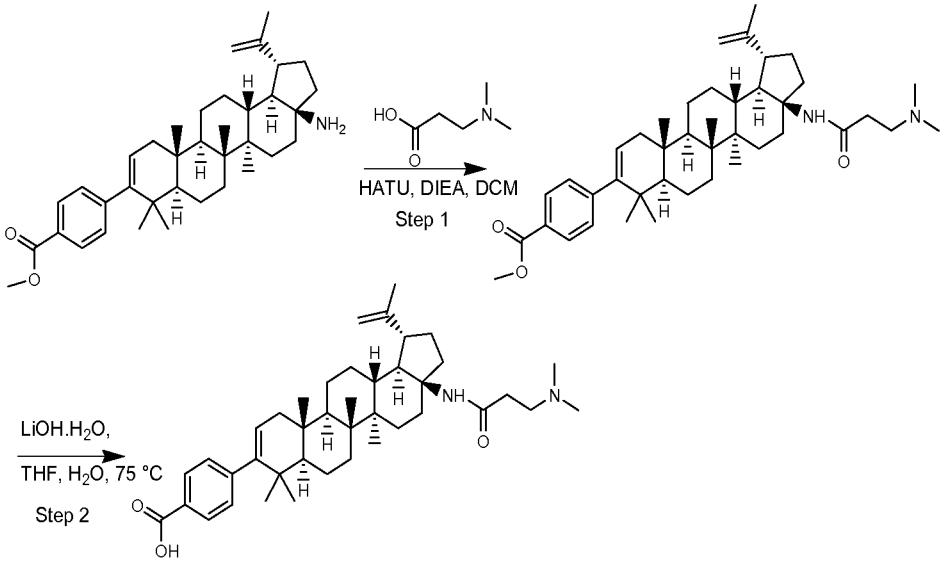
The title compound was prepared in 55% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[[3-(1,1-dioxido-4-

thiomorpholinyl)propoxy]carbonyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl], except 4-(4-hydroxybutyl)thiomorpholine 1,1-dioxide was used instead of 4-(3-hydroxypropyl)thiomorpholine 1,1-dioxide. LCMS: m/e 763.5 $(M+H)^+$, 2.14 min (method 6). ^{1}H NMR (500MHz , *METHANOL-d4*) δ = 7.95 (d, *J* = 8.2 Hz, 2 H), 7.24 (d, *J* = 8.2 Hz, 2 H), 5.32 (dd, *J* = 1.5, 6.1 Hz, 1 H), 4.78 (d, *J* = 1.5 Hz, 1 H), 4.65 (s, 1 H), 4.14 - 4.04 (m, 2 H), 3.87 - 3.79 (m, 4 H), 3.62 - 3.51 (m, 4 H), 2.69 (dt, *J* = 5.0, 11.1 Hz, 1 H), 2.56 (d, *J* = 13.4 Hz, 1 H), 2.32 (dd, *J* = 8.9, 11.3 Hz, 1 H), 2.18 (dd, *J* = 6.3, 17.2 Hz, 1 H), 2.00 - 1.91 (m, 2 H), 1.91 - 1.82 (m, 2 H), 1.82 - 1.75 (m, 3 H), 1.74 (s, 4 H), 1.70 - 1.56 (m, 3 H), 1.51 (d, *J* = 11.0 Hz, 4 H), 1.46 - 1.34 (m, 4 H), 1.33 - 1.26 (m, 2 H), 1.14 (s, 3 H), 1.13 - 1.09 (m, 2 H), 1.08 - 1.06 (m, 3 H), 1.06 (s, 3 H), 0.99 (s, 3 H), 0.97 (s, 3 H).

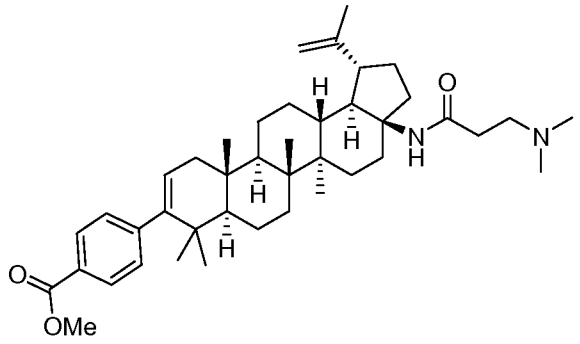
Section 3. Amides

Example 73

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



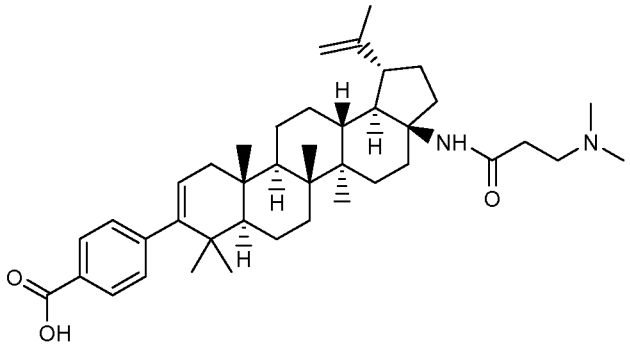
Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.



To a cloudy solution mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.240 g, 0.441 mmol) in THF (5 mL) was added *N,N*-diisopropylethylamine (0.461 mL, 2.65 mmol), 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (0.369 g, 0.971 mmol) and 3-(dimethylamino)propionic acid hydrochloride (0.136 g, 0.883 mmol). The reaction mixture was stirred at rt. After 16 h, the reaction mixture was diluted with EtOAc (50 mL), washed with 1N HCl (5 mL), 5% $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated to a viscous oil product. The crude material was dissolved in THF (1 mL) and MeOH (1.5 mL), filtered and purified by reverse phase preparative HPLC using HPLC method 4 to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate, TFA (93.8 mg, 0.116 mmol, 26.4% yield) as a white solid. LCMS: m/e 643.3 $(M+H)^+$, 4.17 min (method 8). ^1H NMR (500MHz , 1:1 *MeOD:CDCl*$_3$) δ = 7.97 - 7.85 (m, 2 H), 7.29 - 7.23 (m, 2 H), 7.21 (br. s., 1 H), 5.32 (d, J = 4.0 Hz, 1 H), 4.80 (br. s., 1 H), 4.67 (br. s., 1 H), 3.97 - 3.88 (m, 3 H), 3.43 - 3.37 (m, 2 H), 2.92 (br. s., 6 H), 2.84 - 2.77 (m, 2 H), 2.77 - 2.68 (m, 2 H), 2.46 - 2.38 (m, 1 H), 2.22 - 2.13 (m, 1 H), 2.05 - 1.88 (m, 2 H), 1.83 (d, J = 13.4 Hz, 1 H),

1.75 (br. s., 5 H), 1.66 - 1.49 (m, 7 H), 1.48 - 1.34 (m, 4 H), 1.32 (br. s., 1 H), 1.16 (br. s., 4 H), 1.07 (br. s., 6 H), 0.98 (br. s., 3 H), 0.96 (br. s., 3 H). ^{13}C NMR (1:1 *MeOD:CDCl$_3$*) δ ppm 13.8, 15.4, 16.0, 18.4, 19.9, 20.6, 21.4, 25.6, 27.5, 28.7, 29.0, 29.5, 29.7, 33.8, 34.8, 36.4, 37.5, 37.5, 40.8, 41.8, 42.1, 47.0, 49.5, 49.8, 51.5, 53.3, 54.5, 65.8, 102.7, 109.7, 124.3, 128.2, 128.5, 130.3, 146.7, 149.2, 150.1, 167.6, 170.3.

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

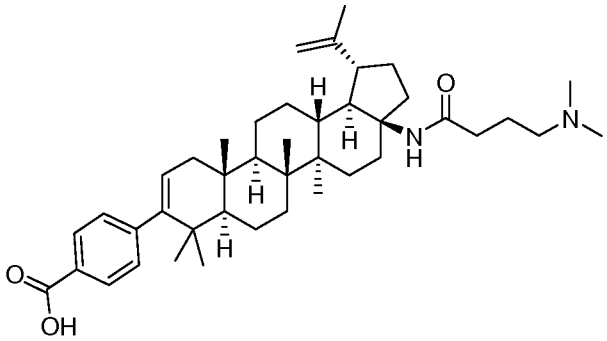


To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate, TFA (87.9 mg, 0.116 mmol) in THF (5 mL) was added a solution of lithium hydroxide monohydrate (19.49 mg, 0.464 mmol) in water (1.00 mL). The reaction was stirred at 75 °C. After 8 h, the reaction was concentrated to dryness. The crude material was dissolved in THF (1 mL) and MeOH (1.5 mL), filtered and purified by reverse phase preparative HPLC using HPLC method 1 to give the title compound (59.5 mg, 0.078 mmol, 67.6% yield) as a white solid. LCMS: m/e 629.4 $(M+H)^+$, 4.17 min (method 8). ^{1}H NMR (500MHz , *METHANOL-d$_4$*) δ = 7.95 (d, *J* = 8.2 Hz, 2 H), 7.24 (d, *J* = 8.2 Hz, 3 H), 5.33 (dd, *J* = 1.5, 6.1 Hz, 1 H), 4.80 (d, *J* = 1.5 Hz, 1 H), 4.67 (s, 1 H), 3.40 (t, *J* = 6.6 Hz, 2 H), 2.92 (s, 6 H), 2.88 - 2.69 (m, 4 H), 2.42 (dd, *J* = 8.4, 12.4 Hz, 1 H), 2.18 (dd, *J* = 6.4, 17.1 Hz, 1 H), 2.05 - 1.89 (m, 2 H), 1.83 (d, *J* = 11.3 Hz, 1 H), 1.79 - 1.76 (m, 1 H), 1.75 (s, 3 H), 1.74 - 1.71 (m, 1 H), 1.66 - 1.56 (m, 3 H), 1.56 - 1.49 (m, 4 H), 1.47 - 1.28 (m, 5 H), 1.22 -

1.17 (m, 1 H), 1.16 (s, 3 H), 1.15 - 1.10 (m, 1 H), 1.07 (s, 6 H), 0.99 (s, 3 H), 0.97 (s, 3 H). ^{13}C NMR (*MeOD*) δ ppm 14.5, 16.1, 16.8, 19.1, 20.6, 21.3, 22.1, 26.2, 28.2, 29.4, 29.7, 30.4, 34.5, 35.5, 37.1, 38.1, 38.2, 41.5, 42.5, 42.8, 43.2, 47.6, 49.3, 50.1, 50.5, 54.0, 55.1, 66.4, 110.4, 124.9, 129.5, 130.9, 147.4, 149.6, 150.8, 169.6, 171.0.

Example 74

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-(dimethylamino)butanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

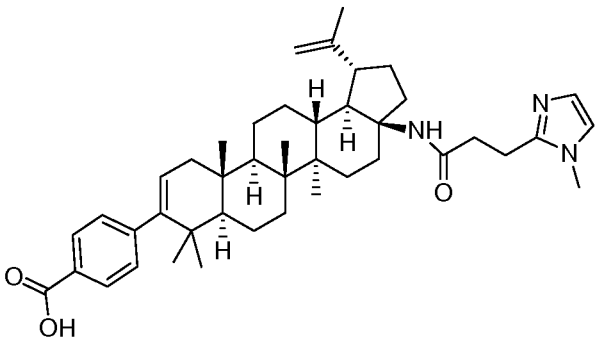


The title compound was prepared in 26% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 4-(dimethylamino)butyric acid hydrochloride was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 643.4 $(M+H)^+$, 4.19 min (method 8). ^{1}H NMR (500MHz , *METHANOL-d$_4$*) δ = 7.95 (d, *J* = 8.2 Hz, 2 H), 7.24 (d, *J* = 8.5 Hz, 2 H), 5.33 (dd, *J* = 1.7, 6.3 Hz, 1 H), 4.80 (d, *J* = 1.5 Hz, 1 H), 4.67 (s, 1 H), 3.21 - 3.14 (m, 2 H), 2.93 (s, 6 H), 2.82 - 2.67 (m, 2 H), 2.49 (t, *J* = 6.9 Hz, 2 H), 2.41 (dd, *J* = 8.2, 12.2 Hz, 1 H), 2.18 (dd, *J* = 6.4, 17.1 Hz, 1 H), 2.06 - 1.96 (m, 3 H), 1.96 - 1.86 (m, 1 H), 1.85 - 1.79 (m, 1 H), 1.77 (br. s., 1 H), 1.75 (s, 3 H), 1.73 - 1.69 (m, 1 H), 1.64 - 1.56 (m, 3 H),

1.55 - 1.48 (m, 4 H), 1.47 - 1.38 (m, 3 H), 1.35 (d, *J* = 12.2 Hz, 1 H), 1.33 - 1.27 (m, 1 H), 1.21 - 1.17 (m, 1 H), 1.15 (s, 3 H), 1.12 (d, *J* = 3.4 Hz, 1 H), 1.07 (s, 6 H), 0.99 (s, 3 H), 0.97 (s, 3 H).

Example 75

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(1-methyl-1H-imidazol-2-yl)propanamido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

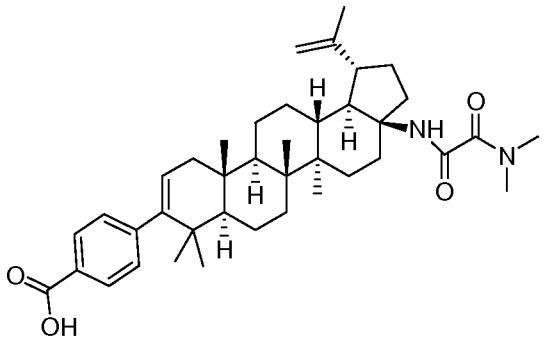


The title compound was prepared in 29% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 3-(1-methyl-1H-imidazol-2-yl)propanoic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 666.4 $(M+H)^+$, 4.15 min (method 8). ^{1}H NMR (500MHz, *METHANOL-d$_4$*) δ = 7.95 (d, *J* = 8.5 Hz, 2 H), 7.53 - 7.46 (m, 2 H), 7.25 (d, *J* = 8.2 Hz, 2 H), 5.33 (dd, *J* = 1.8, 6.1 Hz, 1 H), 4.79 (d, *J* = 1.5 Hz, 1 H), 4.66 (s, 1 H), 3.91 (s, 3 H), 3.30 - 3.18 (m, 2 H), 2.84 - 2.79 (m, 2 H), 2.73 (dt, *J* = 5.2, 11.1 Hz, 1 H), 2.64 (d, *J* = 12.5 Hz, 1 H), 2.35 (dd, *J* = 8.2, 12.2 Hz, 1 H), 2.18 (dd, *J* = 6.4, 17.4 Hz, 1 H), 1.96 (dt, *J* = 3.2, 12.1 Hz, 1 H), 1.91 - 1.78 (m, 2 H), 1.77 (s, 1 H), 1.74 (s, 3 H),

1.71 - 1.66 (m, 1 H), 1.60 (br. s., 2 H), 1.46 - 1.26 (m, 7 H), 1.22 - 1.13 (m, 1 H), 1.11 (s, 3 H), 1.07 (s, 3 H), 1.05 (s, 4 H), 0.99 (s, 3 H), 0.97 (s, 3 H).

Example 76

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoacetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

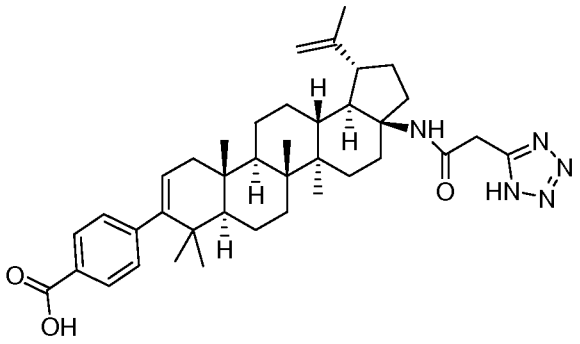


The title compound was prepared in 13% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except *N,N*-dimethyloxamic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 627.6 $(M-H)^-$, 1.91 min (method 5). ^{1}H NMR (500MHz , 2:1 *MeOD:CDCl$_3$*) δ = 7.93 (d, *J* = 8.2 Hz, 2 H), 7.55 (s, 1 H), 7.21 (d, *J* = 8.2 Hz, 2 H), 5.30 (dd, *J* = 1.7, 6.3 Hz, 1 H), 4.77 (d, *J* = 1.2 Hz, 1 H), 4.65 (s, 1 H), 3.22 (s, 3 H), 3.01 (s, 3 H), 2.71 - 2.59 (m, 2 H), 2.46 (dd, *J* = 8.2, 11.9 Hz, 1 H), 2.14 (dd, *J* = 6.3, 17.2 Hz, 1 H), 2.02 - 1.93 (m, 1 H), 1.89 (dt, *J* = 3.4, 12.2 Hz, 1 H), 1.79 (d, *J* = 13.1 Hz, 1 H), 1.75 (d, *J* = 3.7 Hz, 1 H), 1.71 (br. s., 1 H), 1.66 (dt, *J* = 3.5, 13.5 Hz, 1 H), 1.61 - 1.54 (m, 2 H), 1.54 - 1.48 (m, 4 H), 1.46 (br. s., 1 H), 1.45 - 1.40 (m, 3 H), 1.40 - 1.34 (m, 1 H), 1.28

(br. s., 2 H), 1.20 - 1.14 (m, 2 H), 1.13 (s, 3 H), 1.05 (s, 3 H), 1.03 (s, 3 H), 0.96 (s, 3 H), 0.95 (s, 3 H) .

Example 77

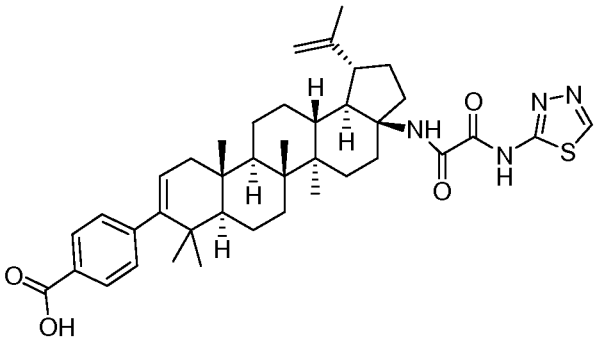
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(1H-tetrazol-5-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared in 8% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except (1H-tetrazol-5-yl)-acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 640.5 $(M+H)^+$, 1.58 min (method 6). ^{1}H NMR (500MHz , *METHANOL-d4*) δ = 7.95 (d, *J* = 8.2 Hz, 2 H), 7.48 (s, 1 H), 7.25 (d, *J* = 8.2 Hz, 2 H), 5.33 (dd, *J* = 1.5, 6.1 Hz, 1 H), 4.82 (d, *J* = 1.8 Hz, 1 H), 4.68 (s, 1 H), 4.12 - 4.00 (m, 2 H), 2.79 (dt, *J* = 5.0, 11.2 Hz, 1 H), 2.72 - 2.62 (m, 1 H), 2.45 - 2.35 (m, 1 H), 2.19 (dd, *J* = 6.4, 17.1 Hz, 1 H), 2.07 - 1.92 (m, 2 H), 1.84 (d, *J* = 11.6 Hz, 1 H), 1.77 (br. s., 1 H), 1.76 (s, 3 H), 1.73 (d, *J* = 7.3 Hz, 1 H), 1.66 - 1.56 (m, 3 H), 1.56 - 1.49 (m, 4 H), 1.48 - 1.27 (m, 6 H), 1.23 - 1.15 (m, 1 H), 1.12 (s, 3 H), 1.08 (s, 3 H), 1.07 (s, 3 H), 1.00 (s, 3 H), 0.97 (s, 3 H).

Example 78

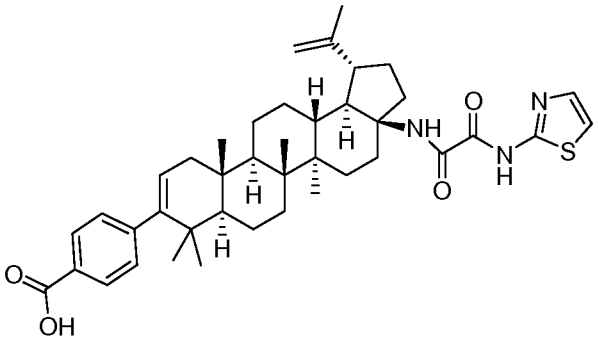
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(1,3,4-thiadiazol-2-ylamino)-2-oxoacetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared in 21% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-(1,3,4-thiadiazol-2-ylamino)-2-oxoacetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 683.6 $(M-H)^-$, 1.77 min (method 9). ^{1}H NMR (500MHz , 2:1 *MeOD:CDCl$_3$*) δ = 9.13 (s, 1 H), 7.92 (d, J = 8.5 Hz, 2 H), 7.45 (s, 1 H), 7.21 (d, J = 8.2 Hz, 2 H), 5.37 - 5.24 (m, 1 H), 4.81 - 4.78 (m, 1 H), 4.67 (s, 1 H), 2.67 - 2.56 (m, 2 H), 2.55 - 2.47 (m, 1 H), 2.15 (dd, J = 6.4, 17.1 Hz, 1 H), 1.99 - 1.90 (m, 1 H), 1.82 (dd, J = 10.5, 16.3 Hz, 3 H), 1.74 (s, 3 H), 1.71 (br. s., 1 H), 1.59 - 1.44 (m, 9 H), 1.44 - 1.39 (m, 1 H), 1.30 - 1.24 (m, 1 H), 1.22 - 1.14 (m, 2 H), 1.10 (s, 3 H), 1.07 (s, 3 H), 1.03 (s, 3 H), 0.95 (s, 3 H), 0.94 (s, 3 H).

Example 79

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-oxo-2-(thiazol-2-ylamino)acetamido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

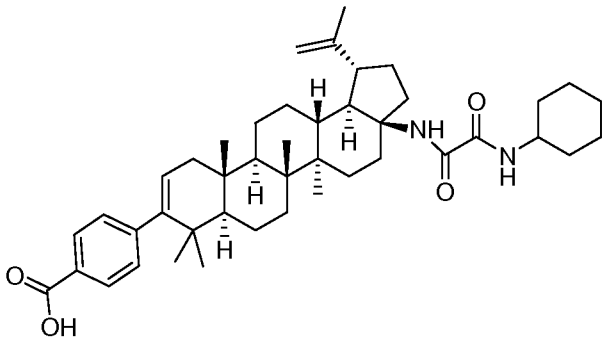


The title compound was prepared in 23% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-oxo-2-(thiazol-2-ylamino)acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 684.5 $(M+H)^+$, 2.04 min (method 9). ^{1}H NMR (500MHz , 1:1 *MeOD:CDCl$_3$*) δ = 7.92 (d, *J* = 8.5 Hz, 2 H), 7.54 (d, *J* = 3.7 Hz, 1 H), 7.49 (s, 1 H), 7.22 - 7.19 (m, 3 H), 5.30 (dd, *J* = 1.8, 6.1 Hz, 1 H), 4.79 (d, *J* = 1.2 Hz, 1 H), 2.65 - 2.55 (m, 2 H), 2.53 - 2.46 (m, 1 H), 2.14 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.98 - 1.89 (m, 1 H), 1.88 - 1.76 (m, 3 H), 1.73 (s, 3 H), 1.70 (s, 1 H), 1.61 - 1.36 (m, 11 H), 1.29 - 1.22 (m, 1 H), 1.21 - 1.14 (m, 2 H), 1.09 (s, 3 H), 1.06 (s, 3 H), 1.02 (s, 3 H), 0.95 - 0.94 (m, 3 H), 0.93 (s, 3 H).

Example 80

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(cyclohexylamino)-2-oxoacetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

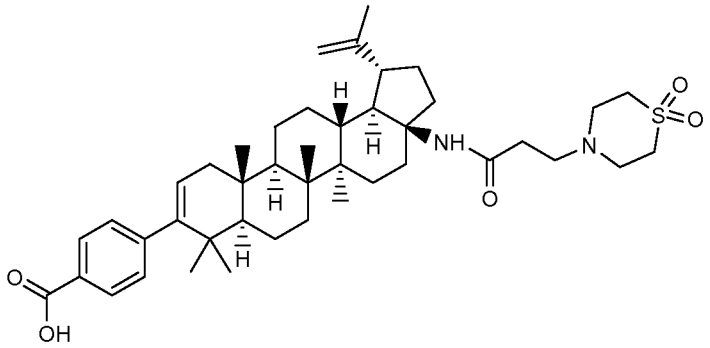
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared in 40% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-(cyclohexylamino)-2-oxoacetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 681.7 $(M-H)^-$, 2.42 min (method 9). ^{1}H NMR (500MHz , *CHLOROFORM-d*) δ = 8.03 (d, *J* = 8.5 Hz, 2 H), 7.61 (s, 1 H), 7.52 (d, *J* = 8.5 Hz, 1 H), 7.25 (d, *J* = 8.2 Hz, 2 H), 6.51 (br. s., 1 H), 5.33 (d, *J* = 4.6 Hz, 1 H), 4.79 (d, *J* = 1.2 Hz, 1 H), 4.67 (s, 1 H), 3.83 - 3.72 (m, 1 H), 2.62 - 2.54 (m, 2 H), 2.50 (dd, *J* = 8.5, 11.6 Hz, 1 H), 2.14 (dd, *J* = 6.3, 17.2 Hz, 1 H), 2.00 - 1.89 (m, 3 H), 1.86 - 1.75 (m, 4 H), 1.71 - 1.62 (m, 2 H), 1.61 - 1.36 (m, 13 H), 1.35 - 1.20 (m, 5 H), 1.18 - 1.11 (m, 2 H), 1.08 (s, 3 H), 1.05 - 1.02 (m, 3 H), 1.00 (s, 3 H), 0.96 (s, 6 H).

Example 81

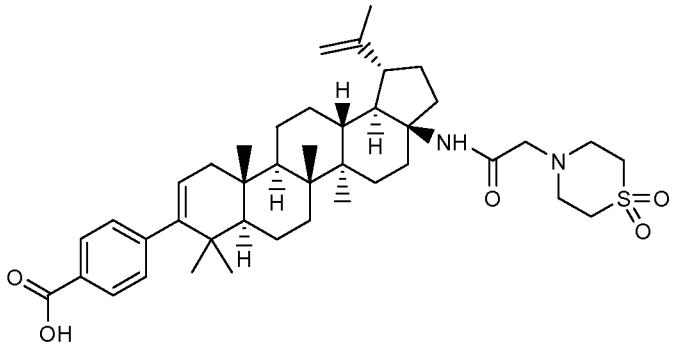
Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-thiomorpholinyl)-1-oxopropyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl].



The title compound was prepared in 70% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 3-(1,1-dioxo-1lamda-6,4-thiazinan-4-yl)propanoic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 719.5 $(M+H)^+$, 1.88 min (method 6). ^{1}H NMR (500MHz , 2:1 *MeOD:CDCl$_3$*) δ = 7.93 (d, *J* = 7.9 Hz, 2 H), 7.25 (br. s., 1 H), 7.21 (d, *J* = 7.9 Hz, 2 H), 5.30 (d, *J* = 6.1 Hz, 1 H), 4.78 (s, 1 H), 4.66 (s, 1 H), 3.47 (br. s., 4 H), 3.36 (br. s., 4 H), 3.19 (br. s., 2 H), 2.72 - 2.59 (m, 4 H), 2.40 (dd, *J* = 8.9, 11.9 Hz, 1 H), 2.15 (dd, *J* = 6.3, 17.2 Hz, 1 H), 1.98 - 1.86 (m, 2 H), 1.80 (d, *J* = 13.1 Hz, 1 H), 1.73 (s, 3 H), 1.71 - 1.66 (m, 1 H), 1.63 - 1.43 (m, 8 H), 1.42 - 1.23 (m, 5 H), 1.22 - 1.13 (m, 2 H), 1.12 (s, 3 H), 1.05 (br. s., 3 H), 1.04 (br. s., 3 H), 0.97 (br. s., 3 H), 0.95 (br. s., 3 H).

Example 82

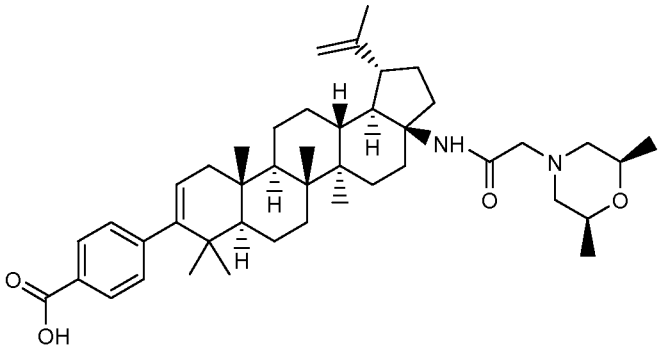
Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[(1,1-dioxido-4-thiomorpholinyl)acetyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl].



The title compound was prepared in 61% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 4-thiomorpholineacetic acid 1,1-dioxide was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 704.5 $(M+H)^+$, 1.90 min (method 6). ^{1}H NMR (500MHz , 2:1 *MeOD:CDCl$_3$*) δ = 7.93 (d, *J* = 8.2 Hz, 2 H), 7.23 (br. s., 1 H), 7.21 (s, 2 H), 5.31 (dd, *J* = 1.7, 6.0 Hz, 1 H), 4.78 (d, *J* = 1.2 Hz, 1 H), 4.67 (s, 1 H), 3.29 (d, *J* = 5.2 Hz, 4 H), 3.24 (d, *J* = 5.2 Hz, 4 H), 2.67 - 2.60 (m, 1 H), 2.53 (dt, *J* = 5.5, 10.8 Hz, 1 H), 2.47 (dd, *J* = 8.1, 12.7 Hz, 1 H), 2.16 (dd, *J* = 6.3, 17.2 Hz, 1 H), 1.94 - 1.78 (m, 3 H), 1.76 (d, *J* = 2.1 Hz, 1 H), 1.74 (s, 3 H), 1.62 - 1.49 (m, 7 H), 1.47 - 1.33 (m, 4 H), 1.31 - 1.25 (m, 1 H), 1.21 - 1.13 (m, 2 H), 1.12 (s, 3 H), 1.07 (s, 3 H), 1.05 (s, 3 H), 0.97 (s, 3 H), 0.96 (s, 3 H).

Example 83

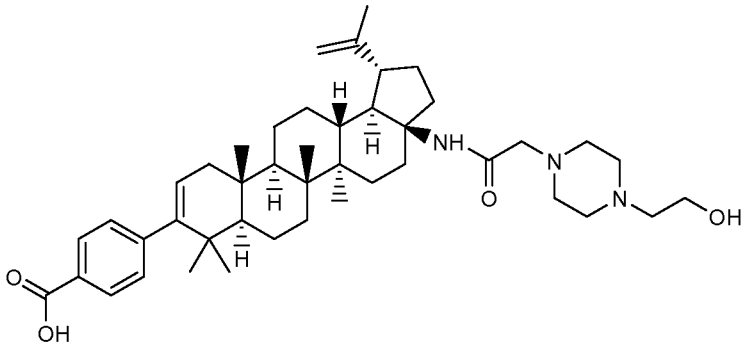
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((2S,6R)-2,6-dimethylmorpholino)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared in 43% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except [(2R,6S)-2,6-dimethylmorpholin-4-yl]acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 685.6 $(M+H)^+$, 2.48 min (method 6). ^{1}H NMR (500MHz , 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 5.29 (dd, *J* = 1.5, 6.1 Hz, 1 H), 4.75 (d, *J* = 1.2 Hz, 1 H), 3.89 (dd, *J* = 6.3, 9.0 Hz, 2 H), 3.64 (br. s., 1 H), 3.24 (br. s., 2 H), 2.69 - 2.49 (m, 4 H), 2.39 (dd, *J* = 8.1, 12.4 Hz, 1 H), 2.13 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.93 - 1.76 (m, 3 H), 1.74 (br. s., 1 H), 1.72 (s, 3 H), 1.70 - 1.66 (m, 1 H), 1.60 - 1.42 (m, 8 H), 1.42 - 1.30 (m, 3 H), 1.25 (d, *J* = 3.1 Hz, 3 H), 1.24 (d, *J* = 2.7 Hz, 3 H), 1.18 - 1.11 (m, 2 H), 1.08 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.95 (s, 3 H), 0.94 (s, 3 H).

Example 84

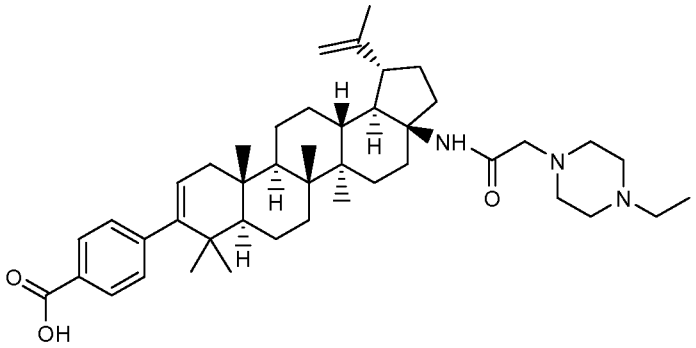
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4-(2-hydroxyethyl)piperazin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared in 23% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except [4-(2-hydroxy-ethyl)-piperazine-1-yl]-acetic acid dihydrochloride was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 700.6 $(M+H)^+$, 2.03 min (method 6). ^{1}H NMR (500MHz , 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.5 Hz, 2 H), 7.20 (d, *J* = 8.5 Hz, 2 H), 6.96 (s, 1 H), 5.30 (dd, *J* = 1.7, 6.0 Hz, 1 H), 4.76 (s, 1 H), 4.66 (s, 1 H), 3.93 - 3.89 (m, 2 H), 3.42 (br. s., 2 H), 3.30 - 3.25 (m, 2 H), 3.22 (d, *J* = 4.6 Hz, 2 H), 2.97 (br. s., 3 H), 2.68 - 2.60 (m, 1 H), 2.55 - 2.47 (m, 1 H), 2.44 (dd, *J* = 8.2, 12.5 Hz, 1 H), 2.13 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.91 - 1.77 (m, 2 H), 1.75 (br. s., 1 H), 1.72 (s, 3 H), 1.72 - 1.68 (m, 1 H), 1.62 - 1.31 (m, 11 H), 1.30 - 1.24 (m, 1 H), 1.15 (d, *J* = 13.1 Hz, 2 H), 1.08 (s, 3 H), 1.05 (s, 3 H), 1.02 (s, 3 H), 0.95 (s, 3 H), 0.94 (s, 3 H).

Example 85

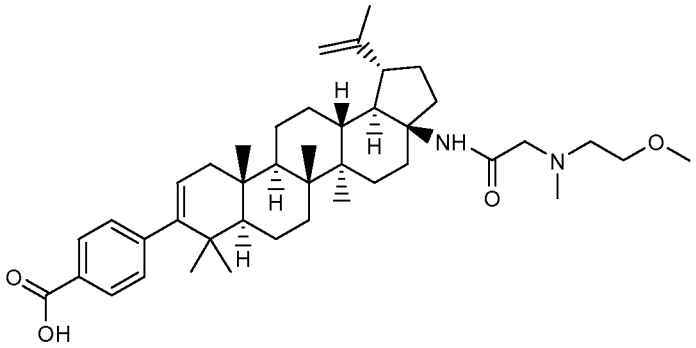
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4-ethylpiperazin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared in 34% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-(4-ethylpiperazin-1-yl)acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 684.6 $(M+H)^+$, 2.35 min (method 6). ^{1}H NMR (500MHz , 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 6.90 (s, 1 H), 5.29 (d, *J* = 6.1 Hz, 1 H), 4.75 (d, *J* = 1.2 Hz, 1 H), 3.27 - 3.14 (m, 5 H), 2.96 (br. s., 3 H), 2.64 (d, *J* = 13.4 Hz, 1 H), 2.55 - 2.38 (m, 2 H), 2.13 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.92 - 1.76 (m, 2 H), 1.74 (br. s., 1 H), 1.72 (s, 3 H), 1.70 - 1.67 (m, 1 H), 1.61 - 1.41 (m, 9 H), 1.37 (t, *J* = 7.3 Hz, 4 H), 1.35 - 1.31 (m, 1 H), 1.29 - 1.23 (m, 1 H), 1.18 - 1.12 (m, 2 H), 1.06 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 2 H), 0.94 (s, 3 H), 0.94 (s, 3 H).

Example 86

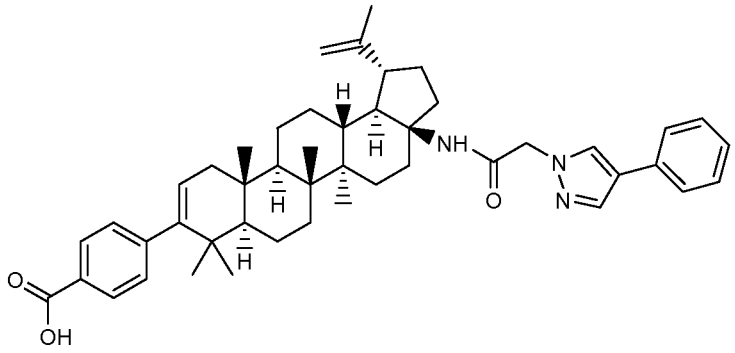
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((2-methoxyethyl)(methyl)amino)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared in 38% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except *N*-(2-methoxyethyl)-*N*-methylglycine was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 659.6 $(M+H)^+$, 2.41 min (method 6). ^{1}H NMR (500MHz , 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 7.9 Hz, 2 H), 7.43 (s, 1 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 5.29 (d, *J* = 5.8 Hz, 1 H), 4.75 (s, 1 H), 3.96 (br. s., 2 H), 3.73 (t, *J* = 4.7 Hz, 2 H), 3.42 (s, 3 H), 3.40 (br. s., 2 H), 2.94 (s, 3 H), 2.73 - 2.61 (m, 2 H), 2.36 (dd, *J* = 8.4, 12.1 Hz, 1 H), 2.12 (dd, *J* = 6.1, 17.1 Hz, 1 H), 1.88 (t, *J* = 11.6 Hz, 2 H), 1.77 (d, *J* = 11.6 Hz, 1 H), 1.73 (br. s., 1 H), 1.71 (s, 3 H), 1.70 - 1.65 (m, 1 H), 1.58 - 1.30 (m, 11 H), 1.25 (d, *J* = 6.1 Hz, 1 H), 1.18 - 1.10 (m, 2 H), 1.09 (s, 3 H), 1.02 (s, 3 H), 1.01 (s, 3 H), 0.94 (br. s., 3 H), 0.93 (br. s., 3 H).

Example 87

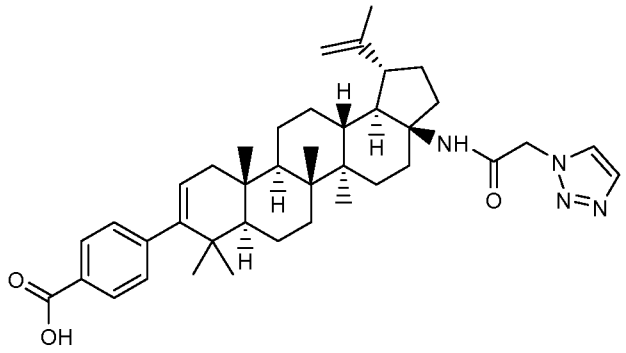
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(4-phenyl-1H-pyrazol-1-yl)acetamido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared in 22% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-(3-phenyl-1H-pyrazol-1-yl)acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 714.6 $(M+H)^+$, 2.59 min (method 6). ^{1}H NMR (500MHz , 1:1 *$CDCl_3$:MeOD*) δ = 7.91 (d, *J* = 8.2 Hz, 4 H), 7.67 (d, *J* = 2.1 Hz, 1 H), 7.42 (d, *J* = 7.3 Hz, 2 H), 7.40 (s, 1 H), 7.37 - 7.31 (m, 1 H), 7.18 (d, *J* = 7.9 Hz, 2 H), 5.24 (d, *J* = 4.6 Hz, 1 H), 4.86 - 4.75 (m, 2 H), 4.59 (s, 1 H), 3.37 (s, 3 H), 2.50 (dd, *J* = 2.4, 9.2 Hz, 1 H), 2.47 - 2.38 (m, 2 H), 1.97 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.93 - 1.83 (m, 1 H), 1.64 (s, 3 H), 1.60 - 1.52 (m, 2 H), 1.50 - 1.37 (m, 4 H), 1.37 - 1.27 (m, 7 H), 1.26 - 1.19 (m, 1 H), 1.16 - 1.11 (m, 1 H), 1.00 (dd, *J* = 2.4, 9.2 Hz, 1 H), 0.90 (s, 3 H), 0.89 (s, 6 H), 0.79 (s, 3 H), 0.61 (s, 3 H), 0.49 (dd, *J* = 4.3, 13.1 Hz, 1 H).

Example 88

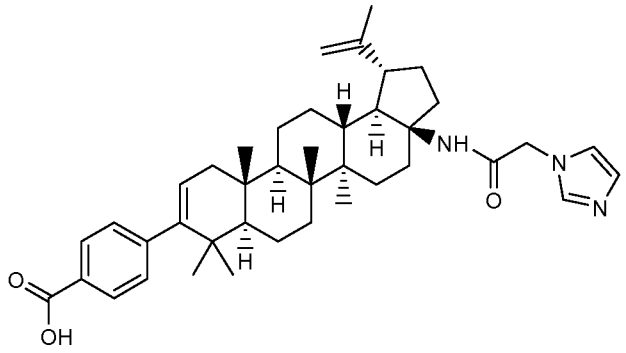
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(1H-1,2,3-triazol-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared in 36% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 1H-1,2,3-triazole-1-acetic acid hydrochloride was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 639.5 $(M+H)^+$, 2.04 min (method 6). ^{1}H NMR (500MHz , 1:1 *$CDCl_3$:MeOD*) δ = 7.94 (d, *J* = 0.9 Hz, 1 H), 7.92 (d, *J* = 8.5 Hz, 2 H), 7.77 (d, *J* = 0.9 Hz, 1 H), 7.20 (d, *J* = 8.5 Hz, 2 H), 6.93 (s, 1 H), 5.29 (dd, *J* = 1.7, 6.3 Hz, 1 H), 5.15 (s, 2 H), 4.75 (d, *J* = 1.5 Hz, 1 H), 4.64 (br. s., 1 H), 2.63 - 2.57 (m, 1 H), 2.57 - 2.50 (m, 1 H), 2.37 (dd, *J* = 8.1, 12.7 Hz, 1 H), 2.12 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.94 - 1.83 (m, 1 H), 1.78 - 1.72 (m, 3 H), 1.70 (s, 3 H), 1.69 - 1.64 (m, 1 H), 1.58 - 1.39 (m, 8 H), 1.38 - 1.29 (m, 3 H), 1.24 (dd, *J* = 3.7, 10.4 Hz, 1 H), 1.15 - 1.06 (m, 2 H), 1.02 (s, 3 H), 1.01 (s, 3 H), 1.00 (s, 3 H), 0.94 (s, 3 H), 0.93 (s, 3 H).

Example 89

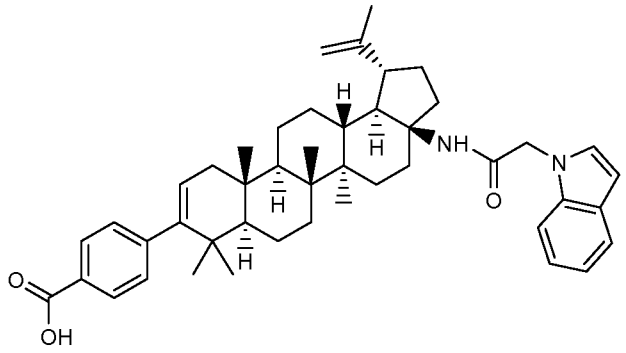
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(1H-imidazol-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared in 60% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except imidazol-1-ylacetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 638.5 $(M+H)^+$, 2.05 min (method 6). ^{1}H NMR (400MHz , 1:1 *$CDCl_3$:MeOD*) δ = 8.88 (s, 1 H), 7.92 (d, *J* = 8.3 Hz, 2 H), 7.47 (ddd, *J* = 1.6, 1.8, 9.7 Hz, 2 H), 7.42 (s, 1 H), 7.20 (d, *J* = 8.5 Hz, 2 H), 5.33 - 5.25 (m, 1 H), 5.02 (d, *J* = 5.0 Hz, 2 H), 4.78 (d, *J* = 1.3 Hz, 1 H), 4.65 (d, *J* = 1.8 Hz, 2 H), 2.72 (dt, *J* = 5.3, 11.0 Hz, 1 H), 2.66 - 2.57 (m, 1 H), 2.33 (dd, *J* = 8.2, 12.7 Hz, 1 H), 2.13 (dd, *J* = 6.3, 17.1 Hz, 1 H), 2.00 - 1.88 (m, 2 H), 1.80 (d, *J* = 14.6 Hz, 1 H), 1.74 (br. s., 1 H), 1.72 (s, 3 H), 1.71 - 1.67 (m, 1 H), 1.60 - 1.32 (m, 11 H), 1.30 - 1.22 (m, 1 H), 1.19 - 1.13 (m, 1 H), 1.12 (s, 3 H), 1.03 (s, 3 H), 1.02 (s, 2 H), 0.95 (s, 3 H), 0.94 (br. s., 3 H).

Example 90

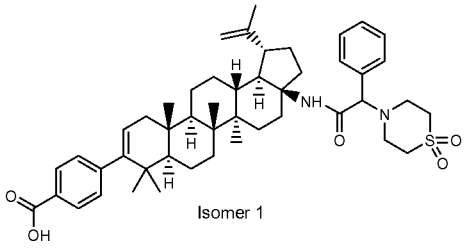
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(1H-indol-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

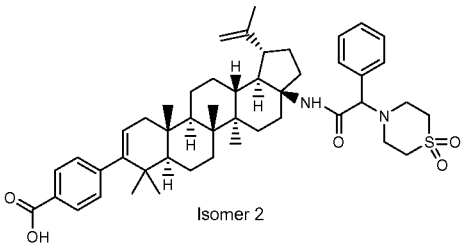


The title compound was prepared in 31% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-(1H-indol-1-yl)acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 687.6 $(M+H)^+$, 2.60 min (method 6). ^{1}H NMR (400MHz , 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.5 Hz, 2 H), 7.72 (d, *J* = 7.8 Hz, 1 H), 7.40 - 7.35 (m, 1 H), 7.32 - 7.25 (m, 1 H), 7.24 - 7.16 (m, 4 H), 6.71 (dd, *J* = 0.8, 3.3 Hz, 1 H), 5.27 (dd, *J* = 1.6, 6.1 Hz, 1 H), 4.90 (s, 1 H), 4.83 (s, 2 H), 4.44 (s, 1 H), 4.33 (d, *J* = 1.8 Hz, 1 H), 2.48 (d, *J* = 12.5 Hz, 1 H), 2.39 - 2.31 (m, 1 H), 2.08 (dd, *J* = 6.4, 17.2 Hz, 1 H), 1.64 (d, *J* = 16.6 Hz, 1 H), 1.54 (d, *J* = 8.0 Hz, 2 H), 1.50 (s, 3 H), 1.39 (br. s., 3 H), 1.37 - 1.23 (m, 6 H), 1.23 - 1.13 (m, 4 H), 1.04 (br. s., 1 H), 1.00 (s, 4 H), 0.95 (s, 3 H), 0.92 (s, 3 H), 0.87 (s, 3 H), 0.82 (s, 3 H).

Example 91 (Isomer 1) and Example 92 (Isomer 2)

Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[(1,1-dioxido-4-thiomorpholinyl)phenylacetyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl].





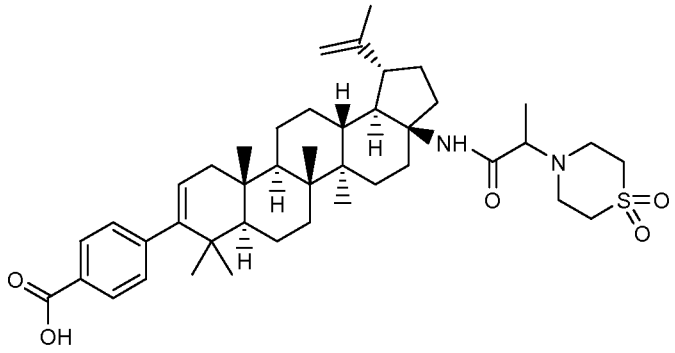
The title compounds were prepared in 21% and 11% yield, respectively, from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-(1,1-dioxo-1-lamda-6-4-thiazinan-4-yl)-2-phenylacetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. The two isomers formed in the reaction were separated by reverse phase preparative HPLC.

Isomer 1: LCMS: m/e 781.6 $(M+H)^+$, 2.21 min (method 6). ^{1}H NMR (400MHz , 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.5 Hz, 2 H), 7.49 - 7.44 (m, 2 H), 7.43 - 7.36 (m, 3 H), 7.20 (d, *J* = 8.3 Hz, 2 H), 6.62 (s, 1 H), 5.29 (dd, *J* = 1.6, 6.1 Hz, 1 H), 4.76 (d, *J* = 1.3 Hz, 1 H), 4.64 (br. s., 1 H), 4.26 (s, 1 H), 3.19 - 3.13 (m, 4 H), 3.12 - 3.01 (m, 4 H), 2.57 - 2.48 (m, 2 H), 2.40 (dd, *J* = 8.0, 11.8 Hz, 1 H), 2.12 (dd, *J* = 6.3, 17.1 Hz, 1 H), 1.76 (d, *J* = 14.6 Hz, 1 H), 1.71 (br. s., 1 H), 1.70 (s, 3 H), 1.66 (d, *J* = 11.0 Hz, 3 H), 1.50 (d, *J* = 16.3 Hz, 3 H), 1.46 - 1.38 (m, 3 H), 1.38 - 1.09 (m, 9 H), 1.00 (s, 3 H), 0.97 (s, 3 H), 0.94 (s, 3 H), 0.92 (s, 3 H), 0.84 (s, 3 H).

Isomer 2: LCMS: m/e 781.6 (M+H)+, 2.22 min (method 6). ^{1}H NMR (400MHz ,1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.3 Hz, 2 H), 7.49 - 7.44 (m, 2 H), 7.43 - 7.34 (m, 3 H), 7.21 (d, *J* = 8.3 Hz, 2 H), 6.64 (s, 1 H), 5.30 (dd, *J* = 1.6, 6.1 Hz, 1 H), 4.75 (s, 1 H), 4.65 (s, 1 H), 4.16 (s, 1 H), 3.25 - 2.99 (m, 8 H), 2.65 - 2.57 (m, 1 H), 2.42 (dt, *J* = 5.6, 10.9 Hz, 1 H), 2.32 (dd, *J* = 8.3, 12.5 Hz, 1 H), 2.15 (dd, *J* = 6.4, 16.9 Hz, 1 H), 1.85 - 1.72 (m, 3 H), 1.70 (s, 3 H), 1.61 - 1.23 (m, 14 H), 1.10 (s, 3 H), 1.05 (s, 3 H), 1.01 (s, 3 H), 0.96 (s, 3 H), 0.94 (s, 3 H).

Example 93

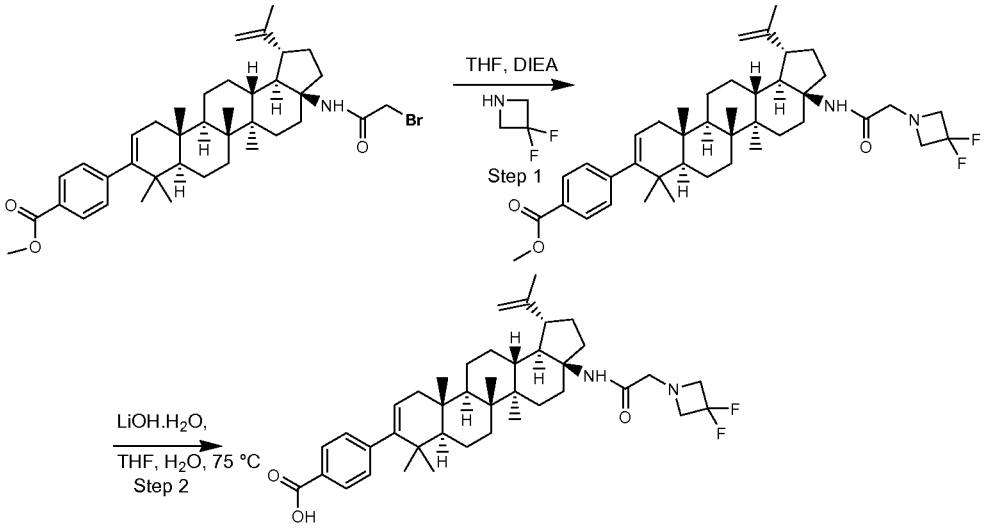
Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxido-4-thiomorpholinyl)-1-oxopropyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl].



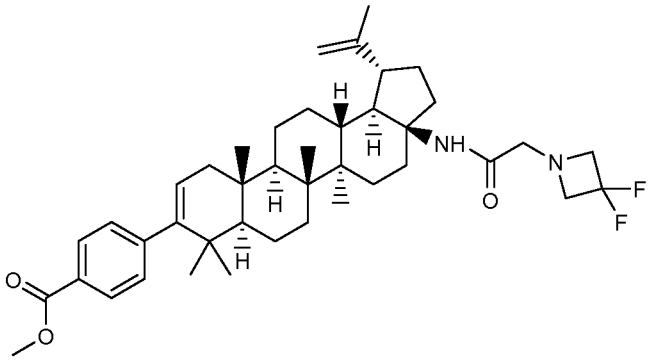
The title compound was prepared in 44% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-(1,1-dioxidothiomorpholin-4-yl)-propionic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 719.5 $(M+H)^+$, 2.03 min (method 6). ^{1}H NMR (500MHz , 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.54 (s, 1 H), 7.20 (d, *J* = 7.9 Hz, 2 H), 5.29 (d, *J* = 5.2 Hz, 1 H), 4.75 (d, *J* = 10.4 Hz, 1 H), 4.66 (br. s., 1 H), 3.48 - 3.39 (m, 1 H), 3.28 - 3.11 (m, 8 H), 2.69 - 2.55 (m, 1 H), 2.50 - 2.34 (m, 2 H), 2.13 (dd, *J* = 6.1, 17.1 Hz, 1 H), 1.80 (d, *J* = 11.6 Hz, 2 H), 1.72 (s, 6 H), 1.59 - 1.44 (m, 8 H), 1.43 - 1.36 (m, 2 H), 1.33 (dd, *J* = 6.9, 14.8 Hz, 4 H), 1.25 (d, *J* = 6.7 Hz, 1 H), 1.15 (d, *J* = 11.0 Hz, 2 H), 1.08 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.94 (br. s., 6 H).

Example 94

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3,3-difluoroazetidin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



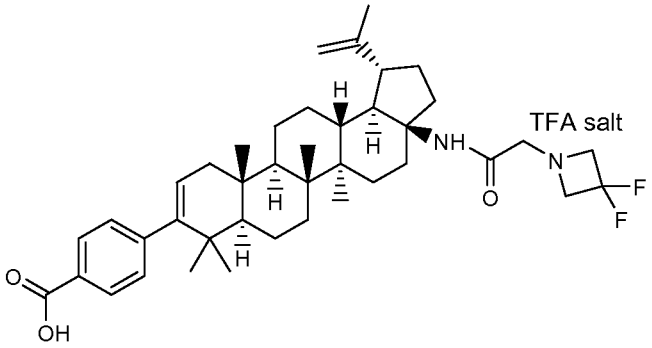
Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3,3-difluoroazetidin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.



To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-bromoacetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (129 mg, 0.194 mmol) in THF (3 mL) was added *N,N*-diisopropylethylamine (0.338 mL, 1.941 mmol) and 3,3-difluoroazetidine, HCl

(126 mg, 0.970 mmol). The reaction mixture was stirred at 160 °C for 5 h. The mixture was concentrated and the crude residue was dissolved in THF (1.5 mL), filtered and purified by reverse phase preparative HPLC using Prep HPLC method 3 to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3,3-difluoroazetidin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (28.8 mg, 0.043 mmol, 21.9 % yield) as brown solid. LC/MS: m/e 677.5 $(M+H)^+$, 2.93 min (method 6).

Step 2. Preparation of give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3,3-difluoroazetidin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, TFA.

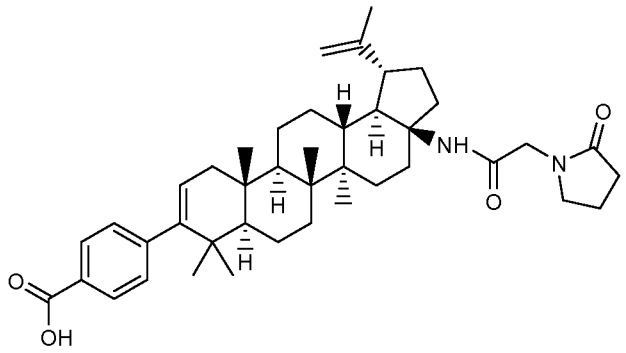


To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3,3-difluoroazetidin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (28.8 mg, 0.043 mmol) in THF (Volume: 3 mL) was added a 0.753 molar solution of Li . H O . H_2O (0.340 mL, 0.170 mmol) in H_2O. The reaction was heated to 75 °C for 6 h and was then concentrated to a brown viscous oil. The crude residue was dissolved in THF (1.3 mL) and 0.2 mL 1N HCl, filtered and purified by reverse phase preparative HPLC using prep HPLC method 3 to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3,3-difluoroazetidin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, TFA (17.6 mg, 0.022 mmol, 52.7 % yield) as a light yellow solid. LCMS: m/e 663.7 $(M+H)^+$, 2.22 min (method 2). ^1H NMR

(500MHz, *1:1 $CDCl_3$:METHANOL-d_4*) δ 7.90 (d, *J*=8.2 Hz, 2H), 7.18 (d, *J*=8.2 Hz, 2H), 5.27 (d, *J*=4.6 Hz, 1H), 4.73 (s, 1H), 3.88 (t, *J*=12.5 Hz, 2H), 3.69 - 3.59 (m, 1H), 3.55 - 3.39 (m, 3H), 2.64 - 2.53 (m, 2H), 2.39 (dd, *J*=12.2, 8.2 Hz, 1H), 2.10 (dd, *J*=17.1, 6.4 Hz, 1H), 1.93 - 1.73 (m, 3H), 1.69 (s, 3H), 1.67 (d, *J*=4.6 Hz, 1H), 1.58 - 1.39 (m, 8H), 1.39 - 1.29 (m, 3H), 1.23 (d, *J*=10.1 Hz, 1H), 1.11 (d, *J*=13.7 Hz, 2H), 1.06 (s, 3H), 1.00 (s, 3H), 0.99 (s, 3H), 0.92 (br. s., 3H), 0.91 (br. s., 3H).

Example 95

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(2-oxopyrrolidin-1-yl)acetamido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

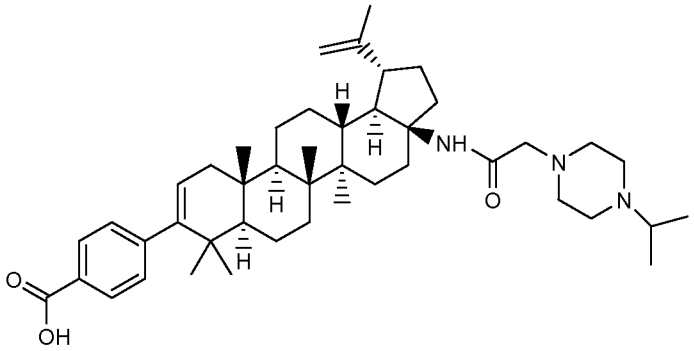


The title compound was prepared in 14% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-(2-oxopyrrolidin-1-yl)acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 655.5 $(M+H)^+$, 1.99 min (method 6). ^{1}H NMR (500MHz , 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 7.9 Hz, 2 H), 7.20 (d, *J* = 7.9 Hz, 2 H), 6.77 (s, 1 H), 5.29 (d, *J* = 4.7 Hz, 1 H), 4.75 (d, *J* = 1.3 Hz, 1 H), 4.63 (s, 1 H), 3.97 - 3.85 (m, 2 H),

3.58 - 3.51 (m, 2 H), 2.65 - 2.54 (m, 2 H), 2.47 (t, *J* = 8.0 Hz, 2 H), 2.38 (dd, *J* = 8.4, 12.5 Hz, 1 H), 2.17 - 2.07 (m, 3 H), 1.95 - 1.85 (m, 1 H), 1.83 - 1.74 (m, 2 H), 1.73 (br. s., 1 H), 1.70 (s, 3 H), 1.68 - 1.62 (m, 1 H), 1.60 - 1.43 (m, 8 H), 1.42 - 1.22 (m, 6 H), 1.13 (br. s., 1 H), 1.09 (s, 3 H), 1.01 (s, 6 H), 0.94 (s, 3 H), 0.93 (s, 3 H).

Example 96

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4-isopropylpiperazin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

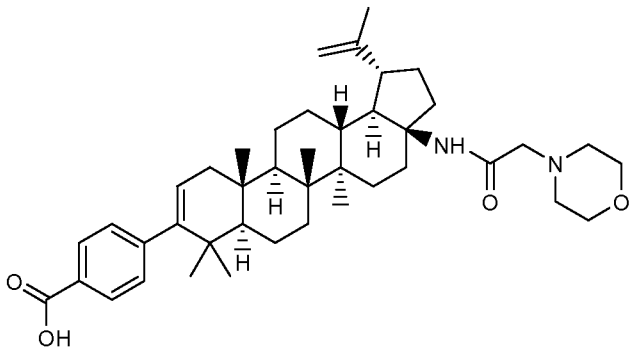


The title compound was prepared in 22% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except (4-isopropyl-piperazin-1-yl)-acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 698.6 $(M+H)^+$, 2.64 min (method 6). ^{1}H NMR (500MHz , 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.37 (br. s., 1 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 6.34 - 6.03 (m, 1 H), 5.29 (d, *J* = 4.6 Hz, 1 H), 4.76 (br. s., 1 H), 4.70 (br. s., 1 H), 3.95 (br. s., 1 H), 3.84 - 3.55 (m, 8 H), 3.17 (q, *J* = 7.2 Hz, 2 H), 2.64 (d, *J* = 13.1 Hz, 2 H), 2.39 (dd, *J* = 8.1, 11.4 Hz, 1 H), 2.12 (dd, *J* = 6.3, 17.2 Hz, 1 H), 1.96 - 1.84 (m,

2 H), 1.79 (d, *J* = 12.5 Hz, 1 H), 1.76 - 1.65 (m, 5 H), 1.59 - 1.40 (m, 14 H), 1.35 (t, *J* = 7.2 Hz, 4 H), 1.29 - 1.21 (m, 1 H), 1.15 (d, *J* = 6.1 Hz, 1 H), 1.10 (br. s., 3 H), 1.02 (s, 3 H), 1.01 (br. s., 2 H), 0.94 (br. s., 3 H), 0.93 (br. s., 3 H).

Example 97

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-morpholinoacetamido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

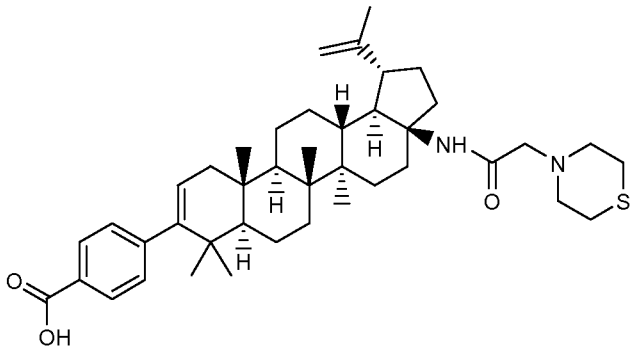


The title compound was prepared in 40% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except morpholin-4-yl-acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 657.6 $(M+H)^+$, 2.20 min (method 6). ^{1}H NMR (500MHz , 1:1 *$CDCl_3$:MeOD*) δ = 7.91 (d, *J* = 7.9 Hz, 2 H), 7.48 (br. s., 1 H), 7.19 (d, *J* = 8.2 Hz, 2 H), 5.28 (d, *J* = 4.9 Hz, 1 H), 4.77 (br. s., 1 H), 4.12 - 3.79 (m, 6 H), 3.57 - 3.40 (m, 2 H), 3.22 - 3.11 (m, 1 H), 2.74 (br. s., 1 H), 2.65 (d, *J* = 12.8 Hz, 1 H), 2.42 - 2.29 (m, 1 H), 2.12 (dd, *J* = 6.1, 17.1 Hz, 1 H), 2.03 - 1.85 (m, 2 H), 1.79 (d, *J* = 12.8 Hz, 1 H), 1.72 (br. s., 1 H), 1.71 (s, 3 H), 1.69 (br. s., 1 H), 1.60 - 1.30 (m, 12 H), 1.24 (d, *J* = 5.8 Hz, 1 H), 1.14

(br. s., 1 H), 1.10 (br. s., 4 H), 1.02 (br. s., 3 H), 1.00 (br. s., 3 H), 0.93 (br. s., 3 H), 0.92 (br. s., 3 H).

Example 98

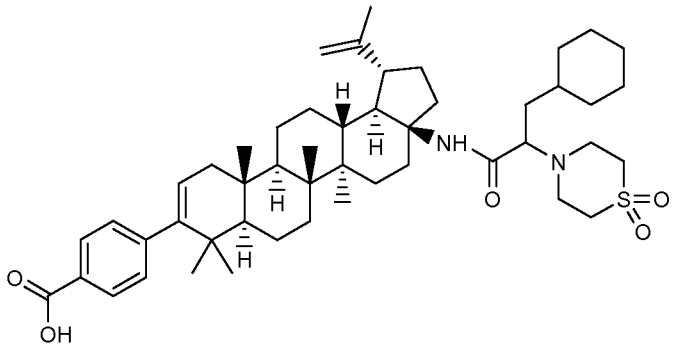
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-thiomorpholinoacetamido)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared in 44% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-thiomorpholinoacetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 671.8 $(M-H)^-$, 2.37 min (method 6). ^{1}H NMR (500MHz , 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, J = 8.2 Hz, 2 H), 7.47 (s, 1 H), 7.20 (d, J = 8.2 Hz, 2 H), 5.29 (d, J = 4.3 Hz, 1 H), 4.75 (s, 1 H), 3.79 - 3.63 (m, 2 H), 3.58 (td, J = 6.5, 12.9 Hz, 1 H), 3.47 - 3.35 (m, 3 H), 2.95 (br. s., 4 H), 2.68 - 2.57 (m, 2 H), 2.37 (dd, J = 8.4, 12.4 Hz, 1 H), 2.13 (dd, J = 6.4, 17.1 Hz, 1 H), 1.92 - 1.82 (m, 2 H), 1.81 - 1.76 (m, 1 H), 1.73 (br. s., 1 H), 1.71 (s, 3 H), 1.69 - 1.64 (m, 1 H), 1.60 - 1.31 (m, 12 H), 1.30 - 1.22 (m, 1 H), 1.19 - 1.11 (m, 2 H), 1.09 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.94 (br. s., 3 H), 0.93 (br. s., 3 H).

Example 99

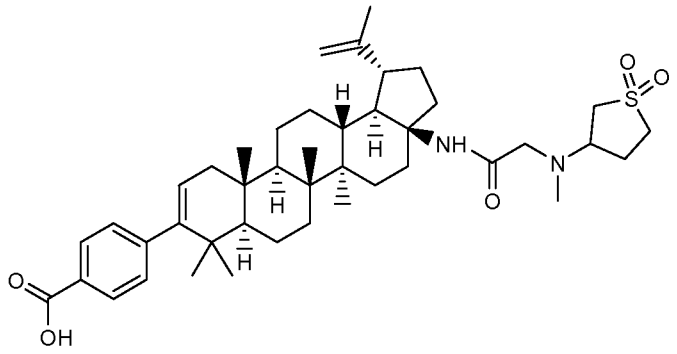
Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-cyclohexyl-2-(1,1-dioxido-4-thiomorpholinyl)-1-oxopropyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl].



The title compound was prepared in 23% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 3-cyclohexyl-2-(1,1-dioxo-1lambda6,-4,thiazinan-4-yl)propanoic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 801.6 $(M+H)^+$, 2.43 min (method 6). ^{1}H NMR (500MHz , 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 6.56 (s, 1 H), 5.29 (d, *J* = 4.6 Hz, 1 H), 4.76 (s, 1 H), 3.58 (td, *J* = 6.6, 13.4 Hz, 1 H), 3.44 (dd, *J* = 5.0, 9.6 Hz, 1 H), 3.30 - 3.25 (m, 3 H), 3.24 - 3.15 (m, 2 H), 3.14 - 3.06 (m, 2 H), 2.68 (d, *J* = 13.4 Hz, 1 H), 2.56 (dt, *J* = 5.6, 11.1 Hz, 1 H), 2.41 (dd, *J* = 8.4, 12.7 Hz, 1 H), 2.13 (dd, *J* = 6.3, 17.2 Hz, 1 H), 1.92 - 1.75 (m, 5 H), 1.73 (br. s., 1 H), 1.72 (s, 3 H), 1.70 - 1.64 (m, 4 H), 1.61 - 1.40 (m, 10 H), 1.40 - 1.29 (m, 3 H), 1.28 - 1.11 (m, 7 H), 1.09 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.97 (d, *J* = 3.1 Hz, 1 H), 0.94 (br. s., 3 H), 0.93 (br. s., 3 H).

Example 100

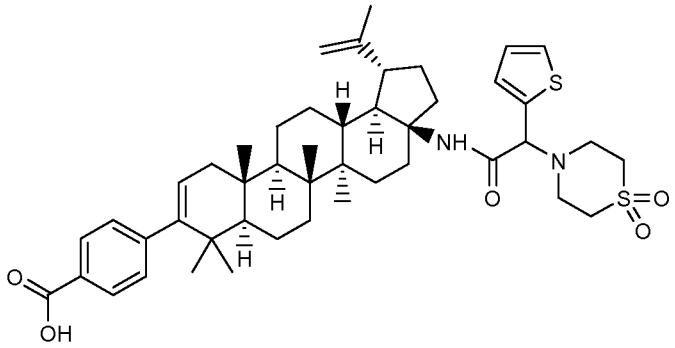
Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-3a-[[[methyl(tetrahydro-1,1-dioxido-3-thienyl)amino]acetyl]amino]-1H-cyclopenta[a]chrysen-9-yl].



The title compound was prepared in 17% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except *N*-(1,1-dioxidotetrahydro-3-thienyl)-*N*-methylglycine was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 719.5 $(M+H)^+$, 2.00 min (method 6). ^{1}H NMR (500MHz , *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.30 (d, *J* = 7.6 Hz, 1 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 5.29 (d, *J* = 4.9 Hz, 1 H), 3.80 (br. s., 1 H), 3.40 (dd, *J* = 7.6, 13.4 Hz, 1 H), 3.30 - 3.05 (m, 4 H), 2.60 (br. s., 1 H), 2.57 (d, *J* = 1.5 Hz, 3 H), 2.55 - 2.41 (m, 3 H), 2.23 (quin, *J* = 10.6 Hz, 1 H), 2.13 (dd, *J* = 6.1, 17.1 Hz, 1 H), 1.91 - 1.76 (m, 2 H), 1.73 (br. s., 1 H), 1.71 (s, 3 H), 1.70 (br. s., 1 H), 1.60 - 1.29 (m, 12 H), 1.25 (d, *J* = 7.0 Hz, 1 H), 1.21 - 1.11 (m, 3 H), 1.09 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.94 (s, 3 H), 0.93 (br. s., 3 H).

Example 101

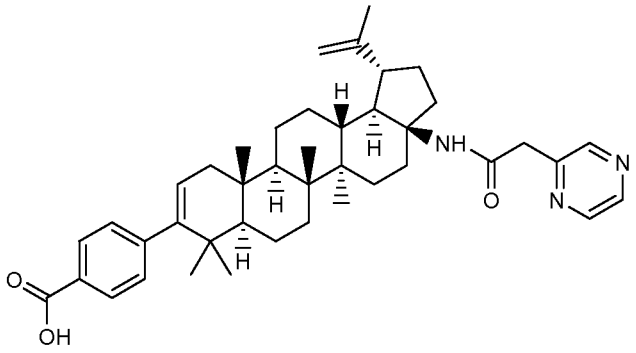
Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-thiomorpholinyl)-1-oxo-3-(2-thienyl)propyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl.



The title compound was prepared in 39% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 3-(1,1-dioxo-1lambda6,4-thiazinan-4-yl)-3-(2-thienyl)propanoic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 801.6 $(M+H)^+$, 2.16 min (method 6). ^{1}H NMR (500MHz , 1:1 *CDCl$_3$:MeOD*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.36 - 7.28 (m, 1 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 7.05 - 6.91 (m, 2 H), 6.59 (s, 1 H), 5.29 (d, *J* = 4.9 Hz, 1 H), 4.74 (d, *J* = 7.6 Hz, 1 H), 4.60 - 4.52 (m, 2 H), 3.18 - 3.05 (m, 6 H), 3.04 - 2.93 (m, 2 H), 2.91 - 2.72 (m, 2 H), 2.68 - 2.49 (m, 2 H), 2.48 - 2.40 (m, 1 H), 2.27 (dd, *J* = 8.5, 11.9 Hz, 1 H), 2.12 (dd, *J* = 4.9, 17.1 Hz, 1 H), 1.93 - 1.72 (m, 3 H), 1.69 (d, *J* = 7.9 Hz, 3 H), 1.64 (d, *J* = 11.6 Hz, 1 H), 1.61 - 1.38 (m, 8 H), 1.37 - 1.19 (m, 5 H), 1.13 (br. s., 1 H), 1.11 (br. s., 15 H), 1.10 (br. s., 2 H), 1.02 (br. s., 1 H), 1.01 (br. s., 2 H), 1.01 (br. s., 1 H), 1.00 (br. s., 2 H), 0.95 (br. s., 1 H), 0.95 (br. s., 2 H), 0.93 (s, 3 H).

Example 102

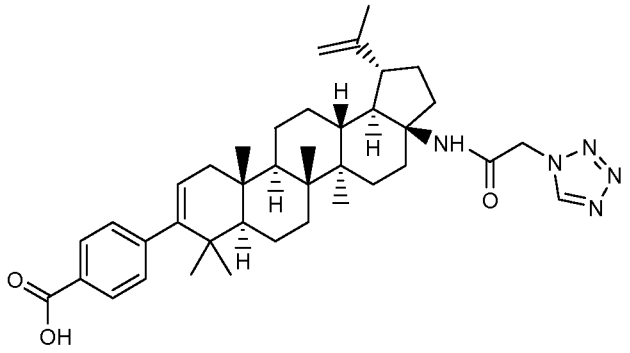
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyrazin-2-yl)acetamido)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared in 14% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-pyrazine acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 650.6 $(M+H)^+$, 2.12 min (method 6). ^{1}H NMR (500MHz , 1:1 *$CDCl_3$:MeOD*) δ = 8.68 - 8.50 (m, 3 H), 7.92 (d, *J* = 8.2 Hz, 2 H), 7.20 (d, *J* = 8.2 Hz, 3 H), 5.29 (dd, *J* = 1.7, 6.0 Hz, 1 H), 4.76 (s, 1 H), 3.79 (q, *J* = 14.3 Hz, 2 H), 2.66 - 2.53 (m, 2 H), 2.42 - 2.31 (m, 1 H), 2.12 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.91 - 1.74 (m, 3 H), 1.72 (br. s., 1 H), 1.71 (s, 2 H), 1.67 (d, *J* = 11.9 Hz, 2 H), 1.57 - 1.18 (m, 13 H), 1.17 - 1.02 (m, 3 H), 1.00 (br. s., 3 H), 1.00 (br. s., 3 H), 0.94 (s, 3 H), 0.92 (br. s., 3 H), 0.92 (br. s., 3 H).

Example 103

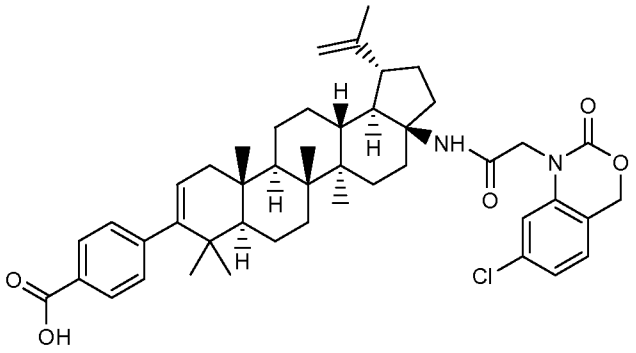
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(1H-tetrazol-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared in 33% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 1-H-tetrazole-1-acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 638.7 $(M-H)^-$, 1.98 min (method 6). ^{1}H NMR (500MHz , 1:1 *$CDCl_3$:MeOD*) δ = 9.10 (s, 1 H), 7.93 (d, *J* = 8.2 Hz, 2 H), 7.39 (s, 1 H), 7.21 (d, *J* = 8.2 Hz, 2 H), 5.30 (dd, *J* = 1.5, 6.1 Hz, 1 H), 5.27 (d, *J* = 1.5 Hz, 2 H), 4.78 (d, *J* = 1.2 Hz, 1 H), 4.65 (s, 1 H), 2.71 (dt, *J* = 5.2, 11.1 Hz, 1 H), 2.64 - 2.56 (m, 1 H), 2.34 (dd, *J* = 8.1, 12.7 Hz, 1 H), 2.13 (dd, *J* = 6.4, 17.1 Hz, 1 H), 2.00 - 1.86 (m, 2 H), 1.80 (d, *J* = 11.0 Hz, 1 H), 1.74 (br. s., 1 H), 1.72 (s, 3 H), 1.71 - 1.66 (m, 1 H), 1.62 - 1.30 (m, 11 H), 1.29 - 1.22 (m, 1 H), 1.20 - 1.14 (m, 1 H), 1.12 (s, 3 H), 1.10 (d, *J* = 4.3 Hz, 1 H), 1.03 (s, 6 H), 0.95 (s, 3 H), 0.94 (s, 3 H).

Example 104

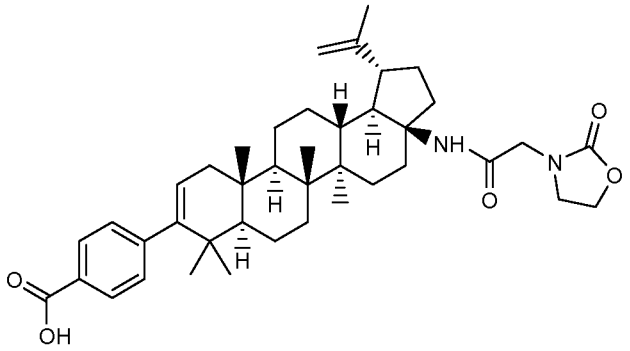
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(7-chloro-2-oxo-2,4-dihydro-1H-benzo[d][1,3]oxazin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared in 36% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-(6-chloro-3-oxo-2H-benzo[b][1,4]oxazin-4(3H)-yl)acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 653.5 $(M+H)^+$, 2.29 min (method 6). ^{1}H NMR (500MHz , 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.5 Hz, 2 H), 7.21 (d, *J* = 8.5 Hz, 2 H), 7.05 - 7.01 (m, 1 H), 7.01 - 6.97 (m, 2 H), 6.83 (s, 1 H), 5.29 (dd, *J* = 1.7, 6.3 Hz, 1 H), 4.73 (d, *J* = 1.8 Hz, 1 H), 4.70 (d, *J* = 1.2 Hz, 2 H), 4.66 (br. s., 1 H), 4.63 (s, 1 H), 4.57 - 4.50 (m, 1 H), 2.65 - 2.57 (m, 1 H), 2.51 - 2.34 (m, 2 H), 2.13 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.96 - 1.85 (m, 1 H), 1.83 - 1.72 (m, 3 H), 1.70 (s, 3 H), 1.69 - 1.64 (m, 1 H), 1.63 - 1.55 (m, 2 H), 1.54 - 1.45 (m, 4 H), 1.45 - 1.30 (m, 5 H), 1.30 - 1.23 (m, 1 H), 1.18 - 1.12 (m, 2 H), 1.10 (s, 3 H), 1.02 (s, 6 H), 0.95 (s, 3 H), 0.94 (s, 3 H).

Example 105

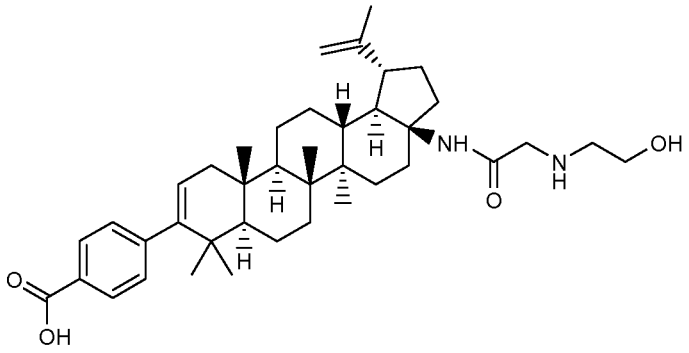
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(2-oxooxazolidin-3-yl)acetamido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared in 29% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-(2-oxooxazolidin-3-yl)acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 657.5 $(M+H)^+$, 1.97 min (method 6). ^{1}H NMR (500MHz , 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.20 (d, *J* = 8.5 Hz, 2 H), 6.82 (s, 1 H), 5.29 (dd, *J* = 1.7, 6.3 Hz, 1 H), 4.76 (d, *J* = 1.5 Hz, 1 H), 4.64 (s, 2 H), 4.43 (dt, *J* = 1.7, 8.2 Hz, 2 H), 3.98 - 3.84 (m, 2 H), 3.74 (t, *J* = 8.1 Hz, 2 H), 2.69 - 2.56 (m, 2 H), 2.40 (dd, *J* = 8.1, 12.4 Hz, 1 H), 2.13 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.98 - 1.81 (m, 2 H), 1.81 - 1.75 (m, 1 H), 1.73 (br. s., 1 H), 1.71 (s, 3 H), 1.70 - 1.65 (m, 1 H), 1.61 - 1.43 (m, 7 H), 1.42 - 1.29 (m, 4 H), 1.29 - 1.21 (m, 2 H), 1.16 - 1.12 (m, 1 H), 1.10 (s, 3 H), 1.02 (s, 3 H), 1.02 (s, 3 H), 0.95 (s, 3 H), 0.94 (s, 3 H).

Example 106

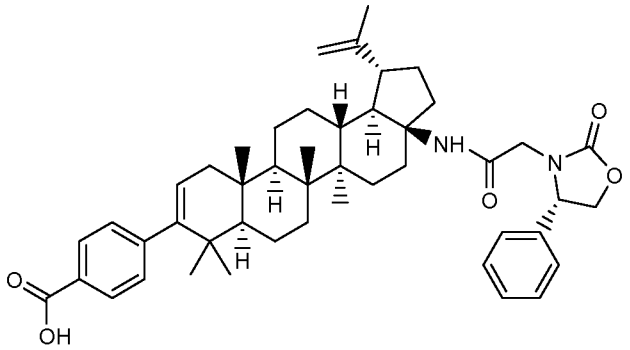
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-hydroxyethylamino)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared in 14% yield as a by-product during the above described preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(2-oxooxazolidin-3-yl)acetamido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid. LCMS: m/e 631.5 $(M+H)^+$, 1.94 min (method 6). ^{1}H NMR (500MHz , 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 5.29 (d, *J* = 4.6 Hz, 1 H), 4.76 (s, 1 H), 4.65 (s, 1 H), 3.87 - 3.75 (m, 4 H), 3.17 - 3.12 (m, 2 H), 2.73 - 2.62 (m, 2 H), 2.37 (dd, *J* = 8.4, 12.1 Hz, 1 H), 2.13 (dd, *J* = 6.3, 17.2 Hz, 1 H), 2.16 - 2.09 (m, 1 H), 1.95 - 1.85 (m, 2 H), 1.79 (d, *J* = 11.0 Hz, 1 H), 1.74 (br. s., 1 H), 1.72 (s, 3 H), 1.71 - 1.66 (m, 1 H), 1.58 - 1.47 (m, 6 H), 1.47 - 1.32 (m, 5 H), 1.30 - 1.23 (m, 1 H), 1.16 - 1.11 (m, 2 H), 1.10 (s, 3 H), 1.03 (s, 3 H), 1.02 (s, 3 H), 0.95 (s, 3 H), 0.94 (br. s., 3 H).

Example 107

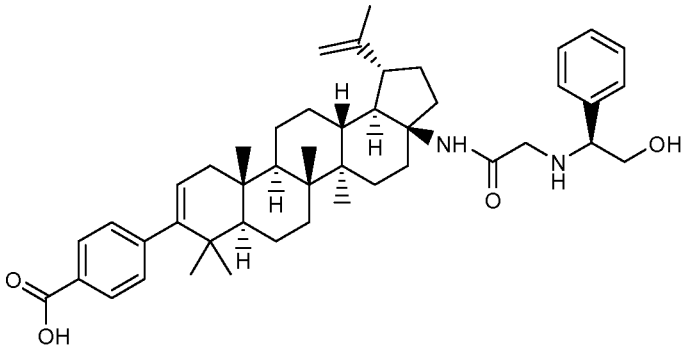
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-((S)-2-oxo-4-phenyloxazolidin-3-yl)acetamido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared in 30% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except (S)-(+)-2-oxo-4-phenyl-3-oxazolidineacetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 733.5 $(M+H)^+$, 2.25 min (method 6). ^{1}H NMR (400MHz , 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.3 Hz, 2 H), 7.47 - 7.39 (m, 3 H), 7.37 - 7.32 (m, 2 H), 7.20 (d, *J* = 8.3 Hz, 2 H), 6.60 (s, 1 H), 5.28 (d, *J* = 4.5 Hz, 1 H), 5.04 (t, *J* = 8.3 Hz, 1 H), 4.75 (t, *J* = 8.9 Hz, 1 H), 4.71 (s, 1 H), 4.61 (br. s., 1 H), 4.25 - 4.19 (m, 1 H), 4.04 (d, *J* = 16.3 Hz, 1 H), 3.40 (d, *J* = 16.3 Hz, 1 H), 2.65 - 2.59 (m, 1 H), 2.47 (dt, *J* = 4.8, 11.0 Hz, 1 H), 2.37 (dd, *J* = 8.2, 11.7 Hz, 1 H), 2.11 (dd, *J* = 6.3, 17.1 Hz, 1 H), 1.84 - 1.70 (m, 4 H), 1.69 (s, 3 H), 1.66 - 1.59 (m, 1 H), 1.58 - 1.40 (m, 7 H), 1.39 - 1.22 (m, 6 H), 1.09 (br. s., 1 H), 1.07 (s, 3 H), 1.00 (s, 6 H), 0.95 (s, 3 H), 0.94 (br. s., 3 H).

Example 108

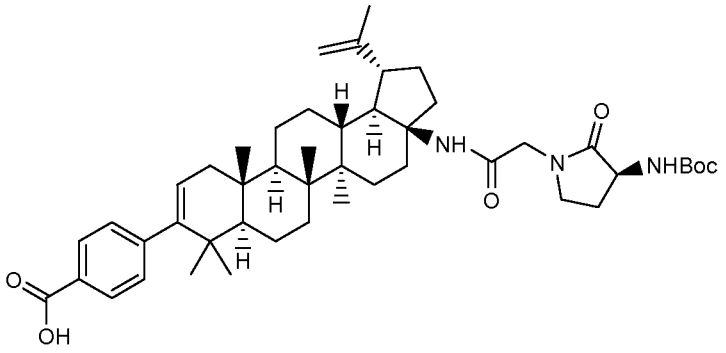
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((S)-2-hydroxy-1-phenylethylamino)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared in 8% yield as a by-product during the above described preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-((S)-2-oxo-4-phenyloxazolidin-3-yl)acetamido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid. LCMS: m/e 707.5 $(M+H)^+$, 2.18 min (method 6). ^{1}H NMR (400MHz , 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.3 Hz, 2 H), 7.49 - 7.45 (m, 3 H), 7.45 - 7.40 (m, 2 H), 7.19 (d, *J* = 8.3 Hz, 2 H), 5.28 (d, *J* = 4.8 Hz, 1 H), 4.71 (s, 1 H), 4.62 (br. s., 2 H), 4.35 (dd, *J* = 4.9, 7.7 Hz, 1 H), 4.04 - 3.90 (m, 2 H), 3.72 - 3.55 (m, 2 H), 2.60 - 2.50 (m, 2 H), 2.36 (dd, *J* = 8.5, 12.0 Hz, 1 H), 2.10 (dd, *J* = 6.4, 17.2 Hz, 1 H), 1.91 - 1.75 (m, 2 H), 1.73 (d, *J* = 7.3 Hz, 2 H), 1.69 (s, 3 H), 1.65 - 1.60 (m, 1 H), 1.50 - 1.37 (m, 6 H), 1.37 - 1.19 (m, 7 H), 1.07 (d, *J* = 18.6 Hz, 3 H), 0.99 (s, 6 H), 0.97 (s, 3 H), 0.94 (br. s., 3 H), 0.94 (br. s., 3 H).

Example 109

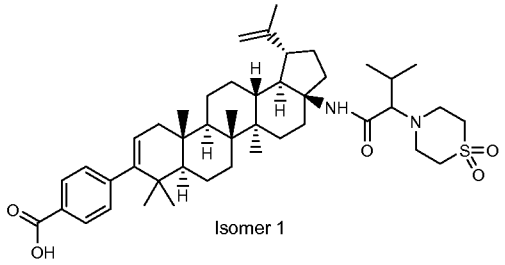
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((S)-3-(tert-butoxycarbonylamino)-2-oxopyrrolidin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

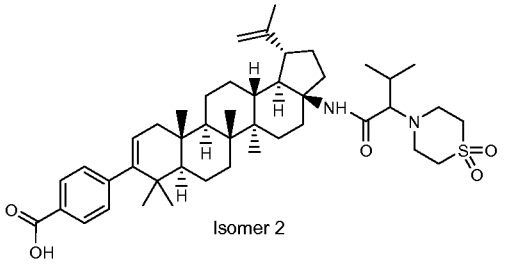


The title compound was prepared in 34% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except (S)-2-(3-(*tert*-butoxycarbonylamino)-2-oxopyrrolidin-1-yl)acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 770.6 (M+H)+, 2.07 min (method 6). ^{1}H NMR (400MHz , 1:1 *CDCl$_3$:MeOD*) δ = 7.92 (d, *J* = 8.0 Hz, 2 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 6.83 - 6.60 (m, 1 H), 5.29 (d, *J* = 4.8 Hz, 1 H), 4.76 (s, 1 H), 4.63 (br. s., 1 H), 4.32 - 4.16 (m, 1 H), 4.07 - 3.84 (m, 2 H), 3.44 (d, *J* = 7.0 Hz, 2 H), 2.70 - 2.56 (m, 2 H), 2.55 - 2.44 (m, 1 H), 2.43 - 2.31 (m, 1 H), 2.13 (dd, *J* = 6.3, 17.1 Hz, 1 H), 2.08 - 1.95 (m, 1 H), 1.94 - 1.82 (m, 2 H), 1.81 - 1.73 (m, 2 H), 1.71 (s, 3 H), 1.68 - 1.62 (m, 1 H), 1.61 - 1.48 (m, 6 H), 1.46 (s, 9 H), 1.43 - 1.22 (m, 6 H), 1.13 (br. s., 1 H), 1.10 (d, *J* = 3.8 Hz, 3 H), 1.02 (s, 6 H), 0.95 (br. s., 3 H), 0.94 (br. s., 3 H).

Example 110 (Isomer 1) and Example 111 (Isomer 2)

Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxido-4-thiomorpholinyl)-3-methyl-1-oxobutyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl].





The title compounds were prepared in 9% yield each from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-(1,1-dioxo-1-lamda-6,4-thiazinan-4-yl)3-methylbutanoic acid (91 mg, 0.388 mmol) was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. The two isomers formed in the reaction were separated by reverse phase preparative HPLC.

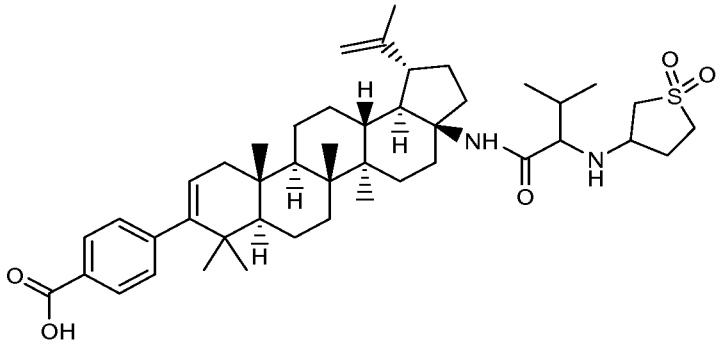
Isomer 1: LCMS: m/e 747.5 $(M+H)^+$, 2.23 min (method 6). ^{1}H NMR (500MHz , 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.20 (d, *J* = 8.5 Hz, 2 H), 6.42 (s, 1 H), 5.29 (dd, *J* = 1.5, 6.1 Hz, 1 H), 4.75 (d, *J* = 1.5 Hz, 1 H), 4.64 (br. s., 1 H), 3.31 - 3.23 (m, 2 H), 3.16 - 3.07 (m, 4 H), 3.06 - 2.97 (m, 2 H), 2.84 (d, *J* = 10.4 Hz, 1 H), 2.77 - 2.71 (m, 1 H), 2.63 (dt, *J* = 5.5, 11.1 Hz, 1 H), 2.42 (dd, *J* = 8.2, 12.5 Hz, 1 H), 2.12 (dd, *J* = 6.4, 17.1 Hz, 1 H), 2.03 (qd, *J* = 6.5, 16.9 Hz, 1 H), 1.91 - 1.81 (m, 2 H), 1.78 (d, *J* = 12.2 Hz, 1 H), 1.73 (br. s., 1 H), 1.71 (s, 3 H), 1.68 (d, *J* = 11.3 Hz, 1 H), 1.62 (dd, *J* = 3.4, 13.4 Hz, 1 H), 1.57 (d, *J* = 4.9 Hz, 1 H), 1.51 (br. s., 3 H), 1.47 (d, *J* = 12.5 Hz, 1 H), 1.44 - 1.28 (m, 5 H), 1.28 - 1.23 (m, 2 H), 1.18 (d, *J* = 13.7 Hz, 1 H), 1.11 (dd, *J* = 4.0, 12.8 Hz, 1 H), 1.08 (s, 3 H), 1.02 (s, 3 H), 1.01 (s, 4 H), 0.99 (s, 2 H), 0.94 (s, 3 H), 0.94 (br. s., 3 H), 0.90 (d, *J* = 6.4 Hz, 3 H).

Isomer 2: LCMS: m/e 747.5 (M+H)+, 2.29 min (method 6). ^{1}H NMR (500MHz , 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.5 Hz, 2 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 6.40 (s, 1 H), 5.29 (dd, *J* = 1.5, 6.1 Hz, 1 H), 4.76 (d, *J* = 1.5 Hz, 1 H), 4.64 (s, 1 H), 3.77 - 3.72 (m, 1 H), 3.23 - 3.14 (m, 2 H), 3.13 - 3.06 (m, 4 H), 3.05 - 2.99 (m, 2 H), 2.80 (d, *J* = 10.4 Hz, 1 H), 2.74 - 2.67 (m, 1 H), 2.61 (dt, *J* = 5.3, 11.1 Hz, 1 H), 2.49 (dd, *J* = 8.4, 12.7

Hz, 1 H), 2.12 (dd, *J* = 6.4, 17.1 Hz, 1 H), 2.08 - 2.01 (m, 1 H), 1.99 - 1.91 (m, 1 H), 1.88 (ddd, *J* = 3.1, 3.3, 6.8 Hz, 1 H), 1.86 - 1.82 (m, 1 H), 1.78 (d, *J* = 11.0 Hz, 1 H), 1.72 (br. s., 1 H), 1.71 (s, 3 H), 1.69 (d, *J* = 4.6 Hz, 1 H), 1.67 - 1.63 (m, 1 H), 1.61 - 1.53 (m, 2 H), 1.51 (br. s., 1 H), 1.48 (br. s., 2 H), 1.47 - 1.41 (m, 2 H), 1.12 (dd, *J* = 3.4, 13.4 Hz, 2 H), 1.07 (s, 3 H), 1.01 (br. s., 3 H), 1.00 (s, 3 H), 0.99 (s, 3 H), 0.97 (d, *J* = 6.7 Hz, 3 H), 0.93 (s, 3 H), 0.93 (s, 3 H).

Example 112

Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-3a-[[3-methyl-1-oxo-2-[(tetrahydro-1,1-dioxido-3-thienyl)amino]butyl]amino]-1H-cyclopenta[a]chrysen-9-yl].

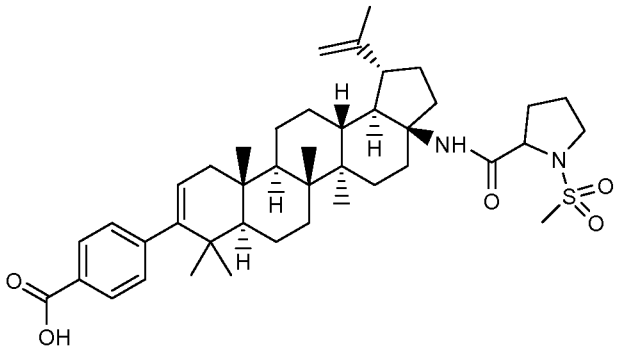


The title compound was prepared in 30% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-(1,1-dioxo-tetrahydro-1lambda6-thiophene-3-yl-amino)-3-methylbutyric acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 747.5 $(M+H)^+$, 2.09 min (method 6). ^{1}H NMR (500MHz , 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.25 (br. s., 1 H), 7.19 (d, *J* = 8.2 Hz, 2 H), 5.28 (d, *J* = 4.9 Hz, 1 H), 4.78 (s, 1

H), 4.65 (br. s., 1 H), 3.73 (ddd, *J* = 6.6, 6.7, 9.3 Hz, 1 H), 3.47 (dd, *J* = 7.2, 13.3 Hz, 1 H), 3.41 (dt, *J* = 4.1, 8.6 Hz, 1 H), 3.27 (br. s., 1 H), 3.17 - 3.07 (m, 1 H), 2.75 - 2.63 (m, 2 H), 2.59 (dd, *J* = 7.2, 13.0 Hz, 1 H), 2.43 (dd, *J* = 8.5, 12.2 Hz, 1 H), 2.35 (dd, *J* = 8.9, 12.8 Hz, 1 H), 2.25 - 2.16 (m, 1 H), 2.12 (dd, *J* = 6.3, 17.2 Hz, 1 H), 1.91 - 1.76 (m, 3 H), 1.74 (br. s., 1 H), 1.71 (s, 3 H), 1.69 (br. s., 1 H), 1.58 - 1.47 (m, 6 H), 1.46 - 1.35 (m, 4 H), 1.35 - 1.28 (m, 1 H), 1.25 (d, *J* = 9.8 Hz, 1 H), 1.18 - 1.12 (m, 2 H), 1.10 (d, *J* = 6.7 Hz, 3 H), 1.08 (s, 3 H), 1.06 (d, *J* = 7.3 Hz, 3 H), 1.03 (s, 3 H), 1.00 (s, 3 H), 0.93 (s, 3 H), 0.93 (br. s., 3 H).

Example 113

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(1-(methylsulfonyl)pyrrolidine-2-carboxamido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

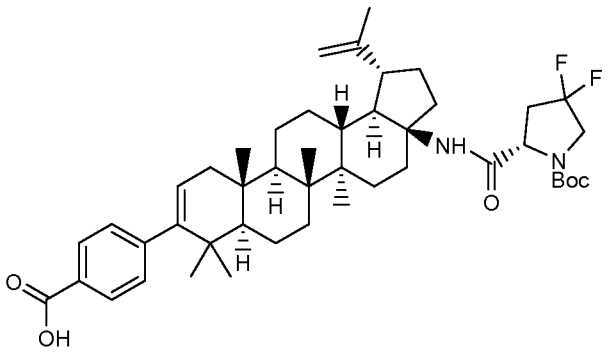


The title compound was prepared in 17% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 1-(methylsulfonyl)pyrrolidine-2-carboxylic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 705.5 $(M+H)^+$, 2.04 min (method 6). ^{1}H NMR (500MHz , 1:1

$CDCl_3$:MeOD) δ = 7.92 (d, *J* = 8.5 Hz, 2 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 6.88 (s, 1 H), 5.29 (dd, *J* = 1.5, 6.1 Hz, 1 H), 4.76 (d, *J* = 1.5 Hz, 1 H), 4.10 (dd, *J* = 3.1, 8.8 Hz, 1 H), 3.60 (ddd, *J* = 3.5, 7.0, 10.2 Hz, 1 H), 3.40 (dt, *J* = 6.4, 9.6 Hz, 1 H), 2.96 (s, 3 H), 2.62 - 2.52 (m, 2 H), 2.42 (dd, *J* = 8.2, 11.6 Hz, 1 H), 2.31 (dddd, *J* = 3.2, 3.4, 6.4, 9.7 Hz, 1 H), 2.21 - 2.16 (m, 1 H), 2.16 - 2.10 (m, 1 H), 2.03 (tdd, *J* = 3.2, 6.6, 13.0 Hz, 1 H), 1.99 - 1.89 (m, 2 H), 1.82 - 1.75 (m, 1 H), 1.75 - 1.72 (m, 1 H), 1.70 (s, 3 H), 1.69 - 1.66 (m, 1 H), 1.58 - 1.46 (m, 6 H), 1.46 - 1.29 (m, 5 H), 1.28 - 1.22 (m, 1 H), 1.14 (d, *J* = 13.1 Hz, 2 H), 1.09 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.93 (s, 6 H).

Example 114

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((S)-1-(tert-butoxycarbonyl)-4,4-difluoropyrrolidine-2-carboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

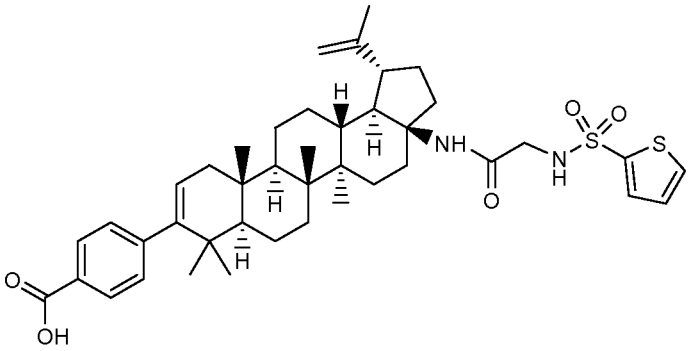


The title compound was prepared in 29% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except (S)-1-(tert-butoxycarbonyl)-4,4-difluoropyrrolidine-2-carboxylic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 763.5 $(M+H)^+$,

2.55 min (method 6). ^{1}H NMR (500MHz , 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.5 Hz, 2 H), 7.20 (d, *J* = 8.5 Hz, 2 H), 6.46 (br. s., 1 H), 5.29 (dd, *J* = 1.7, 6.3 Hz, 1 H), 4.72 (s, 1 H), 4.63 (br. s., 1 H), 4.50 (d, *J* = 9.2 Hz, 1 H), 3.84 (br. s., 1 H), 3.72 (td, *J* = 6.7, 13.4 Hz, 1 H), 2.84 (br. s., 1 H), 2.55 (d, *J* = 13.4 Hz, 1 H), 2.51 - 2.37 (m, 2 H), 2.12 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.96 (br. s., 1 H), 1.73 (br. s., 1 H), 1.70 (s, 4 H), 1.61 (br. s., 2 H), 1.56 (br. s., 9 H), 1.53 - 1.45 (m, 5 H), 1.45 - 1.37 (m, 3 H), 1.36 - 1.29 (m, 2 H), 1.28 - 1.23 (m, 1 H), 1.17 - 1.09 (m, 2 H), 1.08 (s, 3 H), 1.02 (s, 6 H), 0.94 (s, 3 H), 0.93 (s, 3 H).

Example 115

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(thiophene-2-sulfonamido)acetamido)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

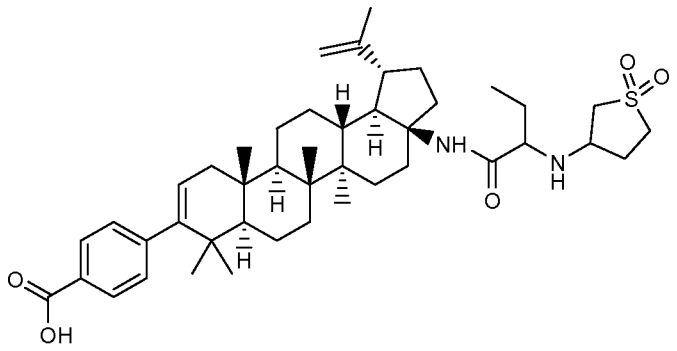


The title compound was prepared in 31% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-(thiophene-2-sulfonamido)acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 733.6 $(M+H)^+$, 2.06 min (method 6). ^{1}H NMR (500MHz , 1:1

$CDCl_3$:MeOD) δ = 7.92 (d, *J* = 8.5 Hz, 2 H), 7.73 (dd, *J* = 1.4, 5.0 Hz, 1 H), 7.66 (dd, *J* = 1.2, 3.7 Hz, 1 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 7.16 (dd, *J* = 3.8, 5.0 Hz, 1 H), 6.88 (s, 1 H), 5.32 - 5.26 (m, 1 H), 4.78 (d, *J* = 1.5 Hz, 1 H), 3.58 - 3.45 (m, 2 H), 2.63 - 2.57 (m, 1 H), 2.56 - 2.50 (m, 1 H), 2.42 (dd, *J* = 8.2, 12.2 Hz, 1 H), 2.13 (dd, *J* = 6.3, 17.2 Hz, 1 H), 1.98 - 1.88 (m, 1 H), 1.87 - 1.76 (m, 2 H), 1.73 (br. s., 1 H), 1.72 (s, 3 H), 1.70 - 1.66 (m, 1 H), 1.63 - 1.53 (m, 3 H), 1.53 - 1.46 (m, 4 H), 1.45 - 1.37 (m, 3 H), 1.37 - 1.30 (m, 2 H), 1.28 - 1.22 (m, 1 H), 1.14 (s, 3 H), 1.10 (d, *J* = 3.1 Hz, 1 H), 1.03 (s, 3 H), 1.02 (s, 3 H), 0.94 (s, 3 H), 0.94 (br. s., 3 H).

Example 116

Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-3a-[[1-oxo-2-[(tetrahydro-1,1-dioxido-3-thienyl)amino]butyl]amino]-1H-cyclopenta[a]chrysen-9-yl].

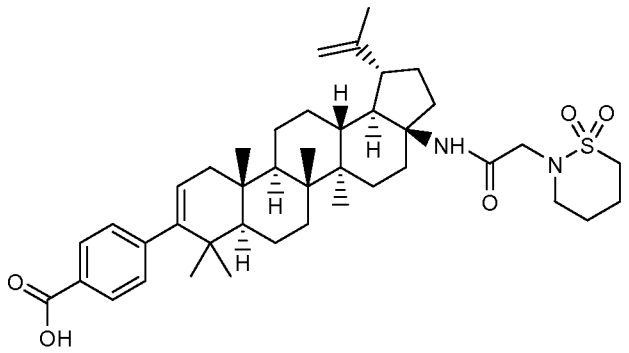


The title compound was prepared in 19% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-(1,1-dioxo-tetrahydro-1lambda6-thiophene-3-yl-amino)-butyric acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 733.6 $(M+H)^+$, 2.00 min (method 6). ^1H

NMR (500MHz , 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.38 (br. s., 1 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 5.29 (d, *J* = 4.6 Hz, 1 H), 4.77 (d, *J* = 8.5 Hz, 1 H), 3.77 (br. s., 1 H), 3.51 - 3.36 (m, 2 H), 3.22 - 3.09 (m, 2 H), 2.65 (d, *J* = 15.9 Hz, 3 H), 2.37 (br. s., 2 H), 2.13 (dd, *J* = 6.4, 17.4 Hz, 1 H), 1.96 - 1.77 (m, 5 H), 1.73 (br. s., 1 H), 1.73 (s, 3 H), 1.72 - 1.67 (m, 1 H), 1.61 - 1.52 (m, 2 H), 1.50 (d, *J* = 2.1 Hz, 3 H), 1.48 - 1.30 (m, 6 H), 1.29 - 1.23 (m, 1 H), 1.22 - 1.14 (m, 2 H), 1.12 (s, 2 H), 1.09 (d, *J* = 1.8 Hz, 2 H), 1.08 - 1.05 (m, 1 H), 1.04 (d, *J* = 1.8 Hz, 4 H), 1.03 (d, *J* = 4.0 Hz, 4 H), 0.95 (br. s., 3 H), 0.94 (br. s., 3 H).

Example 117

Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-3a-[[(tetrahydro-1,1-dioxido-2H-1,2-thiazin-2-yl)acetyl]amino]-1H-cyclopenta[a]chrysen-9-yl].

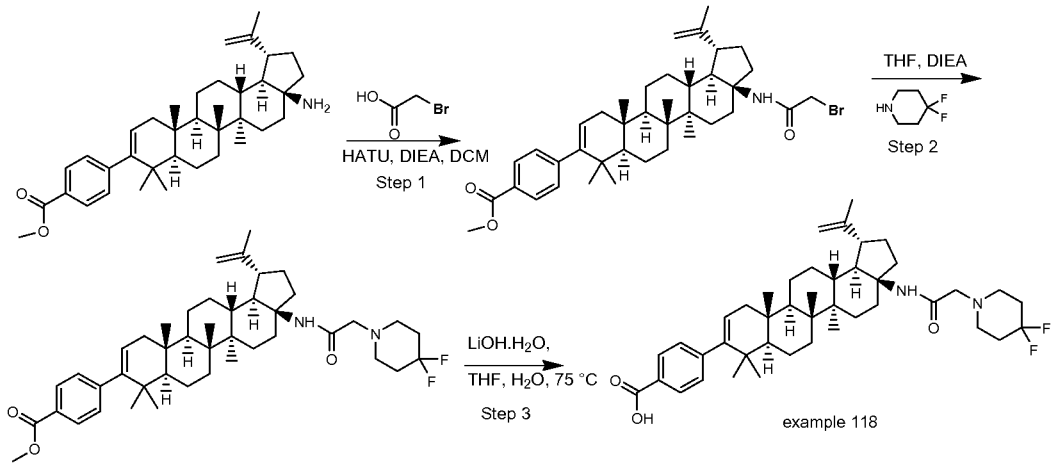


The title compound was prepared in 13% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propanamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except (1,1-dioxo-1,6-[1,2]thiazinan-2-yl)acetic acid was used instead of 3-(dimethylamino)propionic acid hydrochloride in Step 1. LCMS: m/e 705.5 $(M+H)^+$, 2.01 min (method 6). ^{1}H NMR (500MHz ,

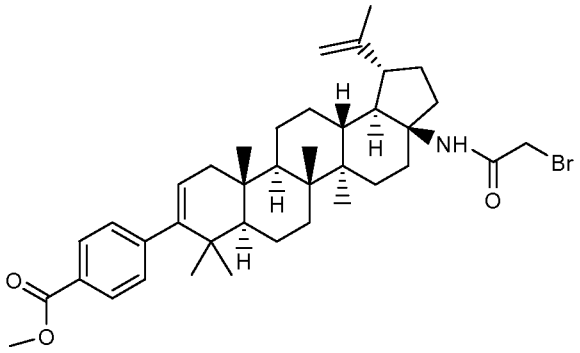
METHANOL-d4) δ = 7.92 (d, *J* = 8.5 Hz, 2 H), 7.20 (d, *J* = 8.5 Hz, 2 H), 6.83 (s, 1 H), 5.32 - 5.26 (m, 1 H), 4.77 (d, *J* = 1.5 Hz, 1 H), 4.64 (s, 1 H), 3.83 - 3.72 (m, 2 H), 3.63 - 3.46 (m, 2 H), 3.37 (s, 2 H), 3.21 - 3.11 (m, 2 H), 2.62 - 2.54 (m, 1 H), 2.53 - 2.50 (m, 1 H), 2.49 - 2.41 (m, 1 H), 2.32 - 2.23 (m, 2 H), 2.13 (dd, *J* = 6.6, 17.2 Hz, 1 H), 1.99 - 1.87 (m, 1 H), 1.78 (br. s., 1 H), 1.77 - 1.73 (m, 3 H), 1.72 (s, 3 H), 1.71 - 1.67 (m, 1 H), 1.62 - 1.51 (m, 3 H), 1.48 (d, *J* = 5.2 Hz, 3 H), 1.46 - 1.31 (m, 5 H), 1.28 - 1.23 (m, 1 H), 1.14 (d, *J* = 13.4 Hz, 2 H), 1.11 (s, 3 H), 1.03 (s, 3 H), 1.02 (s, 3 H), 0.94 (s, 3 H), 0.94 (s, 3 H).

Example 118

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4,4-difluoropiperidin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

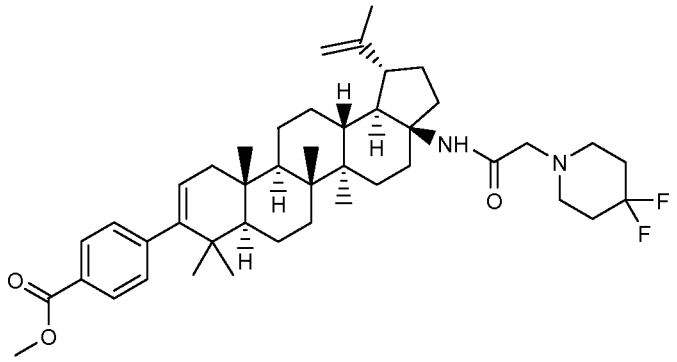


Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-bromoacetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.



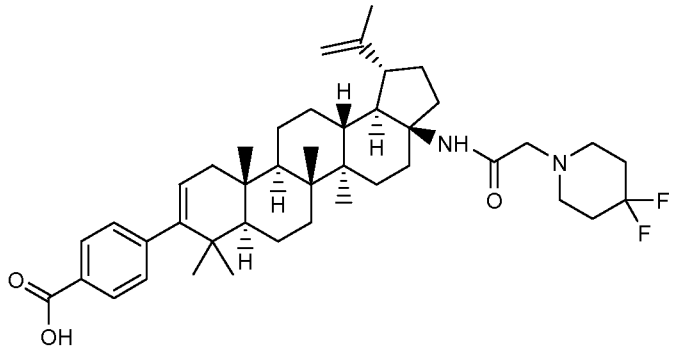
To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate, HCl (403 mg, 0.694 mmol) in DCM (10 mL) was added *N,N*-diisopropylethylamine (0.484 mL, 2.78 mmol), bromoacetic acid (106 mg, 0.764 mmol) and 2-(3H-[1,2,3]triazolo[4,5-β]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (317 mg, 0.833 mmol). The reaction mixture was stirred at rt for 15 h. Then, the reaction was concentrated and the crude residue was dissolved in THF (3.0 mL) filtered and purified by reverse phase preparative HPLC using HPLC method 3 to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-bromoacetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (148.9 mg, 0.224 mmol, 32.3% yield) as white solid. LCMS: m/e 664.6 $(M+H)^+$, 2.41 min (method 6).

Step 2. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4,4-difluoropiperidin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.



To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-bromoacetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (30 mg, 0.045 mmol) in THF (3 mL) was added *N,N*-diisopropylethylamine (0.039 mL, 0.226 mmol) and 4,4-difluoropiperidine, HCl (21.34 mg, 0.135 mmol). The reaction mixture was stirred at 80 °C for 18 h. Additional *N,N*-diisopropylethylamine (0.078 mL, 0.452 mmol) and 4,4-difluoropiperidine, HCl (40 mg, 0.354 mmol) were added, and the mixture was heated to 150 °C in a microwave for 7.5 h. The mixture was concentrated to brown viscous oil. The crude residue was dissolved in THF (1.5 mL), filtered and purified by reverse phase preparative HPLC using HPLC method 3 to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4,4-difluoropiperidin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate, TFA (13.1 mg, 0.016 mmol, 35.4% yield) as white solid. LCMS: m/e 705.6 $(M+H)^+$, 2.95 min (method 6). ^{1}H NMR (500MHz , *CHLOROFORM-d*) δ = 7.94 (d, *J* = 8.5 Hz, 2 H), 7.90 - 7.80 (m, 1 H), 7.21 (d, *J* = 8.2 Hz, 2 H), 6.32 (s, 1 H), 5.31 (dd, *J* = 1.4, 6.0 Hz, 1 H), 4.77 (s, 1 H), 4.67 (s, 1 H), 3.93 (s, 3 H), 3.72 - 3.61 (m, 3 H), 3.51 - 3.41 (m, 5 H), 2.83 (d, *J* = 2.7 Hz, 2 H), 2.63 (d, *J* = 13.1 Hz, 1 H), 2.56 (dt, *J* = 5.3, 10.9 Hz, 1 H), 2.39 (dd, *J* = 8.2, 12.8 Hz, 1 H), 2.12 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.91 - 1.81 (m, 1 H), 1.79 - 1.73 (m, 2 H), 1.72 (s, 3 H), 1.70 - 1.64 (m, 1 H), 1.54 - 1.40 (m, 7 H), 1.39 - 1.26 (m, 3 H), 1.26 - 1.21 (m, 1 H), 1.18 - 1.09 (m, 2 H), 1.04 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H), 0.95 (br. s., 3 H), 0.94 (br. s., 3 H).

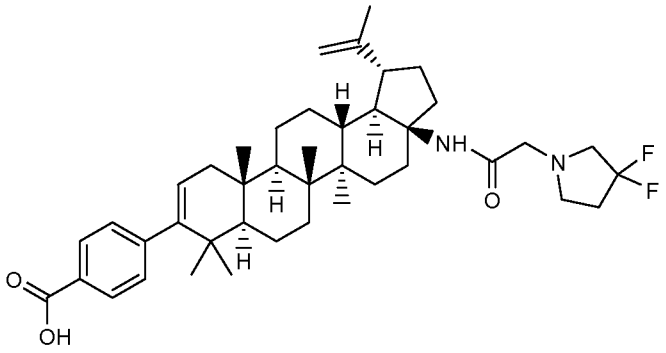
Step 3. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4,4-difluoropiperidin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4,4-difluoropiperidin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (13.1 mg, 0.019 mmol) in THF (3 mL) was added a 0.753 molar aqueous solution of LiOH . H_2O (0.149 mL, 0.074 mmol). The reaction was heated to 75 °C for 6h. The reaction was concentrated to brown viscous oil, and the crude material was purified by reverse phase preparative HPLC using HPLC method 3 to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4,4-difluoropiperidin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, TFA (9.4 mg, 0.012 mmol, 62.8% yield) as white solid. LCMS: m/e 691.6 $(M+H)^+$, 2.34 min (method 6). ^{1}H NMR (500MHz , *METHANOL-d_4*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.43 (s, 1 H), 7.20 (d, *J* = 8.5 Hz, 2 H), 5.30 (dd, *J* = 1.7, 6.3 Hz, 1 H), 4.75 (d, *J* = 1.2 Hz, 1 H), 4.66 (d, *J* = 1.5 Hz, 1 H), 3.71 - 3.58 (m, 2 H), 3.24 (br. s., 3 H), 2.67 - 2.61 (m, 1 H), 2.57 (dt, *J* = 5.3, 11.1 Hz, 1 H), 2.41 (dd, *J* = 8.2, 12.5 Hz, 1 H), 2.33 - 2.22 (m, 4 H), 2.13 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.95 - 1.83 (m, 1 H), 1.81 (d, *J* = 9.2 Hz, 2 H), 1.74 (br. s., 1 H), 1.72 (s, 3 H), 1.71 - 1.67 (m, 1 H), 1.59 - 1.43 (m, 8 H), 1.42 - 1.31 (m, 3 H), 1.29 - 1.23 (m, 1 H), 1.18 - 1.12 (m, 2 H), 1.09 (s, 3 H), 1.04 (s, 3 H), 1.02 (s, 3 H), 0.95 (s, 3 H), 0.94 (br. s., 3 H).

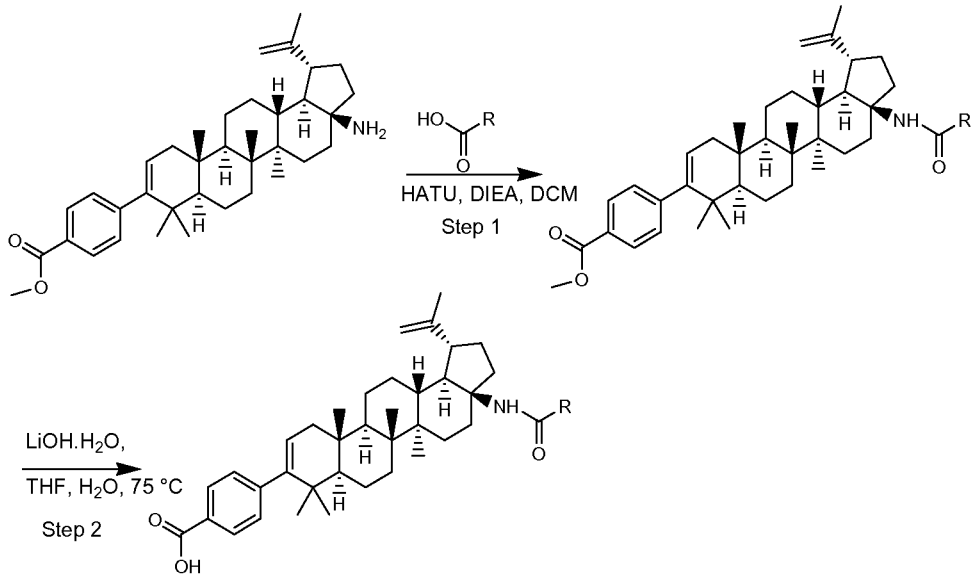
Example 119

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3,3-difluoropyrrolidin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared in 38% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4,4-difluoropiperidin-1-yl)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except and 3,3-difluoropyrrolidine, HCl was used instead of 4,4-difluoropiperidine, HCl in Step 2. LCMS: m/e 677.5 $(M+H)^+$, 2.26 min (method 6). ^{1}H NMR (500MHz, 1:1 *$CDCl_3$:MeO D*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.40 (s, 1 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 5.29 (dd, *J* = 1.7, 6.3 Hz, 1 H), 4.75 (d, *J* = 1.2 Hz, 1 H), 4.65 (s, 1 H), 3.59 - 3.44 (m, 2 H), 3.43 - 3.36 (m, 1 H), 3.31 - 3.20 (m, 2 H), 2.63 - 2.55 (m, 1 H), 2.55 - 2.47 (m, 3 H), 2.47 - 2.39 (m, 1 H), 2.13 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.94 - 1.83 (m, 1 H), 1.81 - 1.76 (m, 2 H), 1.76 - 1.73 (m, 1 H), 1.72 (s, 3 H), 1.70 - 1.65 (m, 1 H), 1.57 - 1.46 (m, 6 H), 1.46 - 1.40 (m, 2 H), 1.39 - 1.31 (m, 2 H), 1.26 (dd, *J* = 2.7, 10.7 Hz, 1 H), 1.19 - 1.10 (m, 2 H), 1.09 (s, 3 H), 1.03 (s, 3 H), 1.02 (s, 3 H), 0.95 (s, 3 H), 0.94 (s, 3 H).

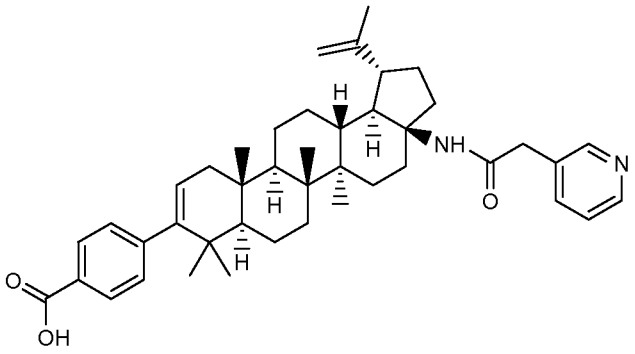
General procedure for parallel synthesis of C-17 amides:



A stock solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate, HCl (0.990 g, 1.7 mmol) and DIPEA (1.10 g, 8.52 mmol) in DCE (13 mL) was prepared. A stock solution of the HATU (1.94 g, 5.11 mmol) in DCE (13 mL) was prepared. To each of the carboxylic acids (0.393 mmol) weighed into 16x100 mm Wheaton vials was added 1 mL of the stock HATU solution. The vials were capped and shaken at rt for 10 min before adding 1 mL of the stock methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate, HCl /DIPEA solution to each vial. The vials were capped and shaken at rt for 18 h. Samples were concentrated. A stock solution of lithium hydroxide monohydrate (0.286 g, 6.81 mmol) in water (6.50 mL) was prepared. To each of the reaction vials was added 2.5 mL of THF and 0.5 mL of the stock lithium hydroxide solution. The vials were capped and the reactions were stirred at 75°C for 18 h. Added an additional 0.5 mL of the stock lithium hydroxide solution and stirred at 75°C for an additional 48 h. Samples were concentrated, redissolved in a small quantity of a mixture of THF and methanol, filtered and purified by reverse phase preparative HPLC.

Example 120

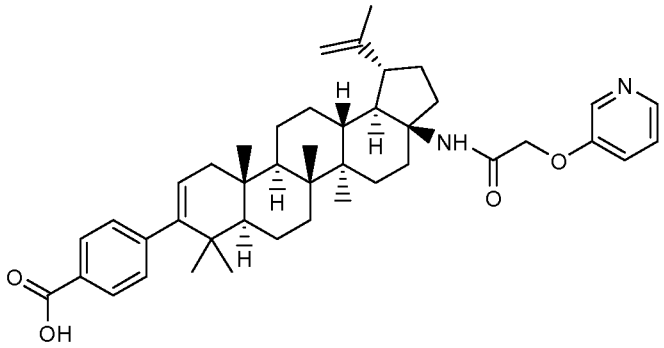
Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-3a-[(3-pyridinylacetyl)amino]-1H-cyclopenta[a]chrysen-9-yl].



The title compound was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure described for the parallel synthesis of C-17 amides above, using pyridylacetic acid hydrochloride as the reacting carboxylic acid. LCMS: m/e 649.6 $(M+H)^+$, 4.09 min (method 3).

Example 121

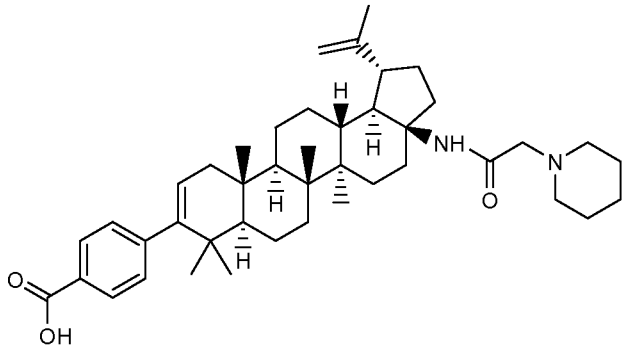
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridin-3-yloxy)acetamido)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure described for the parallel synthesis of C-17 amides above, using 3-pyridyloxyacetic acid as the reacting carboxylic acid. LCMS: m/e 665.6 $(M+H)^+$, 4.37 min (method 3).

Example 122

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(piperidin-1-yl)acetamido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

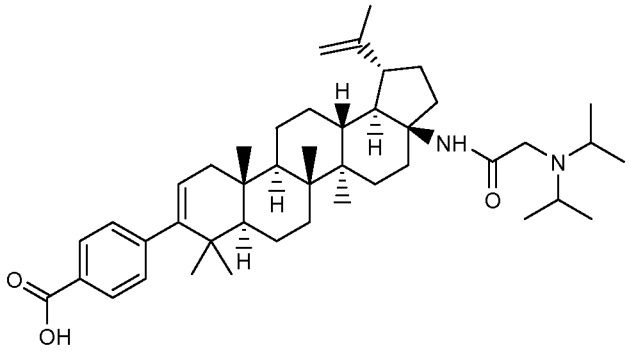


The title compound was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure described for the parallel synthesis of C-17 amides above, using piperidin-1-ylacetic acid hydrochloride as the reacting carboxylic acid. LCMS: m/e 655.7 $(M+H)^+$, 4.68 min (method 3).

Example 123

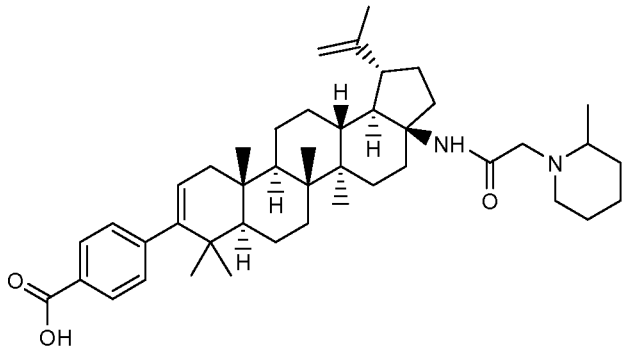
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(diisopropylamino)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure described for the parallel synthesis of C-17 amides above, using diisopropylamino-acetic acid as the reacting carboxylic acid. LCMS: m/e 671.7 $(M+H)^+$, 4.99 min (method 3). ^{1}H NMR (599MHz ,<*DMSO_CDCl3*>) δ = 8.45 - 8.37 (m, 1 H), 7.89 (d, *J* = 8.2 Hz, 2 H), 7.69 - 7.65 (m, 1 H), 7.24 - 7.20 (m, 2 H), 5.31 - 5.24 (m, 1 H), 4.79 - 4.73 (m, 1 H), 4.67 - 4.62 (m, 1 H), 3.95 (br. s., 2 H), 3.66 (d, *J* = 5.9 Hz, 3 H), 2.94 (s, 1 H), 2.78 (s, 1 H), 2.74 (br. s., 1 H), 2.63 (d, *J* = 13.5 Hz, 1 H), 2.30 (t, *J* = 9.1 Hz, 1 H), 2.13 (dd, *J* = 6.2, 16.7 Hz, 1 H), 2.07 - 1.98 (m, 1 H), 1.75 (br. s., 1 H), 1.72 (s, 4 H), 1.69 - 1.61 (m, 1 H), 1.52 - 1.41 (m, 8 H), 1.36 - 1.33 (m, 3 H), 1.33 - 1.31 (m, 2 H), 1.30 - 1.28 (m, 3 H), 1.28 - 1.25 (m, 3 H), 1.09 (s, 6 H), 1.01 (s, 6 H), 0.93 (br. s., 6 H).

Example 124

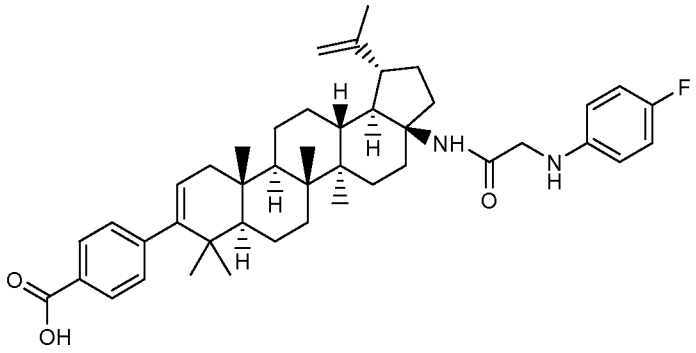
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(2-methylpiperidin-1-yl)acetamido)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure described for the parallel synthesis of C-17 amides above, using (2-methylpiperidin-1-yl)acetic acid as the reacting carboxylic acid. LCMS: m/e 669.7 $(M+H)^+$, 4.73 min (method 3).

Example 125

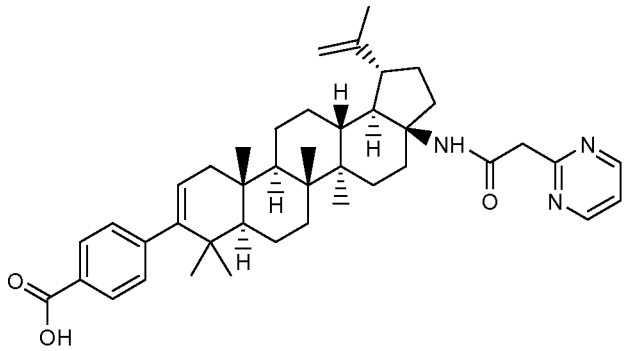
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4-fluorophenylamino)acetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure described for the parallel synthesis of C-17 amides above, using (4-fluorophenylamino)acetic acid as the reacting carboxylic acid. LCMS: m/e 681.7 $(M+H)^+$, 6.62 min (method 3).

Example 126

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyrimidin-2-yl)acetamido)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

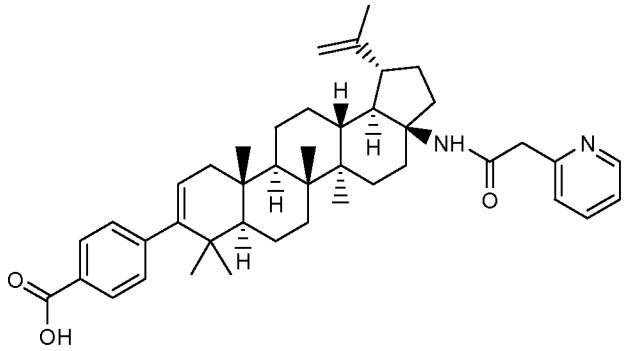


The title compound was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure described for the parallel synthesis of C-17 amides above, using 2-pyrimidine acetic acid as the reacting carboxylic acid. LCMS: m/e 650.6 $(M+H)^+$, 5.57 min (method 3). ^{1}H NMR (599MHz ,<*DMSO_CDCl3*>) δ = 8.78 (d, *J* = 4.7 Hz, 2 H), 7.88 (d, *J* = 8.2 Hz, 2 H), 7.29 (s, 1 H), 7.22 (d, *J* = 7.6 Hz, 2 H), 5.28 (d, *J* = 5.3 Hz, 1 H), 4.75 (s, 1 H), 4.62 (br. s., 1 H), 3.93 (s, 1 H), 3.82 (d, *J* = 14.6 Hz, 1 H), 2.77 - 2.72 (m, 1 H), 2.63 (d, *J* = 12.9 Hz, 1 H), 2.40 - 2.32 (m, 1 H), 2.16 - 2.04 (m, 1 H), 2.00 - 1.81 (m, 2 H), 1.73 (br. s., 2 H), 1.71 (s, 3 H), 1.67 - 1.52 (m, 4 H), 1.50 - 1.39 (m, 7 H), 1.36 - 1.20 (m, 7 H), 0.99 (br. s., 6 H), 0.98 (br. s., 3 H), 0.93 (br. s., 3 H), 0.93 (br. s., 3 H).

Example 127

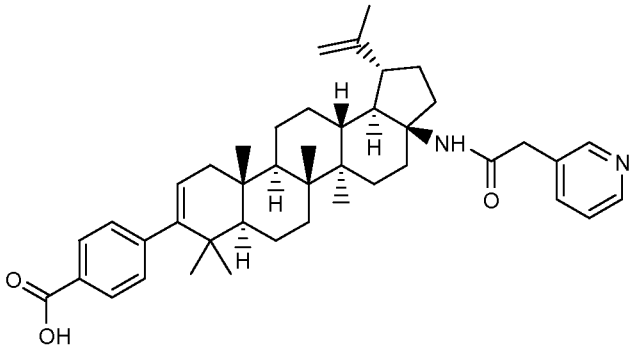
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridin-2-yl)acetamido)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure described for the parallel synthesis of C-17 amides above, using 2-pyridylacetic acid hydrochloride as the reacting carboxylic acid. LCMS: m/e 649.6 $(M+H)^+$, 4.23 min (method 3).

Example 128

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridin-3-yl)acetamido)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

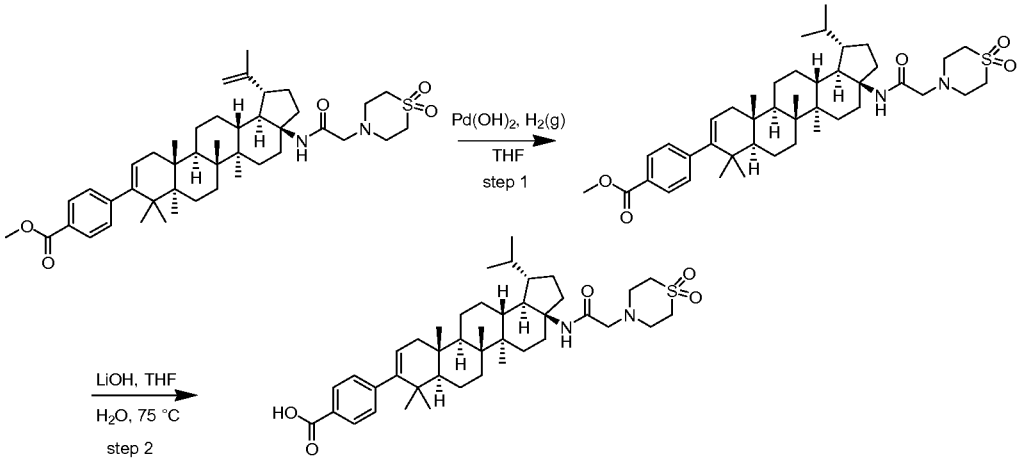


The title compound was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure described for the parallel synthesis of C-17 amides above, using 3-pyridylacetic acid hydrochloride as the reacting carboxylic acid. LCMS: m/e 649.6 $(M+H)^+$, 4.07 min (method 3). ^{1}H NMR (599MHz ,<*DMSO_CDCl$_3$*>) δ = 8.49 (d, *J* = 5.3 Hz, 2 H), 7.88 (s, 2 H), 7.33 (d, *J* = 5.3 Hz, 2 H), 7.22 (d, *J* = 8.2 Hz, 2 H), 7.17 (s, 1 H), 5.28 (d, *J* = 5.3 Hz, 1 H), 4.86 - 4.81 (m, 1 H), 4.76 (s, 1 H), 4.63 (br. s., 1 H), 3.66 (d, *J* = 12.9 Hz, 1 H), 3.49 (d, *J* = 12.9 Hz, 1 H), 2.85 - 2.79 (m, 1 H), 2.60 - 2.56 (m, 1 H), 2.35 - 2.28 (m, 1 H), 2.12 (dd, *J* = 6.4, 17.0 Hz, 1 H), 2.06 (t, *J* = 11.1 Hz, 1 H), 1.87 - 1.79 (m, 1 H), 1.73 (br. s., 2 H), 1.71 (s, 3 H), 1.61 - 1.50 (m, 2 H), 1.50 - 1.35 (m, 6 H), 1.37 - 1.27 (m, 3 H), 1.24 (d, *J* = 9.4 Hz, 3 H), 1.13 - 1.05 (m, *J* = 12.9 Hz, 1 H), 1.03 - 1.00 (m, 6 H), 0.97 (s, 3 H), 0.94 (s, 3 H), 0.93 (s, 3 H).

Example 129

Preparation of 4-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((1,1-dioxido-4-thiomorpholinyl)acetyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



Step 1. Preparation of methyl 4-[(1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxo-1,4-thiazinan-4-yl)acetyl]amino]-1-isopropyl-5a,5b,8,8,11a-pentamethyl-1,2,3,4,5,6,7,7a,11,11b,12,13,13a,13b-tetradecahydrocyclopenta[a]chrysen-9-yl]benzoate.

A solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (152 mg, 0.211 mmol) in THF (10 mL) was flushed with N_2(g) and palladium hydroxide (44.5 mg, 0.063 mmol) was added. The reaction mixture was purged with H_2 (g) then stirred under H_2 (g) atmosphere. After 68 h, the reaction was purged with N_2 (g), the catalyst was removed by filtering through celite and washed with DCM. The resulting liquid filtrate was concentrated to a viscous oil which was dissolved in THF (2.0 mL) filtered and injected into reverse phase HPLC for purification using HPLC method 5 to give the title compound (28.8 mg, 0.040 mmol, 18.89% yield; 62.8% yield based on recovered starting material). LCMS: m/z 721.6 ($M+H^+$), retention time 2.655 min (method 6). ^{1}H NMR (500MHz , *CHLOROFORM-d*) δ = 8.47 (br. s., 2 H), 7.95 (d, *J* = 8.2 Hz, 2 H), 7.22 (d, *J* = 8.5 Hz, 2 H), 6.98 (s, 1 H), 5.32 (dd, *J* = 1.5, 6.1 Hz, 1 H), 3.94 (s, 3 H), 3.69 - 3.61 (m, 1 H), 3.58 - 3.52 (m, 4 H), 3.31 - 3.27 (m, 3 H), 2.65 (d, *J* = 11.6 Hz, 1 H), 2.37 (dd, *J* = 7.5, 12.7 Hz, 1 H), 2.20 - 2.11 (m, 1 H), 1.98 - 1.86 (m, 1 H), 1.72 (d, *J*

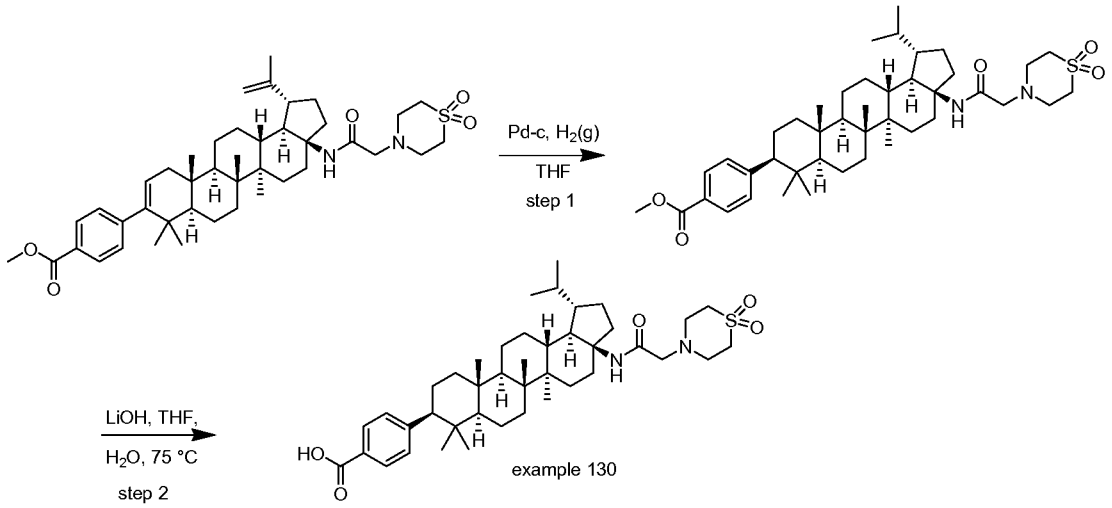
= 15.9 Hz, 3 H), 1.62 - 1.52 (m, 3 H), 1.52 - 1.36 (m, 9 H), 1.34 - 1.23 (m, 3 H), 1.21 - 1.14 (m, 2 H), 1.03 (s, 3 H), 1.02 (br. s., 3 H), 1.01 (br. s., 3 H), 0.95 (s, 6 H), 0.91 (d, *J* = 7.0 Hz, 3 H), 0.81 (d, *J* = 6.7 Hz, 3 H).

Step 2. Preparation of 4-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((1,1-dioxido-4-thiomorpholinyl)acetyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

To a solution of methyl 4-[(1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxo-1,4-thiazinan-4-yl)acetyl]amino]-1-isopropyl-5a,5b,8,8,11a-pentamethyl-1,2,3,4,5,6,7,7a,11,11b,12,13,13a,13b-tetradecahydrocyclopenta[a]chrysen-9-yl]benzoate, TFA (33 mg, 0.040 mmol) in THF (Volume: 3 mL) was added a 0.753 molar solution of lithium hydroxide monohydrate (0.316 mL, 0.158 mmol) in H_2O. The reaction mixture was heated to 75 °C. After 5.5 h, the reaction was concentrated to dryness. The crude residue was dissolved in THF (1.2 mL), MeOH (0.3 mL) and 1N HCl (0.2 mL). The solution was filtered and injected into reverse phase HPLC for purification using HPLC method 3 to give 4-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((1,1-dioxido-4-thiomorpholinyl)acetyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, TFA (17.9 mg, 0.021 mmol, 54.1% yield) as a white solid. LCMS: m/z 707.6 ($M+H^+$), retention time 2.030 min (method 6). ^1H NMR (500MHz , *METHANOL-d4*) δ = 7.93 (d, *J* = 8.5 Hz, 2 H), 7.21 (d, *J* = 8.5 Hz, 2 H), 7.13 (s, 1 H), 5.31 (dd, *J* = 1.5, 6.1 Hz, 1 H), 3.26 - 3.22 (m, 5 H), 3.21 - 3.15 (m, 4 H), 2.66 - 2.59 (m, 1 H), 2.37 (dd, *J* = 6.7, 12.5 Hz, 1 H), 2.17 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.99 - 1.91 (m, 1 H), 1.80 - 1.70 (m, 4 H), 1.67 - 1.57 (m, 2 H), 1.57 - 1.45 (m, 9 H), 1.44 - 1.39 (m, 1 H), 1.39 - 1.26 (m, 3 H), 1.18 - 1.11 (m, 2 H), 1.09 (s, 3 H), 1.04 (s, 6 H), 0.96 (s, 3 H), 0.95 (s, 3 H), 0.91 (d, *J* = 7.0 Hz, 3 H), 0.82 (d, *J* = 6.7 Hz, 3 H).

Example 130

Preparation of 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-(((1,1-dioxido-4-thiomorpholinyl)acetyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



Step 1. Preparation of methyl 4-[(1S,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxo-1,4-thiazinan-4-yl)acetyl]amino]-1-isopropyl-5a,5b,8,8,11a-pentamethyl-1,2,3,4,5,6,7,7a,9,10,11,11b,12,13,13a,13b-hexadecahydrocyclopenta[a]chrysen-9-yl]benzoate.

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (51 mg, 0.071 mmol) in THF (3 mL) was added palladium on activated charcoal (10% Pd content) (18 mg, 0.017 mmol). The reaction mixture was purged by bubbling H_2 (g) slowly into the mixture over 30 mins. and then the mixture was stirred under H_2 (g) atmosphere. After 24 h, the reaction mixture was purged with N_2 (g) and more catalyst (36 mg, 0.034 mmol) was added. The reaction mixture was stirred under H_2 (g) for an additional 24 h. The mixture was then purged with N_2 (g), and the catalyst was filtered and washed with THF. The liquid filtrate was concentrated. The crude residue was purified by preparative HPLC using HPLC method 5 to give methyl 4-[(1S,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxo-1,4-thiazinan-4-yl)acetyl]amino]-1-isopropyl-5a,5b,8,8,11a-pentamethyl-1,2,3,4,5,6,7,7a,9,10,11,11b,12,13,13a,13b-hexadecahydrocyclopenta[a]chrysen-9-yl]benzoate, TFA (24.4 mg, 0.029 mmol, 41.1% yield) as a white solid. LCMS: m/z 723.6 ($M+H^+$),

retention time 2.648 min (method 6). ^{1}H NMR (500MHz , *CHLOROFORM-d*) δ = 7.94 (d, *J* = 8.2 Hz, 2 H), 7.25 (d, *J* = 8.2 Hz, 2 H), 7.13 (br. s., 2 H), 7.05 (s, 1 H), 3.56 - 3.49 (m, 1 H), 3.48 - 3.39 (m, 5 H), 3.27 - 3.19 (m, 4 H), 2.66 (d, *J* = 12.5 Hz, 1 H), 2.42 (dd, *J* = 3.2, 13.3 Hz, 1 H), 2.40 - 2.34 (m, 1 H), 2.16 - 2.07 (m, 1 H), 1.96 - 1.90 (m, 1 H), 1.74 - 1.60 (m, 6 H), 1.59 - 1.51 (m, 2 H), 1.51 - 1.38 (m, 9 H), 1.37 - 1.31 (m, 2 H), 1.30 - 1.26 (m, 1 H), 1.21 - 1.10 (m, 2 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.98 (s, 3 H), 0.95 (s, 1 H), 0.91 (d, *J* = 7.0 Hz, 3 H), 0.81 (d, *J* = 6.7 Hz, 3 H), 0.78 (s, 3 H), 0.72 (s, 3 H). ^{13}C NMR (*CHLOROFORM-d*) δ ppm 167.7, 167.2, 149.5, 129.8, 129.4, 128.4, 128.3, 127.5, 65.9, 58.8, 57.3, 55.7, 51.8, 51.3, 49.9, 49.9, 48.2, 44.7, 41.9, 40.4, 40.3, 37.9, 37.4, 37.3, 34.5, 34.0, 29.4, 29.2, 28.1, 26.8, 26.2, 24.6, 22.6, 21.8, 20.4, 18.5, 17.4, 16.1, 15.6, 14.5, 14.1.

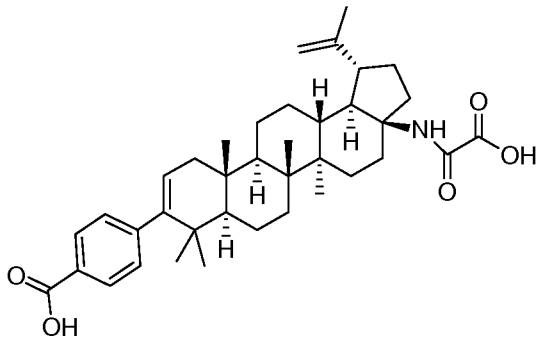
Step 2. Preparation 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-(((1,1-dioxido-4-thiomorpholinyl)acetyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

To a solution of 4-[(1S,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxo-1,4-thiazinan-4-yl)acetyl]amino]-1-isopropyl-5a,5b,8,8,11a-pentamethyl-1,2,3,4,5,6,7,7a,9,10,11,11b,12,13,13a,13b-hexadecahydrocyclopenta[a]chrysen-9-yl]benzoate, TFA (24.3 mg, 0.029 mmol) in THF (3 mL) was added a 0.753 molar aqueous solution of lithium hydroxide monohydrate (0.232 mL, 0.116 mmol). The reaction mixture was heated to 75 °C. After 5.5 h, the reaction mixture was concentrated to dryness. The crude residue was dissolved in THF (1.2 mL), MeOH (0.3 mL) and 1N HCl (0.2 mL). The resulting solution was filtered and purified using prep HPLC method 3 to give 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-(((1,1-dioxido-4-thiomorpholinyl)acetyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, TFA (16.5 mg, 0.020 mmol, 69.1% yield) as a white solid. LCMS: m/z 709.6 ($M+H^+$), retention time 2.072 min (method 6). ^{1}H NMR (500MHz , *METHANOL-d$_4$*) δ = 7.91 (d, *J* = 8.2 Hz, 2 H), 7.26 (d, *J* = 8.2 Hz, 2 H), 7.11 (s, 1 H), 3.25 - 3.20 (m, 6 H), 3.17 (d, *J* = 5.5 Hz, 4 H), 2.65 - 2.59 (m, 1 H), 2.44 (dd, *J* = 2.7, 13.1 Hz, 1 H), 2.37 (dd, *J* = 7.0, 12.5 Hz, 1 H), 2.19 - 2.04 (m, 1 H), 1.98 - 1.89 (m, 1 H), 1.85 (d, *J* = 13.1 Hz, 1 H), 1.74 (dd, *J* = 3.7, 7.9 Hz, 2 H), 1.71 - 1.60 (m, 3 H), 1.56 - 1.45 (m, 8 H), 1.44 - 1.37 (m, 4 H), 1.36 - 1.25 (m, 2 H), 1.16 - 1.09 (m, 2 H), 1.05 (s, 3 H), 1.04 (s, 3 H), 1.00 (s, 3 H),

0.95 (d, J = 2.1 Hz, 1 H), 0.91 (d, J = 6.7 Hz, 3 H), 0.81 (d, J = 6.7 Hz, 3 H), 0.78 (s, 3 H), 0.72 (s, 3 H).

Example 130-1

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(carboxyformamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

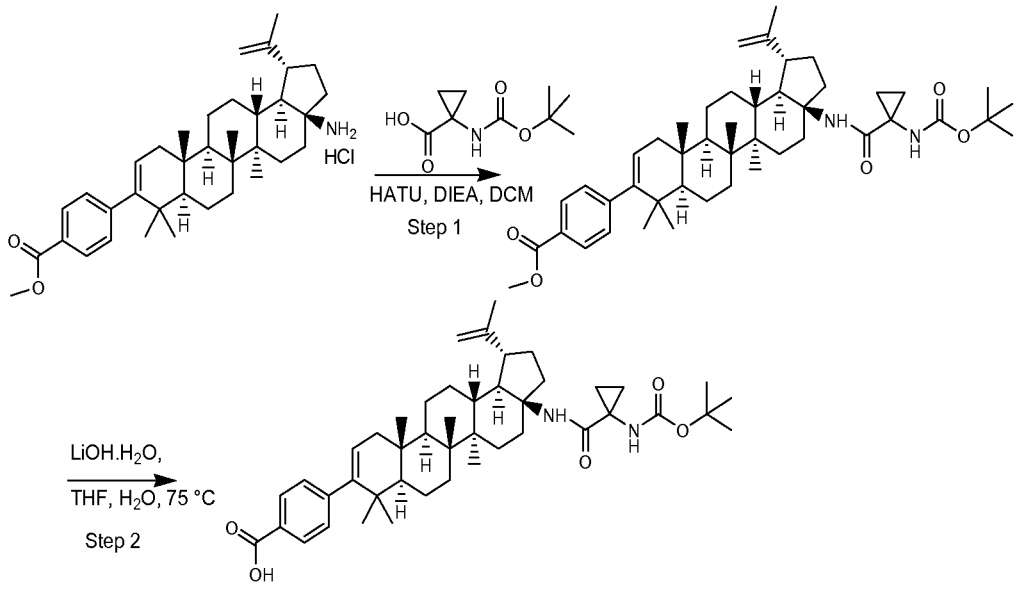


The title compounds was obtained in 25% yield as a by-product during the ester hydrolysis in Step 2 of the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoacetamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid. LCMS: m/e 600.5 $(M-H)^-$, 1.33 min (method 5). ^{1}H NMR (500MHz, *CHLOROFORM-d*) δ = 8.02 (d, J = 8.2 Hz, 2 H), 7.26 (d, J = 8.2 Hz, 3 H), 5.33 (d, J = 4.9 Hz, 1 H), 4.80 (s, 1 H), 4.70 (s, 1 H), 3.84 - 3.80 (m, 1 H), 2.59 (d, J = 10.1 Hz, 1 H), 2.54 (d, J = 5.2 Hz, 1 H), 2.46 (dd, J = 8.4, 11.7 Hz, 1 H), 2.18 - 2.11 (m, 1 H), 1.91 (ddd, J = 3.1, 3.3, 6.8 Hz, 2 H), 1.83 - 1.75 (m, 2 H), 1.74 (s, 3 H), 1.62 - 1.34 (m, 12 H), 1.28 (s, 1 H), 1.27 - 1.12 (m, 3 H), 1.07 (s, 3 H), 1.05 (s, 3 H), 1.02 (s, 3 H), 0.97 (br. s., 3 H), 0.96 (br. s., 3 H).

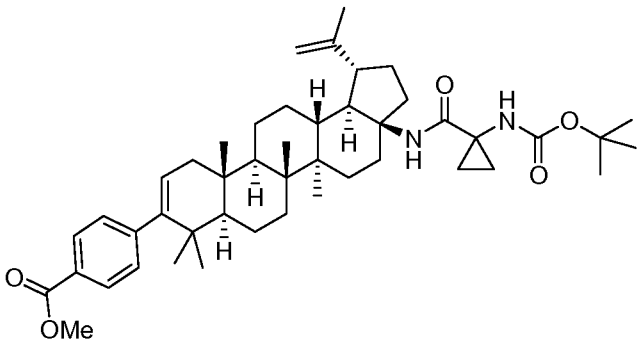
Example 130-2

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(1-(tert-butoxycarbonylamino)cyclopropanecarboxamido)-5a,5b,8,8,11a-pentamethyl-1-

(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



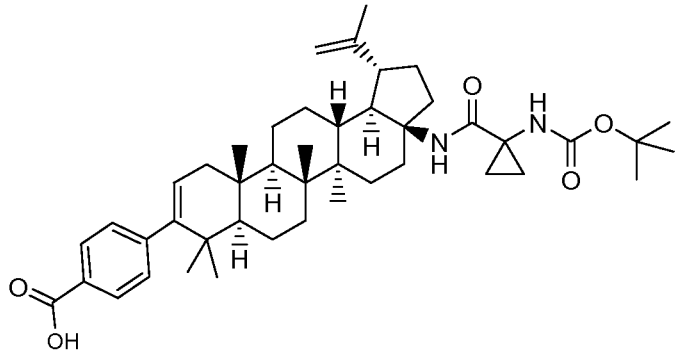
Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(1-(tert-butoxycarbonylamino)cyclopropanecarboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.



To a solution mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.302 g, 0.555 mmol) and *N,N*-diisopropylethylamine (0.580 mL, 3.33 mmol) in DCM (5 mL) was added 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (0.465 g, 1.222 mmol) and 1-(tert-

butoxycarbonylamino)cyclopropanecarboxylic acid (0.223 g, 1.111 mmol). The reaction mixture was stirred at rt. After 18 h, the reaction was diluted with DCM (20 mL) and silica gel (4g) was added. The mixture was concentrated to dryness and dried *in vacuo* to a free flowing powder. The material was loaded onto a silica gel column (25g cartridge) gradient 100% hexanes to 25% EtOAc in hexanes over 240 mL, hold 25% EtOAc in hexanes to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(1-(tert-butoxycarbonylamino)cyclopropanecarboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (234 mg, 0.309 mmol, 55.6 % yield) as a white solid. LCMS: m/e 727.4 $(M+H)^+$, 5.17 min (method 2). ^{1}H NMR (500MHz, *CHLOROFORM-d*) δ 7.97 - 7.89 (m, 2H), 7.20 (d, *J*=8.5 Hz, 2H), 6.47 (br. s., 1H), 5.30 (dd, *J*=6.3, 1.7 Hz, 1H), 5.16 - 5.06 (m, 1H), 4.72 (d, *J*=1.8 Hz, 1H), 4.62 (s, 1H), 4.19 - 4.09 (m, 1H), 3.92 (s, 3H), 2.66 - 2.60 (m, 1H), 2.49 (d, *J*=4.6 Hz, 2H), 2.11 (dd, *J*=17.1, 6.4 Hz, 1H), 2.07 - 1.96 (m, 1H), 1.53 (s, 9H), 1.46 (s, 3H), 1.43 (d, *J*=2.7 Hz, 1H), 1.37 (d, *J*=3.4 Hz, 1H), 1.34 (d, *J*=3.7 Hz, 1H), 1.26 (dd, *J*=7.0, 3.1 Hz, 1H), 1.19 - 1.16 (m, 1H), 1.12 (br. s., 3H), 1.10 - 1.07 (m, 1H), 1.01 (s, 3H), 1.01 - 0.99 (m, 3H), 0.94 (s, 3H), 0.94 (s, 3H).

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(1-(tert-butoxycarbonylamino)cyclopropanecarboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

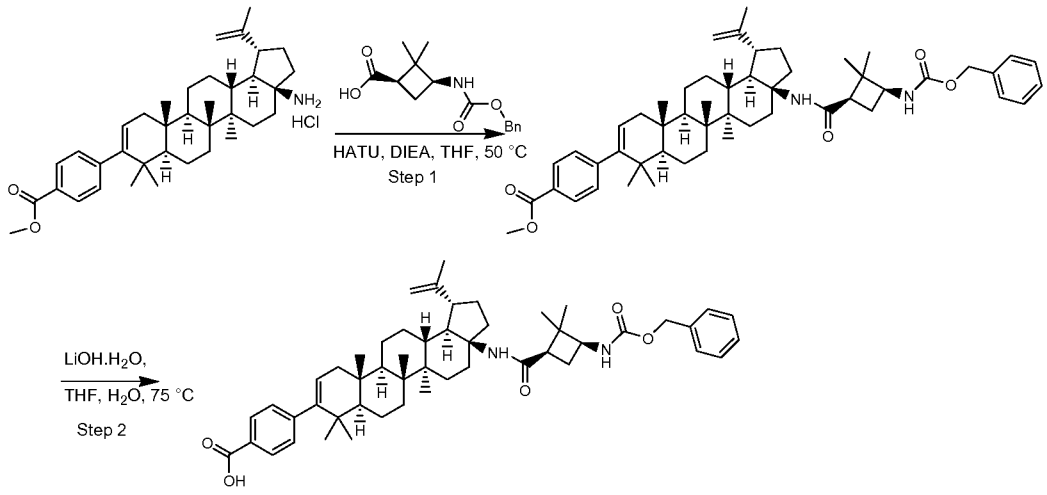


To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(1-(tert-butoxycarbonylamino)cyclopropanecarboxamido)-5a,5b,8,8,11a-pentamethyl-

1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (101 mg, 0.139 mmol) in THF (5 mL) was added a solution of lithium hydroxide monohydrate (17.49 mg, 0.417 mmol) in water (1.000 mL). The resulting mixture was stirred at 75°C. After 18 h, the reaction mixture was concentrated. The residue was redissolved in THF/MeOH, silica gel (2g) was added and the mixture was concentrated to dryness. The absorbed material was loaded onto a silica gel column (25g cartridge) and eluted with 0%B (solvent B = (90:10 DCM:MeOH, A = 100% DCM) to 50% B for 180 mL, then hold at 50 % B for 900 mL. Thus was obtained 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(1-(tert-butoxycarbonylamino)cyclopropanecarboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (39 mg, 0.054 mmol, 38.6 % yield) as white solid. LCMS: m/e 713.6 $(M+H)^+$, 2.32 min (method 1). ^{1}H NMR (500MHz, *1:1 $CDCl_3$:METHANOL-d_4*) δ 7.92 (d, *J*=8.2 Hz, 2H), 7.20 (d, *J*=8.2 Hz, 3H), 6.62 (br. s., 1H), 5.33 - 5.24 (m, 1H), 4.72 (s, 1H), 4.63 (s, 1H), 2.61 - 2.36 (m, 3H), 2.13 (dd, *J*=17.2, 6.3 Hz, 1H), 2.04 - 1.95 (m, 1H), 1.73 (br. s., 1H), 1.71 (s, 3H), 1.41 (d, *J*=6.1 Hz, 2H), 1.26 (br. s., 9H), 1.15 (s, 3H), 1.10 (br. s., 1H), 1.03 (s, 3H), 1.02 (s, 3H), 0.95 (s, 3H), 0.94 (s, 3H), 0.88 (d, *J*=6.7 Hz, 2H), 0.86 - 0.83 (m, 2H).

Example 130-3

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(1-(tert-butoxycarbonylamino)cyclopropanecarboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1R,3S)-3-(((benzyloxy)carbonyl)amino)-2,2-dimethylcyclobutanecarboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate, HCl (265 mg, 0.457 mmol) in tetrahydrofuran (5 mL) was added *N,N*-di-iso-propylethylamine (0.278 mL, 1.598 mmol), (1R,3S)-3-(((benzyloxy)carbonyl)amino)-2,2-dimethylcyclobutanecarboxylic acid (152 mg, 0.548 mmol) (for preparation see: J. Aguilera et al. *Tetrahedron Asymmetry* **2008**, *19*, 302) and O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (226 mg, 0.594 mmol). The reaction mixture was heated to 50 °C . After 6h, the mixture was dilute with EtOAc (30 mL) and washed with 1N HCl (5 mL). The aqueous layer was extracted with EtOAc (25 mL). The combined organic layer was washed with 5% $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated to afford a light brown viscous oil. The material was dissolved in DCM, loaded onto a silicagel column and eluted with 97:3 DCM:MeOH to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1R,3S)-3-(((benzyloxy)carbonyl)amino)-2,2-dimethylcyclobutanecarboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (335 mg, 0.355 mmol, 78 %

yield) as brown foam. LC/MS: m/e 802.4 $(M+H)^+$, 4.23 min (method 8). ^{1}H NMR (400MHz, *CHLOROFORM-d*) δ 7.95 (d, *J*=8.3 Hz, 2H), 7.40 - 7.37 (m, 5H), 7.21 (d, *J*=8.3 Hz, 2H), 5.31 (d, *J*=4.6 Hz, 1H), 5.18 - 5.12 (m, 2H), 5.10 - 5.06 (m, 1H), 4.97 (s, 1H), 4.76 (s, 1H), 4.66 (s, 1H), 3.93 (s, 3H), 2.85 (s, 6H), 2.69 - 2.55 (m, 2H), 2.44 - 2.29 (m, 3H), 2.17 - 2.09 (m, 2H), 1.94 - 1.81 (m, 3H), 1.72 (s, 3H), 1.70 - 1.66 (m, 1H), 1.62 - 1.52 (m, 4H), 1.46 (d, *J*=7.3 Hz, 1H), 1.42 (d, *J*=2.7 Hz, 1H), 1.37 (s, 3H), 1.32 - 1.22 (m, 3H), 1.15 (d, *J*=11.7 Hz, 2H), 1.09 (s, 2H), 1.02 (s, 3H), 1.01 (s, 3H), 1.00 (s, 3H), 0.95 (s, 6H).

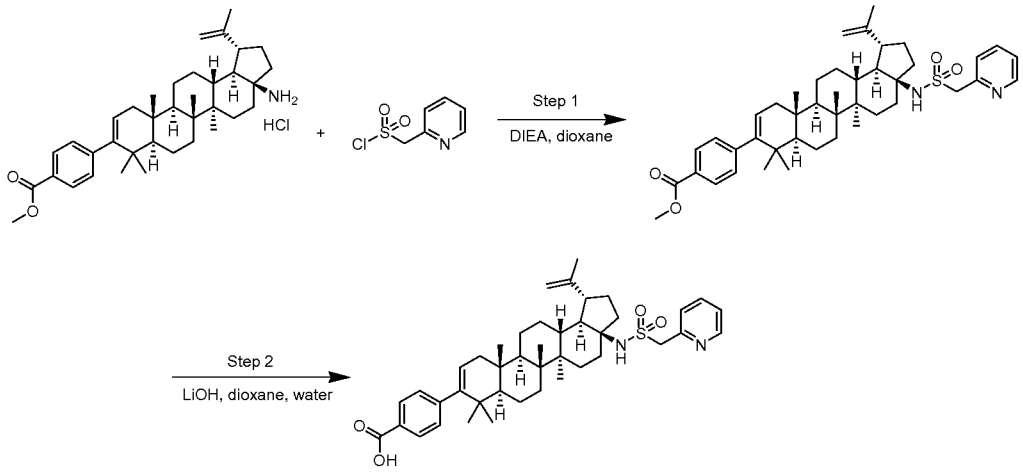
Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1R,3S)-3-(((benzyloxy)carbonyl)amino)-2,2-dimethylcyclobutanecarboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1R,3S)-3-(((benzyloxy)carbonyl)amino)-2,2-dimethylcyclobutanecarboxamido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (135 mg, 0.168 mmol) in THF (5 mL), MeOH (2 mL) was added a solution of lithium hydroxide monohydrate (0.014 mL, 0.504 mmol) in water (1 mL). The reaction mixture was stirred at 75 °C. After 4h, the mixture was concentrated to a white paste. The crude material was dissolved in THF (1.75 mL), MeOH (1 mL) and 1N HCl (0.25 mL) and injected into a reverse phase prep-HPLC using HPLC method **11** and dried in a vacuum oven to give the title compound (30.4 mg, 0.035 mmol, 21.09 % yield) as white solid. LCMS: m/e 789.4 $(M+H)^+$, 3.14 min (method 8). ^{1}H NMR (400MHz, *CHLOROFORM-d*) δ 8.02 (d, *J*=8.3 Hz, 2H), 7.41 - 7.37 (m, 4H), 7.36 (d, *J*=3.4 Hz, 1H), 7.25 (d, *J*=8.3 Hz, 2H), 5.33 (d, *J*=4.6 Hz, 1H), 5.19 - 5.07 (m, 3H), 4.99 (br. s., 1H), 4.77 (s, 1H), 4.66 (s, 1H), 3.98 - 3.88 (m, 1H), 2.70 - 2.55 (m, 3H), 2.47 - 2.28 (m, 3H), 2.19 - 2.09 (m, 2H), 1.99 - 1.87 (m, 1H), 1.76 (d, *J*=7.8 Hz, 1H), 1.72 (s, 3H), 1.71 - 1.63 (m, 2H), 1.58 (d, *J*=8.1 Hz, 3H), 1.50 (br. s., 3H), 1.43 (br. s., 1H), 1.37 (br. s., 3H), 1.33 (d, *J*=12.2 Hz, 2H), 1.28 (s, 3H), 1.24 (d, *J*=7.1 Hz, 1H), 1.16 (d, *J*=12.2 Hz, 2H), 1.09 (s, 3H), 1.02 (s, 6H), 1.01 (br. s., 3H), 0.96 (s, 6H).

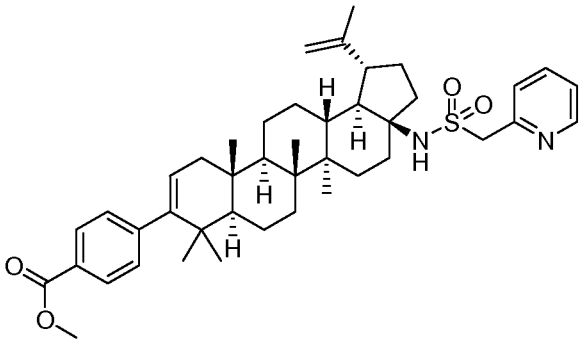
Section 4. Sulfonyl amides

Example 131

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(pyridin-2-ylmethylsulfonamido)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

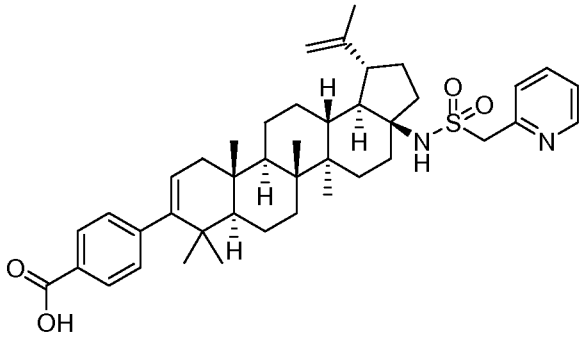


Step 1: Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(pyridin-2-ylmethylsulfonamido)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.



Methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.100 g, 0.184 mmol) was combined with pyridin-2-ylmethanesulfonyl chloride, triflic acid salt (0.189 g, 0.552 mmol). To the mixture was added dry 1,4-dioxane (1.5 mL) followed by addition of DIPEA (0.095 g, 0.736 mmol). The mixture was shaken at rt for 3 h. The crude reaction mixture was concentrated, redissolved in a mixture of MeOH and THF, and purified by reverse phase preparative HPLC. The title compound was isolated as a mono-TFA salt white solid (66 mg, 44% yield). LCMS: m/z 699 ($M+H^+$), retention time 3.03 min (method 11). 1H NMR (400 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.93 (s, 3 H) 0.94 (s, 3 H) 1.01 (d, *J*=1.76 Hz, 6 H) 1.07 - 1.20 (m, 5 H) 1.21 - 1.28 (m, 1 H) 1.34 - 1.57 (m, 11 H) 1.63 - 1.78 (m, 6 H) 1.78 - 1.95 (m, 2 H) 1.95 - 2.05 (m, 1 H) 2.12 (dd, *J*=17.19, 6.40 Hz, 1 H) 2.31 - 2.41 (m, 1 H) 2.41 - 2.51 (m, 1 H) 2.61 (td, *J*=10.98, 4.64 Hz, 1 H) 3.90 (s, 3 H) 4.56 - 4.59 (m, 1 H) 4.64 (br. s., 1 H) 4.75 (d, *J*=1.51 Hz, 1 H) 5.28 (dd, *J*=6.02, 1.51 Hz, 1 H) 7.20 (m, *J*=8.28 Hz, 2 H) 7.53 (br. s., 1 H) 7.70 (d, *J*=6.27 Hz, 1 H) 7.90 (m, *J*=8.28 Hz, 2 H) 7.98 (t, *J*=7.78 Hz, 1 H) 8.67 (br. s., 1 H).

Step 2: Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(pyridin-2-ylmethylsulfonamido)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



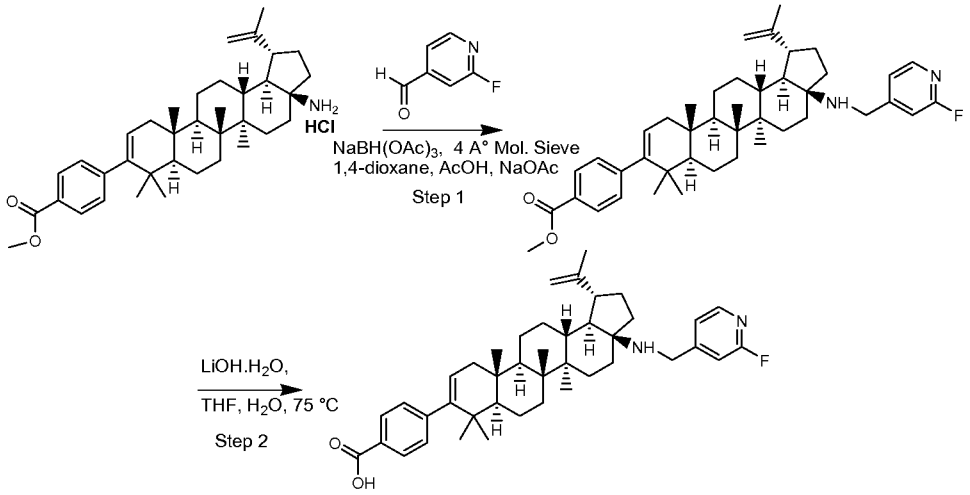
In a 1 dram vial with PTFE lined screw cap were combined methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(pyridin-2-ylmethylsulfonamido)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.060 g, 0.086 mmol), lithium hydroxide monohydrate (0.022 g, 0.515 mmol), 1,4-dioxane (0.8 mL) and water (0.4 mL). The vial was sealed and heated with stirring to 75 °C for 7 min. Small quantities of MeOH and THF were added to completely dissolve all solids, and the mixture was filtered and purified by reverse phase preparative HPLC. The mono-TFA salt product was isolated after purification as a white solid (56 mg, 96% yield). LCMS: m/z 685 ($M+H^+$), retention time 2.62 min (method 11). 1H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 0.94 (s, 3 H) 0.95 (s, 3 H) 1.02 (d, *J*=2.14 Hz, 6 H) 1.09 - 1.20 (m, 5 H) 1.22 - 1.29 (m, 1 H) 1.29 - 1.40 (m, 1 H) 1.40 - 1.60 (m, 9 H) 1.65 - 1.80 (m, 6 H) 1.82 - 2.02 (m, 3 H) 2.13 (dd, *J*=17.09, 6.41 Hz, 1 H) 2.33 - 2.41 (m, 1 H) 2.41 - 2.49 (m, 1 H) 2.64 (td, *J*=11.06, 4.73 Hz, 1 H) 4.64 (s, 3 H) 4.77 (d, *J*=1.53 Hz, 1 H) 5.29 (dd, *J*=6.26, 1.68 Hz, 1 H) 7.20 (d, *J*=8.54 Hz, 2 H) 7.61 - 7.67 (m, 1 H) 7.80 (d, *J*=7.93 Hz, 1 H) 7.92 (d, *J*=8.24 Hz, 2 H) 8.11 (td, *J*=7.78, 1.53 Hz, 1 H) 8.69 (d, *J*=3.97 Hz, 1 H).

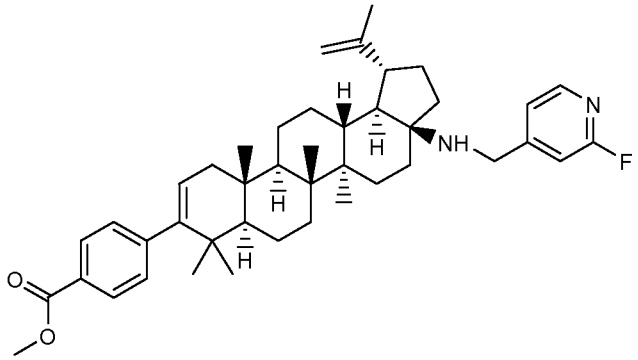
Section 5. Amines

Example 132

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoropyridin-4-yl)methylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



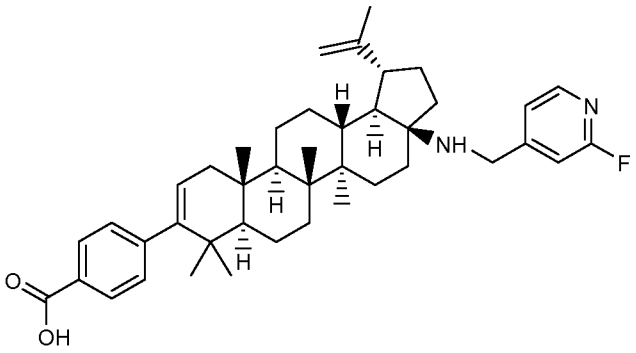
Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoropyridin-4-yl)methylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.



To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate, HCl (318 mg, 0.548 mmol) in DCE (10 mL) was added glacial acetic acid (0.314 mL, 5.48 mmol), sodium acetate (67.4 mg, 0.822 mmol), 2-fluoropyridine-4-carboxaldehyde (206 mg, 1.644 mmol) and 4A molecular sieves. The reaction mixture was heated to 65 °C for 18 h. To the reaction mixture was added sodium triacetoxyhydroborate (581 mg, 2.74 mmol) and the resulting mixture was heated to 65 °C for 7.5 h, then the mixture was left at rt for 48 h. The reaction was diluted with DCM (50 mL) and washed with saturated $NaHCO_3$ (20

mL). The aqueous layer was extracted with DCM (2 x 25 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting dark brown residue was dissolved in THF (3 mL) and MeOH (0.6 mL), filtered and purified by reverse phase preparative HPLC using HPLC method 3 to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoropyridin-4-yl)methylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate, TFA (218.4 mg, 0.285 mmol, 52.0% yield) as a white solid. LCMS: m/e 653.4 $(M+H)^+$, 2.69 min (method 6).

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoropyridin-4-yl)methylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

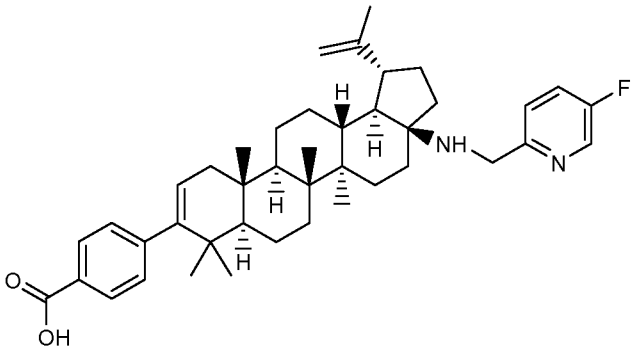


To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoropyridin-4-yl)methylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate, TFA (77.7 mg, 0.101 mmol) in THF (3 mL) was added a 0.753 molar aqueous solution of LiOH . H_2O (0.539 mL, 0.405 mmol). The reaction mixture was heated to 75 °C. After 4 h, the reaction mixture was concentrated. The crude residue was dissolved in THF (1.5 mL) and MeOH (200 µL), filtered and purified by reverse phase preparative HPLC using HPLC method 3 to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoropyridin-4-yl)methylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

cyclopenta[a]chrysen-9-yl)benzoic acid, TFA (30.6 mg, 0.037 mmol, 36.1% yield) as a white solid. LCMS: m/e 637.7 $(M-H)^-$, 3.12 min (method 6). ^{1}H NMR (500MHz , 1:1 *CDCl$_3$:MeOD*) δ = 8.24 (d, *J* = 5.2 Hz, 1 H), 7.92 (d, *J* = 8.2 Hz, 2 H), 7.43 (d, *J* = 5.2 Hz, 1 H), 7.24 (s, 1 H), 7.20 (d, *J* = 8.5 Hz, 2 H), 5.29 (dd, *J* = 1.7, 6.3 Hz, 1 H), 4.78 (s, 1 H), 4.17 (br. s., 2 H), 2.78 - 2.69 (m, 1 H), 2.18 - 2.10 (m, 2 H), 2.09 - 2.01 (m, 2 H), 1.98 (dd, *J* = 3.1, 11.9 Hz, 1 H), 1.96 - 1.88 (m, 1 H), 1.83 - 1.76 (m, 1 H), 1.72 (s, 3 H), 1.70 - 1.64 (m, 1 H), 1.63 - 1.40 (m, 10 H), 1.39 - 1.31 (m, 1 H), 1.31 - 1.23 (m, 2 H), 1.13 (s, 3 H), 1.07 (s, 3 H), 1.02 (s, 3 H), 0.95 (s, 3 H), 0.94 (s, 3 H). ^{13}C NMR (1:1 *CDCl$_3$:MeOD*) d ppm 15.3, 16.6, 17.4, 19.5, 20.6, 21.8, 22.2, 26.1, 27.6, 29.0, 29.5, 30.2, 33.9, 34.6, 37.2, 38.2, 38.4, 41.8, 42.8, 43.1, 45.7, 47.2, 49.7, 49.9, 50.3, 50.5, 53.9, 78.8, 123.1, 123.2, 124.9, 129.3, 129.7, 131.0, 147.4, 149.7, 164.0, 166.0, 170.1.

Example 133

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((5-fluoropyridin-2-yl)methylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

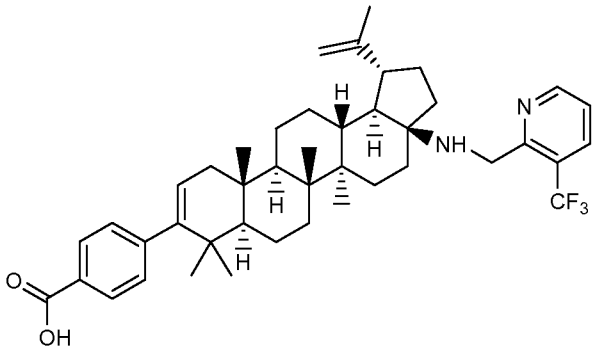


The title compound was prepared in 47% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoropyridin-4-yl)methylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-

yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 5-fluoro-2-formylpyridine was used instead of 2-fluoropyridine-4-carboxaldehyde in Step 1. LCMS: m/e 639.5 $(M+H)^+$, 3.33 min (method 6). ^{1}H NMR (500MHz , 1:1 *$CDCl_3$:MeOD*) δ = 8.46 (d, *J* = 2.7 Hz, 1 H), 7.93 (d, *J* = 8.2 Hz, 2 H), 7.68 (dt, *J* = 2.7, 8.2 Hz, 1 H), 7.53 (dd, *J* = 4.1, 8.7 Hz, 1 H), 7.21 (d, *J* = 8.5 Hz, 2 H), 5.31 (dd, *J* = 1.7, 6.3 Hz, 1 H), 4.83 (s, 1 H), 4.74 (s, 1 H), 4.49 (d, *J* = 15.3 Hz, 1 H), 4.32 (d, *J* = 15.0 Hz, 1 H), 2.78 (dt, *J* = 5.3, 10.9 Hz, 1 H), 2.22 - 2.06 (m, 5 H), 1.96 (dt, *J* = 3.4, 12.2 Hz, 1 H), 1.89 - 1.82 (m, 1 H), 1.80 (d, *J* = 10.7 Hz, 2 H), 1.76 (s, 3 H), 1.74 - 1.66 (m, 2 H), 1.64 - 1.54 (m, 4 H), 1.53 - 1.47 (m, 2 H), 1.46 - 1.42 (m, 1 H), 1.41 - 1.37 (m, 1 H), 1.33 (s, 3 H), 1.29 (dd, *J* = 3.8, 9.9 Hz, 1 H), 1.24 (dd, *J* = 4.1, 13.0 Hz, 1 H), 1.13 (s, 3 H), 1.07 (s, 3 H), 0.97 (s, 3 H), 0.95 (s, 3 H).

Example 134

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((3-(trifluoromethyl)pyridin-2-yl)methylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

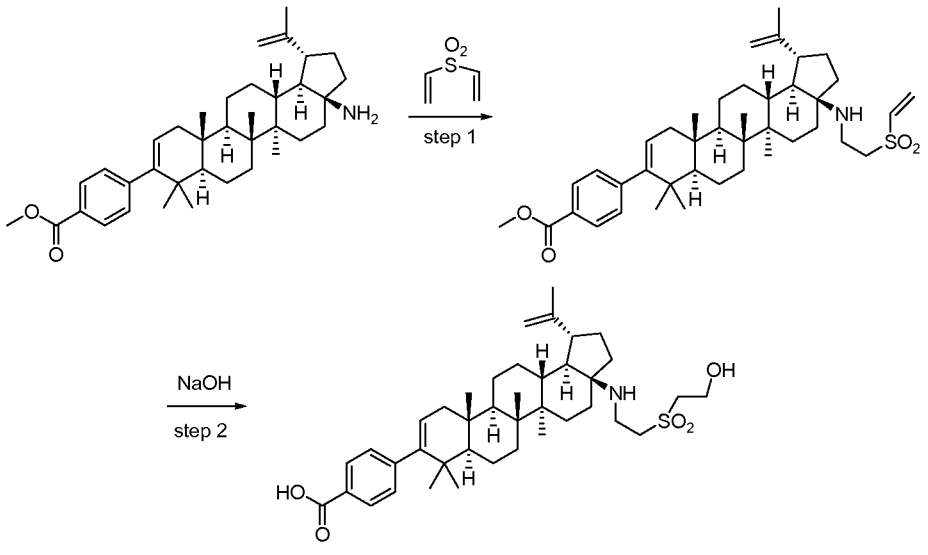


The title compound was prepared in 42% yield from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the same procedure as described for the preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoropyridin-4-yl)methylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-

yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 3-trifluoromethylpyridine-2-carbaldehyde was used instead of 2-fluoropyridine-4-carboxaldehyde in Step 1. LCMS: m/e 689.6 $(M+H)^+$, 4.12 min (method 6). ^1H NMR (500MHz , 1:1 *$CDCl_3$:MeOD*) δ = 8.83 (d, *J* = 4.3 Hz, 1 H), 8.28 (d, *J* = 7.9 Hz, 1 H), 7.93 (d, *J* = 8.5 Hz, 2 H), 7.72 (dd, *J* = 5.0, 7.8 Hz, 1 H), 7.21 (d, *J* = 8.5 Hz, 2 H), 5.31 (dd, *J* = 1.5, 6.1 Hz, 1 H), 4.85 (s, 1 H), 4.76 (s, 1 H), 4.44 (d, *J* = 16.2 Hz, 1 H), 2.80 (dt, *J* = 5.5, 11.0 Hz, 1 H), 2.25 - 2.10 (m, 5 H), 2.02 (dt, *J* = 3.5, 12.1 Hz, 1 H), 1.92 - 1.79 (m, 2 H), 1.78 (s, 3 H), 1.76 - 1.68 (m, 3 H), 1.64 - 1.54 (m, 4 H), 1.52 - 1.43 (m, 3 H), 1.40 (br. s., 1 H), 1.36 (s, 3 H), 1.32 - 1.22 (m, 2 H), 1.16 - 1.13 (m, 3 H), 1.08 (s, 3 H), 0.97 (s, 3 H), 0.95 (s, 3 H).

Example 135

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-hydroxyethylsulfonyl)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(vinylsulfonyl)ethylamino)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (30 mg, 0.055 mmol), TEA (0.023 mL, 0.165 mmol) and vinylsulfonylethene (19.5 mg, 0.165 mmol) in EtOH (1 mL) was heated for 3 h at 100 °C. The reaction mixture was quenched with water, extracted with DCM (3 x 2 mL). The organic phases were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to provide the title compound as a brown oil (25 mg, 68%). LCMS: m/e 662.42 $(M+H)^+$, 3.45 min (method 10).

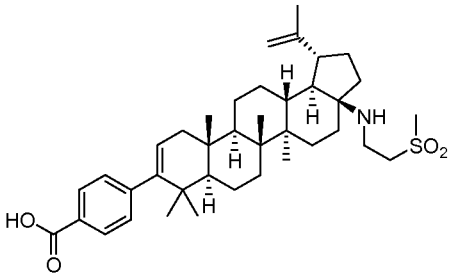
Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-hydroxyethylsulfonyl)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(vinylsulfonyl)ethylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (25 mg, 0.038 mmol) and sodium hydroxide (0.189 mL, 0.189 mmol) in dioxane (1 mL) was heated at 78 °C for 3 h. The reaction mixture was filtered and the clear solution was purified by prep HPLC to provide the title compound as a white solid (14 mg, 53%). LCMS: m/e 666.39 $(M+H)^+$, 2.48 min (method 10). ^{1}H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.03 (d, *J*=8.24 Hz, 2 H), 7.30 (d, *J*=8.24 Hz, 2 H), 5.37 (d, *J*=4.27 Hz, 1 H), 4.87 (s, 1 H), 4.75 (s, 1 H), 4.31 - 4.01 (m, 3 H), 3.93 - 3.74 (m, 3 H), 3.68 - 3.41 (m, 2 H), 3.06 – 2.73 (m, 1 H), 2.48 – 1.26 (m, 22 H), 1.76 (s, 3 H), 1.23 (s, 3 H), 1.14 (s, 3 H), 1.09 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H).

Example 136

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(methylsulfonyl)ethylamino)-1-(prop-1-en-2-yl)-

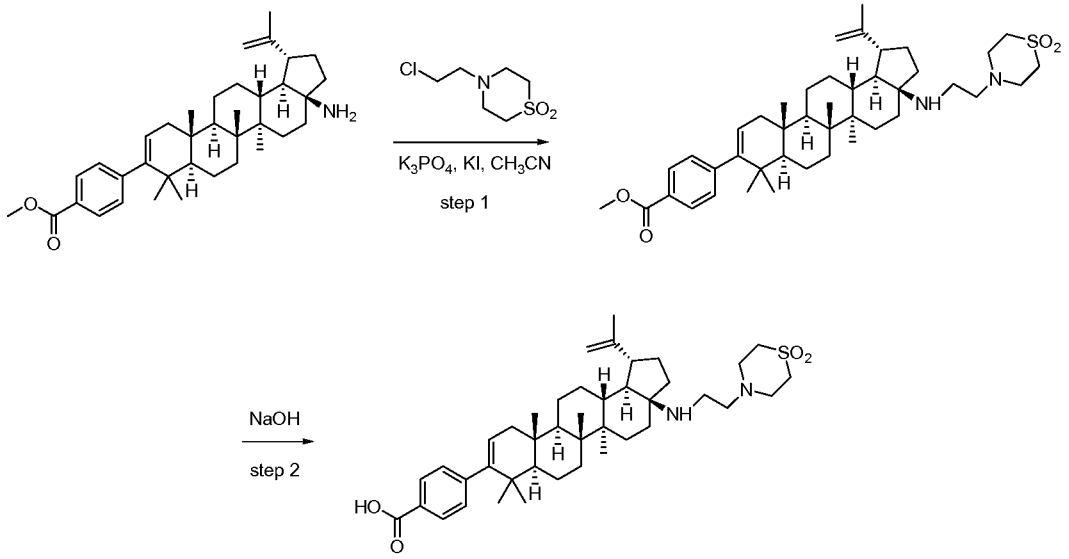
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-hydroxyethylsulfonyl)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using methylsulfonylethene instead of vinylsulfonylethene in Step 1. The product was isolated as a white solid (6 mg, 39%). LCMS: m/e 636.37 $(M+H)^+$, 2.53 min (method 10). ^{1}H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.04 (d, *J*=8.24 Hz, 2 H), 7.30 (d, *J*=8.24 Hz, 2 H), 5.44 - 5.33 (m, 1 H), 4.88 (s, 1 H), 4.76 (s, 1 H), 4.17 - 4.00 (m, 1 H), 3.93 - 3.69 (m, 3 H), 3.22 (s, 3 H), 3.00 – 2.85 (m, 1 H), 2.40 – 1.26 (m, 22 H), 1.77 (s, 3 H), 1.23 (s, 3 H), 1.14 (s, 3 H), 1.10 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H).

Example 137

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (600 mg, 1.10 mmol), 4-(2-chloroethyl)thiomorpholine 1,1-dioxide (600 mg, 2.56 mmol) (prepared as described in WO2002045652), anhydrous potassium phosphate (3.00 g, 14.1 mmol) and potassium iodide (10 mg, 0.060 mmol) in acetonitrile (50 mL) was placed in 150 mL AceGlass resealable pressure vessel. The white suspension was blanketed with nitrogen. The vessel was sealed and warmed to 115-125°C for 48 h. The crude reaction was filtered through a short bed of silica gel and washed with ethyl acetate. The filtrate was concentrated *in vacuo* and purified by silica gel chromatography eluted with ethyl acetate and hexanes (0-50%) to afford the title compound as a colorless foam (566 mg, 73%). ^{1}H NMR (500MHz, CHLOROFORM-d) δ 7.95 (d, J=8.2 Hz, 2H), 7.22 (d, J=8.2 Hz, 2H), 5.31 (d, J=4.6 Hz, 1H), 4.74 (d, J=1.8 Hz, 1H), 4.62 (s, 1H), 3.93 (s, 3H), 3.22 - 2.99 (m, 9H), 2.79 - 2.55 (m, 4H), 2.52 - 2.42 (m, 1H), 2.18 - 2.09 (m, 1H), 1.99-1.02 (m, 20H), 1.72 (s, 3H), 1.11 (s, 3H), 1.01 (s., 3H),

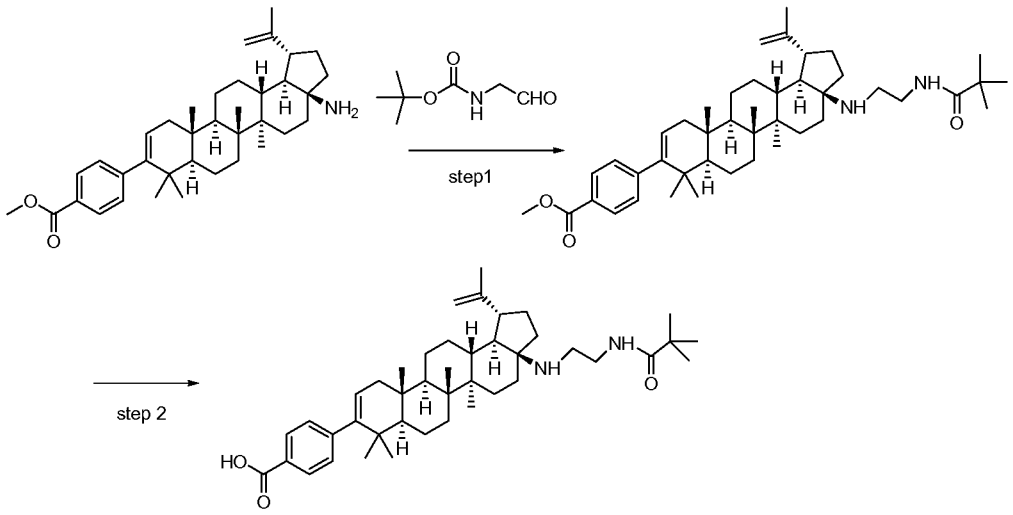
1.10 (s, 3H), 0.95 (s, 3H), 0.95 (s., 3H).LCMS: m/e 705.51 $(M+H)^+$, 3.01 min (method 10).

Step 2. Preparation of 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxido-4-thiomorpholinyl)ethyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl]- benzoic acid

A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (500 mg, 0.709 mmol) and aqueous sodium hydroxide 10N (1.42 mL, 14.2 mmol) in dioxane (10 mL) was heated at 78 °C for 3 h. The reaction was filtered and the resulting clear solution was purified by prep HPLC to provide the title compound as white solid (200 mg, 39%). LCMS: m/e 691.59 $(M+H)^+$, 2.53 min (method 10). ^{1}H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.04 (d, *J*=8.24 Hz, 2 H), 7.30 (d, *J*=8.24 Hz, 2 H), 5.45 - 5.34 (m, 1 H), 4.85 (s, 1 H), 4.74 (s, 1 H), 3.55 - 3.40 (m, 1 H), 3.39 - 3.22 (m, 6 H), 3.22 - 3.11 (m, 4 H), 3.11 - 3.03 (m, 1 H), 3.04 – 2.94 (m, 1 H), 2.36 – 1.18 (m, 22 H), 1.76 (s, 3 H), 1.30 (s, 3 H), 1.15 (s, 3 H), 1.12 (s, 3 H), 1.03 (s, 3 H), 1.00 (s, 3 H).

Example 138

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(*tert*-butoxycarbonylamino)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(*tert*-butoxycarbonylamino)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

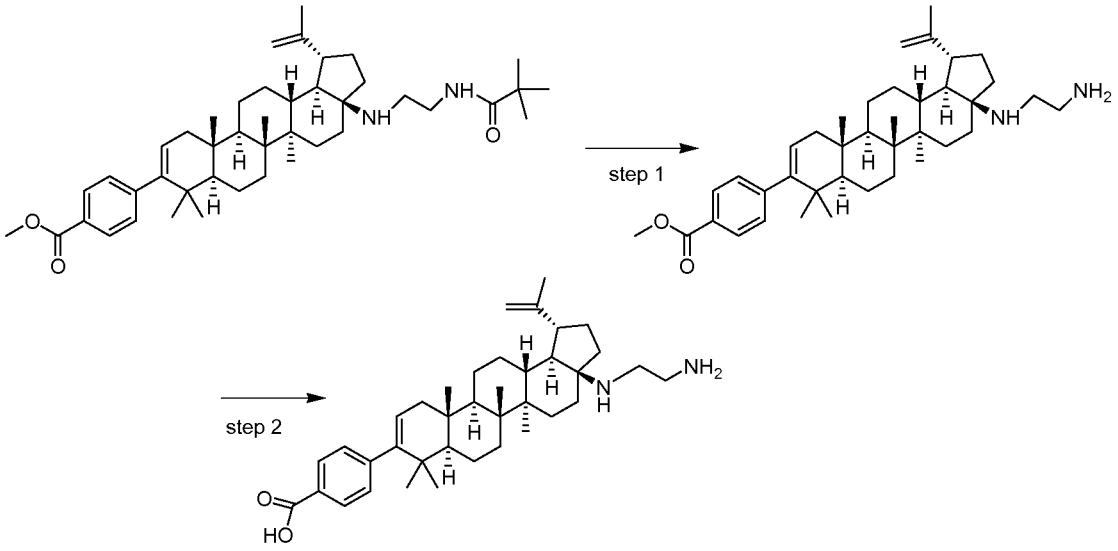
To methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (1.00 g, 1.84 mmol) in DCE (5 mL) was added *tert*-butyl 2-oxoethylcarbamate (1.17 g, 7.36 mmol) and tetraisopropoxytitanium (0.700 mL, 2.39 mmol). The reaction mixture was stirred for 1 h, then sodium triacetoxyborohydride (1.17 g, 5.52 mmol) was added. The reaction mixture was stirred for 18 h. The reaction mixture was quenched with sodium bicarbonate and was extracted with DCM (3 x 40 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography using ethyl acetate and hexanes (20-100%) as the eluent to provide the title compound as a pale yellow oil. (900 mg, 71%). LCMS: m/e 688.24 $(M+H)^+$, 2.51 min (method 11).

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(*tert*-butoxycarbonylamino)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

The title compound was prepared following the hydrolysis method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-hydroxyethylsulfonyl)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(*tert*-butoxycarbonylamino)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate(10 mg, 0.015 mmol) as starting material. The title compound was isolated as a white solid (4 mg, 39%). LCMS: m/e 673.45 $(M+H)^+$, 2.65 min (method 10). ^{1}H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.04 (d, *J*=8.24 Hz, 2 H), 7.30 (d, *J*=8.55 Hz, 2 H), 5.51 - 5.32 (m, 1 H), 4.87 (s, 1 H), 4.75 (s, 1 H), 3.82 - 3.53 (m, 1 H), 3.53 - 3.24 (m, 3 H), 3.04 – 2.83 (m, 1 H), 2.37 – 1.15 (m, 22 H), 1.77 (s, 3 H), 1.53 - 1.49 (m, 9 H), 1.27 (s, 3 H), 1.14 (s, 3 H), 1.11 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H).

Example 139

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-aminoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-aminoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

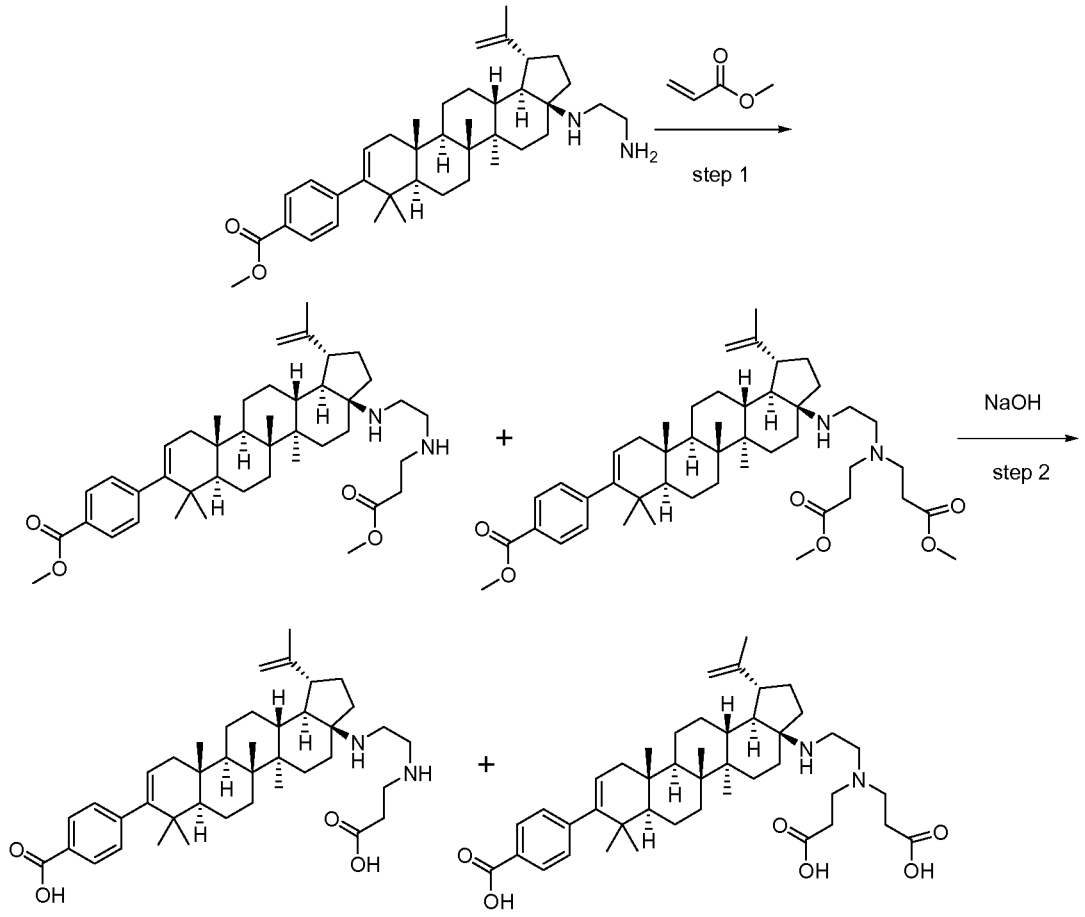
To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(tert-butoxycarbonylamino)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (900 mg, 1.310 mmol) in dioxane (1 mL) was added HCl (4M in dioxane) (4.26 mL, 17.03 mmol) and the reaction mixture was stirred for 4 h at rt. The reaction mixture was concentrated under reduced pressure to provide the title compound as a brown solid (769 mg, 100%). LCMS: m/e 588.08 $(M+H)^+$, 2.44 min (method 11).

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-aminoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

The title compound was prepared following the hydrolysis method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-hydroxyethylsulfonyl)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-aminoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (4 mg, 0.006 mmol) as starting material. The title compound was isolated as a white solid (2.4 mg, 67%). LCMS: m/e 573.2 $(M+H)^+$, 2.39 min (method 10). ^{1}H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.03 (d, *J*=8.24 Hz, 2 H), 7.30 (d, *J*=8.24 Hz, 2 H), 5.37 (d, *J*=4.27 Hz, 1 H), 4.87 (s, 1 H), 4.76 (s, 1 H), 3.80 - 3.68 (m, 3 H), 3.68 - 3.59 (m, 1 H), 2.97 - 2.80 (m, 1 H), 2.38 – 1.21 (m, 22 H), 1.78 (s, 3 H), 1.20 (s, 3 H), 1.14 (s, 3 H), 1.09 (s, 3 H), 1.01 (s, 3 H), 1.00 (s, 3 H).

Examples 140 and 141

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-carboxyethylamino)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid and 3,3'-(2-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-carboxyphenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-ylamino)ethylazanediyl)dipropanoic acid.



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3-methoxy-3-oxopropylamino)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate and dimethyl 3,3'-(2-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-ylamino)ethylazanediyl)dipropanoate.

Methyl acrylate (9.97 mg, 0.116 mmol) was added to a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-aminoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (34 mg, 0.058 mmol) in MeOH (2 mL) and the mixture was stirred for 16 h at room temperature. The reaction mixture was concentrated under reduced pressure to provide a mixture of the two title compounds as a brown oil (20 mg, 51%). LCMS: m/e 673.47 $(M+H)^+$, 2.96 min and 759.51 $(M+H)^+$, 3.43 min (method 10). The mixture was taken to the next step without further purification.

Step 2. Ester hydrolysis.

The mixture of esters from above (20 mg) in dioxane (1 mL) was treated with sodium hydroxide (0.297 mL, 0.297 mmol) at 78 °C for 3 hours. The reaction mixture was filtered and purified by prep. HPLC to provide the following two compounds:

Example 140

4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-carboxyethylamino)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

White solid (16 mg, 43% over 2 steps). LCMS: m/e 645.44 $(M+H)^+$, 2.37 min (method 10). ^{1}H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.04 (d, *J*=8.2 Hz, 2 H), 7.30 (d, *J*=8.5 Hz, 2 H), 5.37 (d, *J*=4.6 Hz, 1 H), 4.87 (s, 1 H), 4.75 (s, 1 H), 3.78 (s., 2 H), 3.77 - 3.59 (m, 2 H), 3.45 (t, *J*=6.4 Hz, 2 H), 2.90 (t, *J*=6.4 Hz, 2 H), 2.87 - 2.72 (m, 1 H), 2.42 – 1.22 (m, 22 H), 1.78 (s, 3 H), 1.20 (s, 3 H), 1.13 (s, 3 H), 1.09 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H).

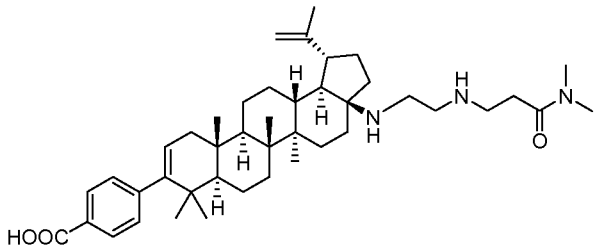
Example 141

3,3'-(2-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-carboxyphenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-ylamino)ethylazanediyl)dipropanoic acid

White solid (5.7 mg, 57% over 2 steps). LCMS: m/e 717.51 $(M+H)^+$, 2.25 min (method 10). ^{1}H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.03 (d, *J*=8.2 Hz, 2 H), 7.29 (d, *J*=8.2 Hz, 2 H), 5.36 (d, *J*=4.9 Hz, 1 H), 4.88 (s, 1 H), 4.76 (s, 1 H), 3.83 - 3.66 (m, 4 H), 3.51 (t, *J*=6.3 Hz, 4 H), 2.93 (t, *J*=6.9 Hz, 4 H), 2.88 - 2.74 (m, 1 H), 2.42 – 1.22 (m, 22 H), 1.78 (s, 3 H), 1.19 (s, 3 H), 1.14 (s, 3 H), 1.08 (s, 3 H), 1.01 (s, 3 H), 0.99 (s, 3 H).

Example 142

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3-(dimethylamino)-3-oxopropylamino)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

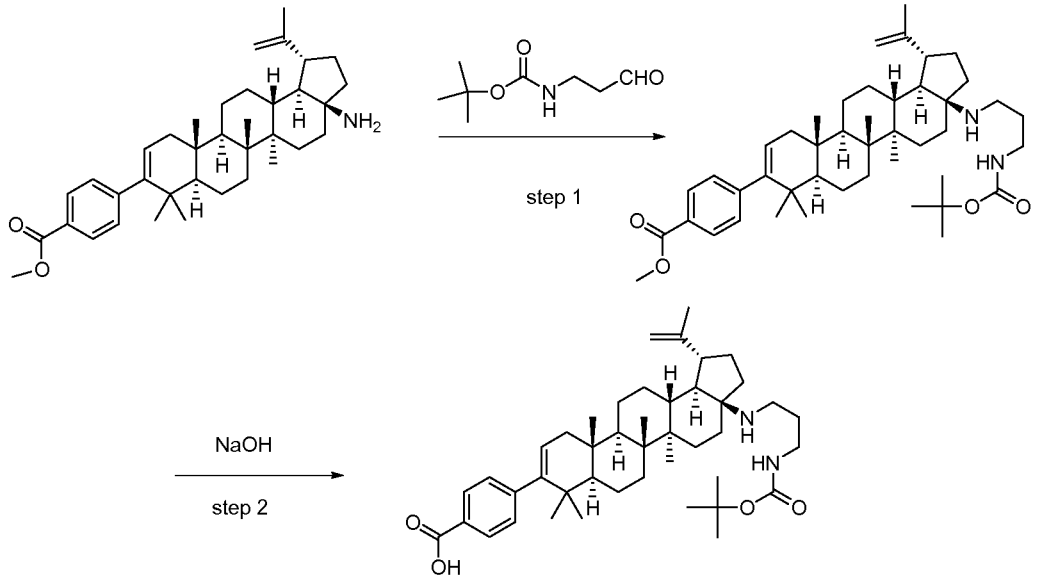


The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-carboxyethylamino)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using *N,N*-dimethylacrylamide as the Michael aceptor reagent in the first step. The product was isolated as a white solid (9 mg, 50%). LCMS: m/e 672.47 $(M+H)^+$, 2.33 min (method 2). ^{1}H NMR (500 MHz, *Acetic*

acid d4) δ ppm 8.04 (d, J=8.2 Hz, 2 H), 7.30 (d, J=8.2 Hz, 2 H), 5.37 (d, J=4.6 Hz, 1 H), 4.88 (s, 1 H), 4.76 (s, 1 H), 3.86 - 3.59 (m, 4 H), 3.51 - 3.37 (m, 2 H), 3.07 (s, 3 H), 2.99 (s, 3 H), 2.95 (t, J=5.6 Hz, 2 H), 2.90 - 2.76 (m, 1 H), 2.37 – 1.22 (m, 22 H), 1.78 (s, 3 H), 1.20 (s, 3 H), 1.14 (s, 3 H), 1.09 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H).

Example 142

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(*tert*-butoxycarbonylamino)propylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(*tert*-butoxycarbonylamino)propylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

Acetic acid (0.013 mL, 0.221 mmol) and *tert*-butyl 3-oxopropylcarbamate (38.2 mg, 0.221 mmol) were added to a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (40 mg, 0.074 mmol) in EtOH

(1 mL) and dioxane (1.0 mL) and the mixture was stirred for 2 h at rt. Sodium triacetoxyborohydride (78 mg, 0.368 mmol) was added and the reaction mixture was stirred at 20 °C for two hours. The reaction was quenched with a saturated aqueous solution of sodium bicarbonate (3 mL), washed with 0.1N HCl (5 mL) and brine (5 mL) and extracted with DCM (3 x 5 mL). All the extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to provide the title compound as pale yellow oil (28 mg, 54%). LCMS: m/e 701.51 $(M+H)^+$, 4.0 min (method 10).

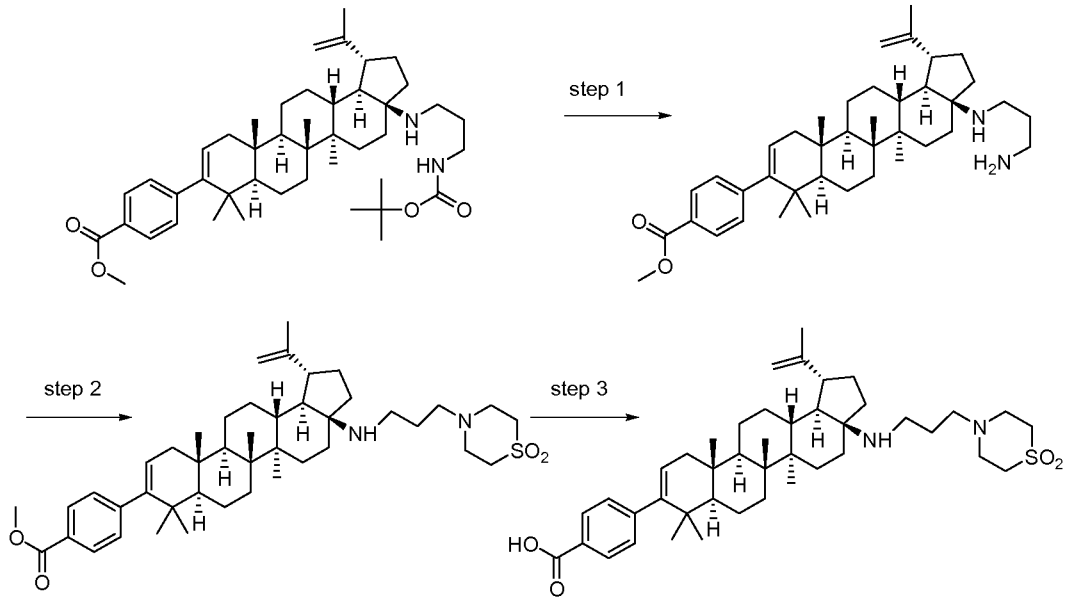
Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(*tert*-butoxycarbonylamino)propylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

The title compound was prepared following the hydrolysis method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-hydroxyethylsulfonyl)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(*tert*-butoxycarbonylamino)propylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (5 mg, 0.007 mmol) as starting material. The title compound was isolated as a white solid (3 mg, 58%). LCMS: m/e 687.54 $(M+H)^+$, 2.69 min (method 10). ^{1}H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.04 (d, *J*=8.24 Hz, 2 H), 7.30 (d, *J*=8.24 Hz, 2 H), 5.37 (d, *J*=4.58 Hz, 1 H), 4.87 (s, 1 H), 4.74 (s, 1 H), 3.38 - 3.17 (m, 4 H), 3.04 – 2.86 (m, 1 H), 2.36 – 1.17 (m, 24 H), 1.77 (s, 3 H), 1.50 (s, 9 H), 1.25 (s, 3 H), 1.14 (s, 3 H), 1.09 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H).

Example 144

Preparation of 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-thiomorpholinyl)propyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl]- benzoic acid.



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-aminopropylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

4.0M HCl in dioxane (32.8 µl, 0.131 mmol) was added to a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(*tert*-butoxycarbonylamino)propylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (23 mg, 0.033 mmol) in dioxane (1 mL) and the mixture was stirred for 6 h at room temperature. The reaction mixture was concentrated under reduced pressure to provide the title compound as a brown oil (15 mg, 76%). LCMS: m/e 601.48 $(M+H)^+$, 2.88 min (method 10).

Step 2. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((3-(1,1-dioxido-4-thiomorpholinyl)propyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

Vinylsulfonylethene (5.90 mg, 0.050 mmol) and triethylamine (6.96 µl, 0.050 mmol) were added to a mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-aminopropylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (15 mg, 0.025 mmol) in EtOH (1 mL). The reaction mixture was heated to 100 °C for 3 hours. The reaction mixture was concentrated under reduced pressure to provide the desired product as a brown solid (15 mg, 76%). LCMS: m/e 719.46 $(M+H)^+$, 3.68 min (method 10).

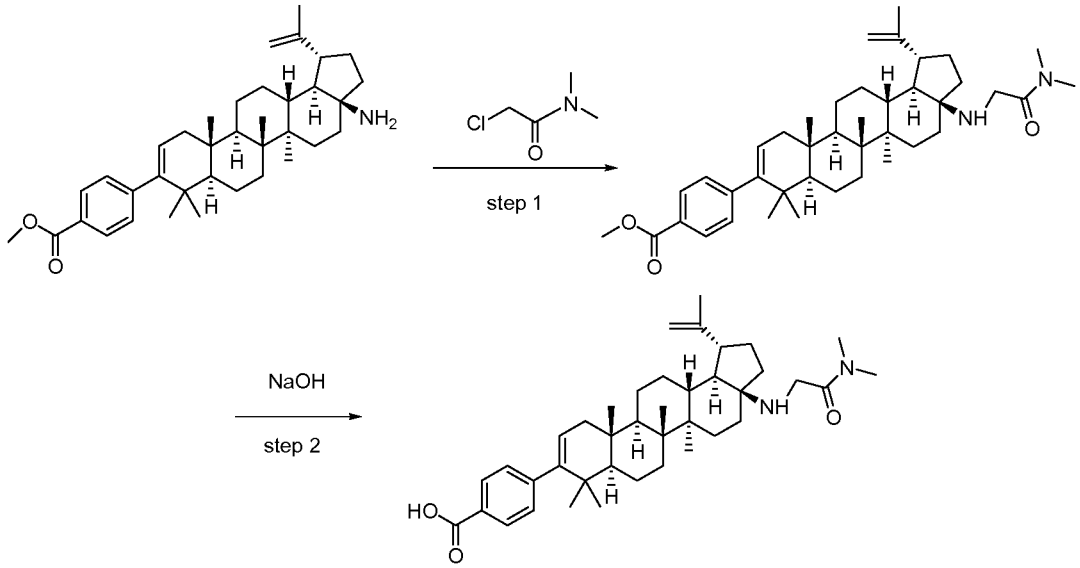
Step 3. Preparation of, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-thiomorpholinyl)propyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl]-benzoic acid

A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((3-(1,1-dioxido-4-thiomorpholinyl)propyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (15 mg, 0.021 mmol) and 1N sodium hydroxide (0.104 mL, 0.104 mmol) in dioxane (1 mL) was heated at 78 °C for 3 hours. The reaction mixture was purified by prep HPLC to provide the title compound as a white solid (9 mg, 58%). LCMS: m/e 705.49 $(M+H)^+$, 2.60 min (method 10). ^{1}H NMR (400 MHz, *Acetic acid d4*) δ ppm 7.99 (d, *J*=8.28 Hz, 2 H), 7.25 (d, *J*=8.28 Hz, 2 H), 5.33 (d, *J*=4.77 Hz, 1 H), 4.82 (s, 1 H), 4.71 (s, 1 H), 3.87 (br. s., 4 H), 3.56 (d, *J*=4.27 Hz, 4 H), 3.51 - 3.40 (m, 2 H), 3.39 - 3.22 (m, 2 H), 2.86 - 2.69 (m, 1 H), 2.57 - 2.34 (m, 2 H), 2.27 – 1.18 (m, 22 H), 1.72 (s, 3 H), 1.16 (s, 3 H), 1.10 (s, 3 H), 1.04 (s, 3 H), 0.98 (s, 3 H), 0.96 (s, 3 H).

Example 145

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

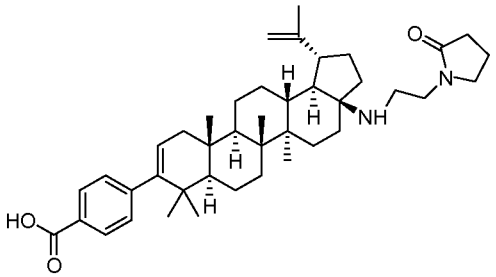
A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (50 mg, 0.092 mmol), 2-chloro-*N,N*-dimethylacetamide (33.5 mg, 0.276 mmol), potassium phosphate (78 mg, 0.368 mmol) and potassium iodide (36.6 mg, 0.221 mmol) in acetonitrile (1 mL) was heated at 120 °C for 33 h in a sealed tube. The reaction mixture was quenched with distilled water (5 mL) and extracted with DCM (3 x 5 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure to provide the title compound as a pale yellow solid (30 mg, 52%). LCMS: m/e 629.51 $(M+H)^+$, 3.03 min (method 10). The product was used in the next step without further purification.

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (30 mg, 0.048 mmol) and aqueous 1N sodium hydroxide (0.048 mL, 0.048 mmol) in dioxane (1 mL) was heated up at 78 °C for 3 h. The reaction mixture was filtered and the clear solution was purified by prep HPLC to provide the title compound as a white solid (9.5 mg, 31%). LCMS: m/e 615.56 $(M+H)^+$, 2.52 min (method 10). ^{1}H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.04 (d, *J*=8.24 Hz, 2 H), 7.30 (d, *J*=8.24 Hz, 2 H), 5.38 (d, *J*=4.58 Hz, 1 H), 4.89 (s, 1 H), 4.76 (s, 1 H), 4.52 (d, *J*=16.17 Hz, 1 H), 4.04 (d, *J*=16.17 Hz, 1 H), 3.08 (d, *J*=10.99 Hz, 6 H), 3.01 – 2.86 (m, 1 H), 2.37 – 1.22 (m, 22 H), 1.79 (s, 3 H), 1.30 (s, 3 H), 1.14 (s, 3 H), 1.10 (s, 3 H), 1.03 (s, 3 H), 1.00 (s, 3 H).

Example 146

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(2-oxopyrrolidin-1-yl)ethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

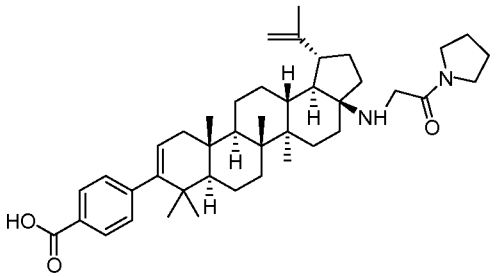


The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

cyclopenta[a]chrysen-9-yl)benzoic acid using 1-(2-chloroethyl)pyrrolidin-2-one as the alkylating reagent in Step 1. The product was isolated as a white solid (19 mg, 62%). LCMS: m/e 641.57 $(M+H)^+$, 2.58 min (method 10). ^{1}H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.04 (d, *J*=8.24 Hz, 2 H), 7.30 (d, *J*=8.55 Hz, 2 H), 5.37 (d, *J*=4.88 Hz, 1 H), 4.91 (s, 1 H), 4.76 (s, 1 H), 3.89 - 3.73 (m, 2 H), 3.72 - 3.56 (m, 3 H), 3.55 - 3.45 (m, 1 H), 2.93 - 2.80 (m, 1 H), 2.57 (td, *J*=8.24, 3.97 Hz, 2 H), 2.34 – 1.19 (m, 24 H), 1.78 (s, 3 H), 1.23 (s, 3 H), 1.13 (s, 3 H), 1.10 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H).

Example 147

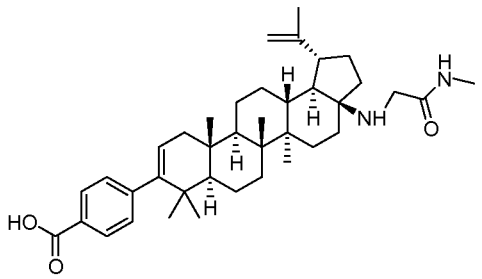
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-oxo-2-(pyrrolidin-1-yl)ethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 2-chloro-1-(pyrrolidin-1-yl)ethanone as the alkylating reagent in Step 1. The product was isolated as a white solid (19 mg, 46%). LCMS: m/e 641.46 $(M+H)^+$, 2.55 min (method 10). ^{1}H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.04 (d, *J*=8.24 Hz, 2 H), 7.30 (d, *J*=8.24 Hz, 2 H), 5.38 (d, *J*=4.58 Hz, 1 H), 4.89 (s, 1 H), 4.76 (s, 1 H), 4.43 (d, *J*=16.48 Hz, 1 H), 3.99 (d, *J*=16.17 Hz, 1 H), 3.73 - 3.42 (m, 4 H), 3.15 – 2.86 (m, 1 H), 2.41 – 1.19 (m, 26 H), 1.79 (s, 3 H), 1.28 (s, 3 H), 1.14 (s, 3 H), 1.10 (s, 3 H), 1.03 (s, 3 H), 1.00 (s, 3 H).

Example 148

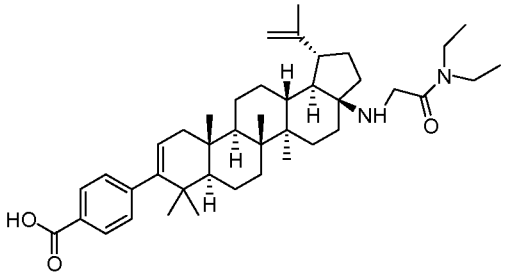
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(methylamino)-2-oxoethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 2-chloro-*N*-methylacetamide as the alkylating reagent in Step 1. The product was isolated as a white solid (41 mg, 80%). LCMS: m/e 601.45 $(M+H)^+$, 2.31 min (method 11). ^{1}H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.04 (d, *J*=8.24 Hz, 2 H), 7.30 (d, *J*=8.24 Hz, 2 H), 5.38 (d, *J*=4.58 Hz, 1 H), 4.88 (s, 1 H), 4.76 (s, 1 H), 4.24 (d, *J*=15.56 Hz, 1 H), 3.92 (d, *J*=15.26 Hz, 1 H), 2.88 (s, 3 H), 3.08 – 2.74 (m, 1 H), 2.31 – 1.30 (m, 22 H), 1.78 (s, 3 H), 1.29 (s, 3 H), 1.14 (s, 3 H), 1.10 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 3 H).

Example 149

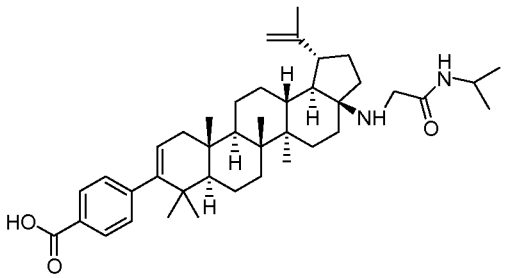
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(diethylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 2-chloro-*N,N*-diethylacetamide as alkylating reagent in Step 1. The product was isolated as a white solid (20 mg, 39%). LCMS: m/e 643.50 $(M+H)^+$, 2.35 min (method 11). ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.99 (d, *J*=8.28 Hz, 2 H), 7.24 (d, *J*=8.28 Hz, 2 H), 5.31 (d, *J*=4.52 Hz, 1 H), 4.74 (d, *J*=1.76 Hz, 1 H), 4.60 (s, 1 H), 3.58 - 3.21 (m, 6 H), 2.82 - 2.69 (m, 1 H), 2.22 – 1.02 (m, 28 H), 1.72 (s, 3 H), 1.18 (s, 3 H), 1.01 (s, 3 H), 1.00 (s, 3 H), 0.95 (s, 6 H).

Example 150

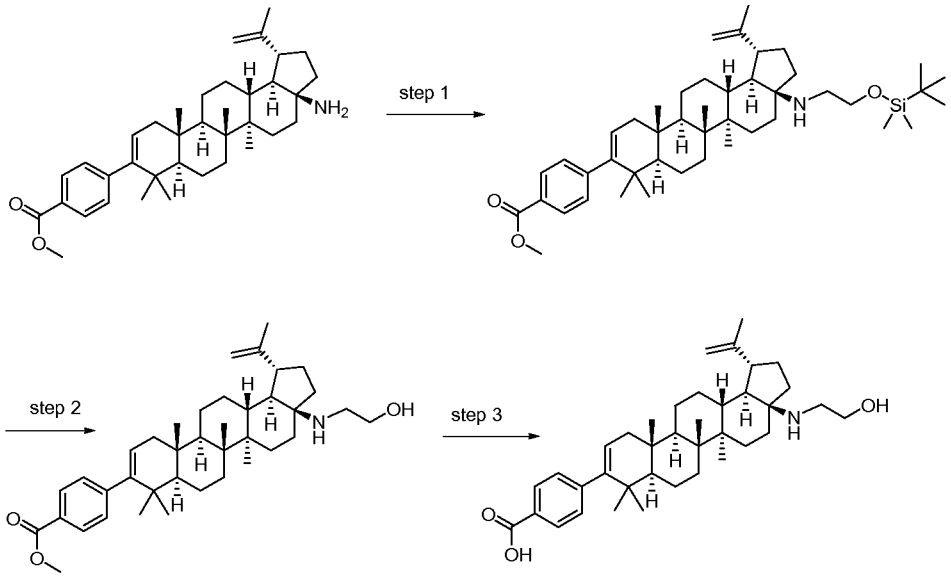
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(isopropylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 2-chloro-*N*-isopropylacetamide as the alkylating reagent in Step 1. The product was isolated as a white solid (50 mg, 81%). LCMS: m/e 629.46 $(M+H)^+$, 2.60 min (method 10). ^{1}H NMR (400 MHz, *Acetic acid d4*) δ ppm 7.99 (d, *J*=8.53 Hz, 2 H), 7.26 (d, *J*=8.53 Hz, 2 H), 5.34 (d, *J*=4.77 Hz, 1 H), 4.84 (s, 1 H), 4.72 (s, 1 H), 4.15 (d, *J*=15.31 Hz, 1 H), 4.06 (dt, *J*=13.11, 6.62 Hz, 1 H), 3.85 (d, *J*=15.31 Hz, 1 H), 3.07 – 2.77 (m, 1 H), 2.41 – 1.26 (m, 22 H), 1.74 (s, 3 H), 1.24 (s, 3 H), 1.16 (d, *J*=6.53 Hz, 6 H), 1.10 (s, 3 H), 1.06 (s, 3 H), 0.99 (s, 3 H), 0.97 (s, 3 H).

Example 151

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-hydroxyethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(*tert*-butyldimethylsilyloxy)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-

2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (300 mg, 0.552 mmol) in DCE (4 mL) was added (*tert*-butyldimethylsilyloxy)acetaldehyde (131 mL, 0.690 mmol) and titanium(IV) isopropoxide (0.202 mL, 0.690 mmol). The mixture was stirred at rt for 45 minutes and sodium triacetoxyborohydride (234 mg, 1.103 mmol) was added. The mixture was stirred at rt for 23 h and an additional 0.1 mL of (*tert*-butyldimethylsilyloxy)acetaldehyde and an additional 150 mg of sodium triacetoxyborohydride were added. The mixture was stirred at rt for an additional 22 h, then was diluted with 15 mL of sat. $NaHCO_3$ and was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried with Na_2SO_4, the drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was adsorbed to silica gel and was purified by flash chromatography using a 0-10% EtOAc in hexanes gradient. The fractions containing the expected product were combined and were concentrated under reduced pressure to give the title compound (0.211 g, 0.301 mmol, 54.5% yield) as a clear yellow film. The product was used in the next step with no additional purification. LCMS: m/e 702.7 $(M+H)^+$, 2.35 min (method 2).

Step 2. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-hydroxyethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(*tert*-butyldimethylsilyloxy)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.211 g, 0.301 mmol) in THF (2 mL) was added TBAF (1M in THF) (0.601 mL, 0.601 mmol). The mixture was stirred at rt for 2.75 h then was diluted with water (10 mL) and was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried with Na_2SO_4, the drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The

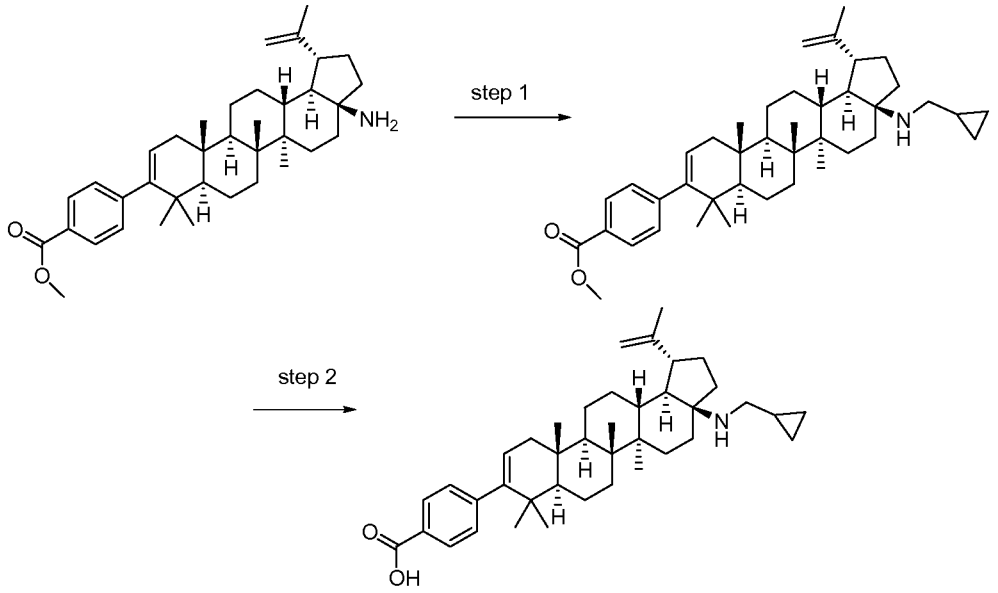
residue was adsorbed to silica gel and was purified by flash chromatography using a 0-25% EtOAc in hexanes gradient. The title compound (93.4 mg, 0.159 mmol, 52.9% yield), was isolated as a colorless film. LCMS: m/e 588.6 $(M+H)^+$, 1.98 min (method 2). ^{1}H NMR (500 MHz, *CHLOROFORM-d*) d ppm 7.91 (d, *J*=8.24 Hz, 2 H), 7.18 (d, *J*=8.24 Hz, 2 H), 5.27 (d, *J*=4.58 Hz, 1 H), 4.70 (d, *J*=1.83 Hz, 1 H), 4.59 (s, 1 H), 3.89 (s, 3 H), 3.54 - 3.64 (m, 2 H), 2.52 - 2.69 (m, 3 H), 2.09 (dd, *J*=17.09, 6.41 Hz, 1 H), 1.68 (s, 3 H), 1.07 (s, 3 H), 0.98 (s, 3 H), 0.97 (s, 3 H), 0.93 - 2.05 (m, 21 H), 0.91 (s, 3 H), 0.91 (s, 3 H).

Step 3. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-hydroxyethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-hydroxyethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (35 mg, 0.060 mmol) in dioxane (1 mL) was added NaOH (1N) (0.298 mL, 0.298 mmol). The mixture was heated to 85 °C for 15 h then was cooled to rt. The mixture was diluted with MeOH and was purified by prep HPLC. The fractions containing the expected product were combined and concentrated under reduced pressure to give the title compound (25 mg, 0.041 mmol, 69.5% yield) as a white solid. LCMS: m/e 574.5 $(M+H)^+$, 1.69 min (method 2). ^{1}H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.04 (2 H, d, *J*=8.2 Hz), 7.30 (2 H, d, *J*=8.2 Hz), 5.37 (1 H, d, *J*=4.6 Hz), 4.86 (1 H, s), 4.75 (1 H, s), 3.95 - 4.11 (2 H, m), 3.25 - 3.43 (2 H, m), 2.90 - 2.98 (1 H, m), 1.77 (3 H, s), 1.21 (3 H, s), 1.14 (3 H, s), 1.09 (3 H, s), 1.02 (3 H, s), 1.00 (3 H, s), 0.97 - 2.32 (22 H, m).

Example 152

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(cyclopropylmethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(cyclopropylmethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.022 g, 0.040 mmol) in DCE (0.25 mL) was added cyclopropanecarbaldehyde (2.84 mg, 0.040 mmol) and titanium (IV) isopropoxide (0.015 mL, 0.051 mmol). The mixture was stirred at rt for 1 h and sodium triacetoxyborohydride (0.017 g, 0.081 mmol) was added. After stirring the mixture for 16.75 h, the mixture was diluted with 3 mL of water and was filtered through a pad of celite, then was extracted with dichloromethane (3 x 4 mL). The combined organic layers were dried with Na_2SO_4. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure to give the title compound (0.024 g, 0.040 mmol, 99% yield) as a clear film. The crude product was used in the next step with no additional purification. LCMS: m/e 598.6 $(M+H)^+$, 2.13 min (method 2).

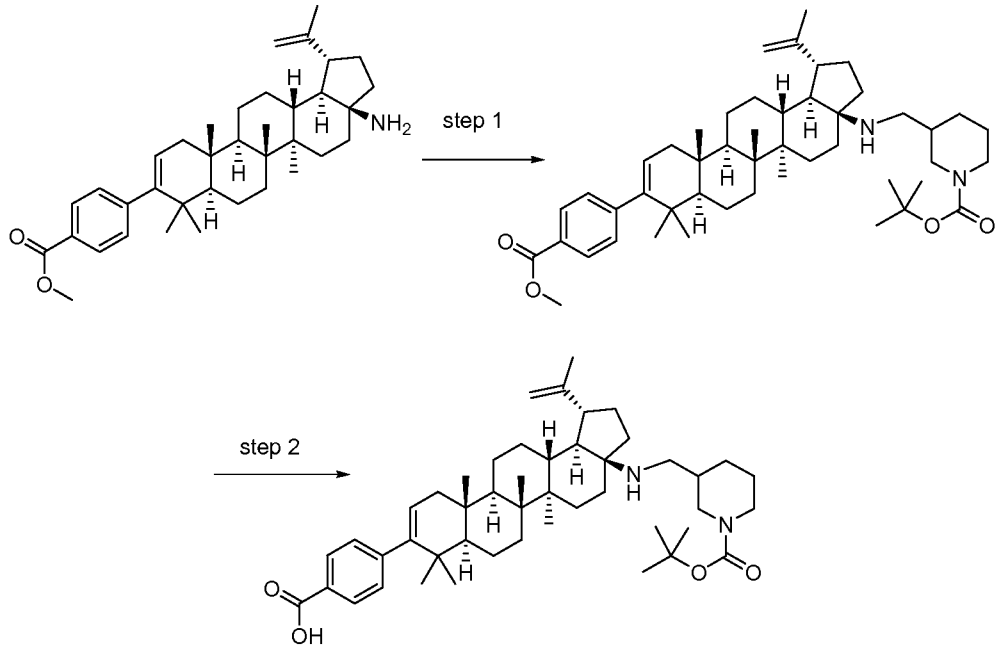
Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(cyclopropylmethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

To a cloudy mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(cyclopropylmethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.024 g, 0.040 mmol) in 1,4-dioxane (1.5 mL) was added NaOH (1N) (0.5 mL, 0.5 mmol). The mixture was heated to 65 °C. After two hours, the mixture was cooled to rt and stirred at rt overnight. The mixture was filtered through plug of glass wool and was purified by prep HPLC to afford the title compound (0.007 g, 10.79 μmol, 26.9% yield) as a white film. LCMS: m/e 584.6 $(M+H)^+$, 1.83 min (method 2). ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.00 (2 H, d, *J*=8.0 Hz), 7.21 (2 H, d, *J*=8.0 Hz), 5.31 (1 H, d, *J*=5.0 Hz), 4.75 (1 H, d, *J*=1.5 Hz), 4.61 (1 H, s), 2.76 (1 H, td, *J*=10.9, 5.6 Hz), 2.62 (1 H, dd, *J*=11.2, 6.1 Hz), 2.23 (1 H, dd, *J*=11.5, 7.8 Hz), 1.97 - 2.16 (3 H, m), 1.82 - 1.95 (2 H, m), 1.70 (3 H, s), 1.16 (3 H, s), 1.01 (3 H, s), 1.00 (3 H, s), 0.96 (3 H, s), 0.95 (3 H, s), 0.80 - 1.77 (19 H, m), 0.48 - 0.58 (2 H, m), 0.09 - 0.24 (2 H, m).

Example 153

Preparation of *tert*-butyl 3-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-ylamino)methyl)piperidine-1-carboxylate.



Step 1. Preparation of tert-butyl 3-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-ylamino)methyl)piperidine-1-carboxylate.

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (30 mg, 0.055 mmol) in DCE (0.5 mL) was added 3-formyl-piperidine-1-carboxylic acid *tert*-butyl ester (14.71 mg, 0.069 mmol) and titanium(IV) isopropoxide (0.020 mL, 0.069 mmol). The mixture was stirred at rt for 1 h and sodium triacetoxyborohydride (23.38 mg, 0.110 mmol) was added. After stirring the mixture for 16.5 h, the mixture was diluted with 3 mL of sat. $NaHCO_3$ and was extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried with Na_2SO_4. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was adsorbed to silica gel and was purified by silica gel flash chromatography using a 0-10% EtOAc in hexanes gradient and a Thomson 12 g silica gel column. The fractions containing the expected product were combined and concentrated under reduced pressure to afford the title compound (29 mg, 0.039 mmol, 70.9% yield) as an off-white film. The product was used in the

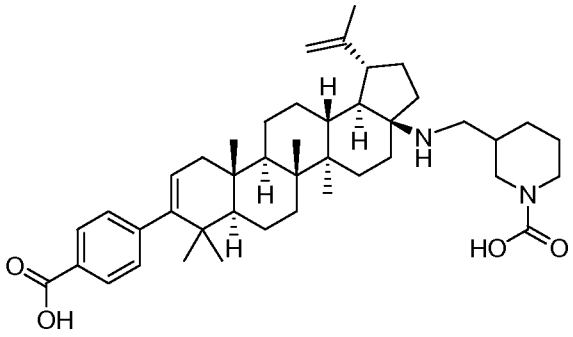
next step with no additional purification. LCMS: m/e 741.7 $(M+H)^+$, 3.76 min (method 2).

Step 2. Preparation of *tert*-butyl 3-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-ylamino)methyl)piperidine-1-carboxylate.

To a solution of *tert*-butyl 3-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-ylamino)methyl)piperidine-1-carboxylate (0.029 g, 0.039 mmol) in dioxane (2 mL) was added NaOH (1N) (0.196 mL, 0.196 mmol). The mixture was heated to 85°C overnight. After heating the mixture for 22 h, it was cooled to rt, diluted with MeOH, and purified by prep HPLC to afford the title compound (24 mg, 0.031 mmol, 80% yield) as a clear, colorless film. LCMS: m/e 727.7 $(M+H)^+$, 2.00 min (method 2). ^{1}H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 7.98 (2 H, d, *J*=7.9 Hz), 7.21 (2 H, d, *J*=7.9 Hz), 5.29 (1 H, d, *J*=5.5 Hz), 4.70 (1 H, br. s.), 4.58 (1 H, br. s.), 3.83 - 4.22 (4 H, m), 2.46 - 2.85 (4 H, m), 2.29 (2 H, br. s.), 1.68 (3 H, s), 1.47 (9 H, d, *J*=4.6 Hz), 1.10 (3 H, d, *J*=7.9 Hz), 0.98 (6 H, br. s.), 0.93 (3 H, s), 0.92 (3 H, s), 0.77 - 2.15 (25 H, m).

Example 154

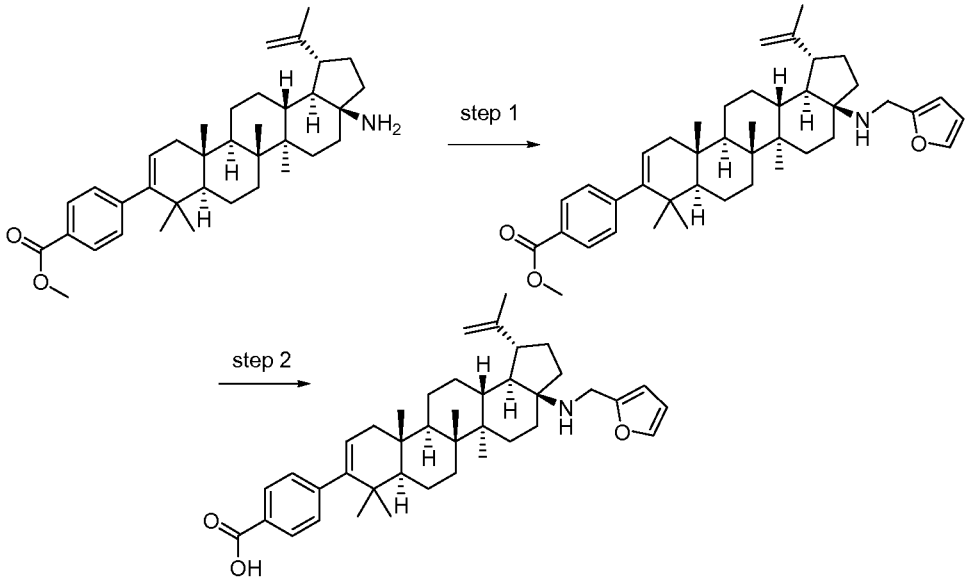
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(piperidin-3-ylmethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



To a solution of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1-(*tert*-butoxycarbonyl)piperidin-3-yl)methylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (0.019 g, 0.026 mmol) in DCM (1 mL) was added TFA (0.25 mL, 3.24 mmol). The mixture was stirred at rt for 1.75 h. Then, the mixture was concentrated under reduced pressure and purified by prep HPLC to give the title compound (14.2 mg, 0.021 mmol, 81% yield) as a white solid. LCMS: m/e 627.6 $(M+H)^+$, 1.50 min (method 2). ^{1}H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.04 (2 H, d, *J*=8.2 Hz), 7.30 (2 H, d, *J*=7.9 Hz), 5.37 (1 H, s), 4.85 (1 H, d, *J*=5.5 Hz), 4.75 (1 H, s), 2.98 - 3.83 (6 H, m), 2.82 - 2.91 (1 H, m), 2.57 - 2.72 (1 H, m), 0.85 - 2.33 (44 H, m).

Example 155

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(furan-2-ylmethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(furan-2-ylmethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (30 mg, 0.055 mmol) in DCE (0.5 mL) was added furfural (5.71 μL, 0.069 mmol) and titanium(IV) isopropoxide (0.020 mL, 0.069 mmol). The mixture was stirred at rt for 1 h and sodium triacetoxyborohydride (23.38 mg, 0.110 mmol) was added. After stirring the mixture for 16 h at rt an additional 5 μL of furfural was added along with an additional 0.025 g of sodium triacetoxborohydride. After stirring the mixture overnight at rt, it was purified by passing through a plug of silica gel and washing with 0-25% EtOAc in hexanes. The fractions containing the product were combined and concentrated under reduced pressure to give the title compound (31 mg, 0.050 mmol, 90% yield) as a light-yellow film. The product was used in the next step with no additional purification. LCMS: m/e 625.6 $(M+H)^+$, 3.08 min (method 2).

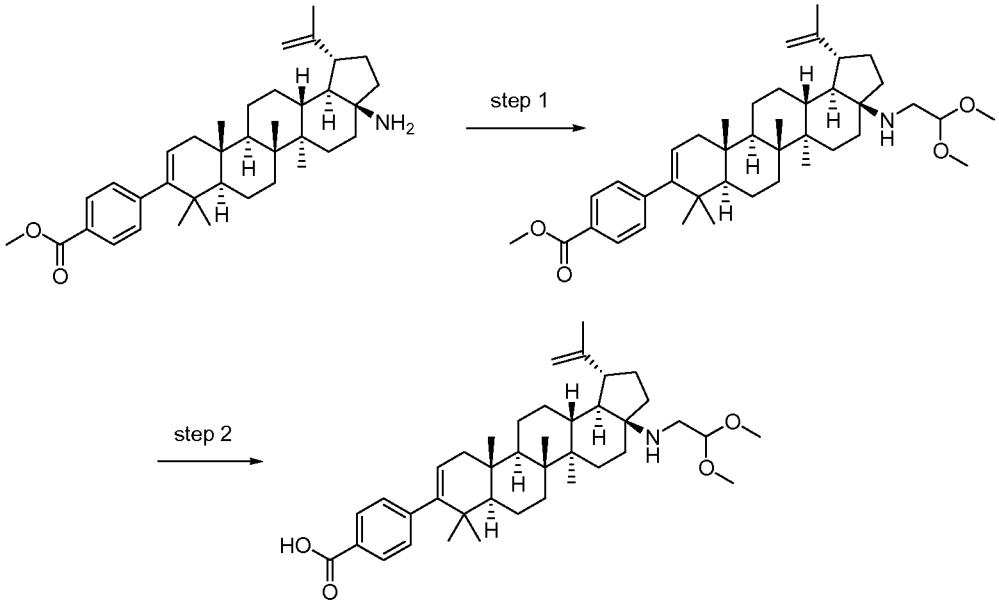
Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(furan-2-ylmethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(furan-2-ylmethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (31 mg, 0.050 mmol) in 1,4-dioxane (2 mL) was added 1N NaOH (0.248 mL, 0.248 mmol). The mixture was heated to 85 °C for 22 h then was cooled to rt. The crude product was purified by prep HPLC. The fractions containing the expected product were combined and were concentrated under reduced pressure to afford the title compound (19.3 mg, 0.030 mmol, 60.5% yield) as a clear film. LCMS: m/e 610.69 $(M+H)^+$, 2.35 min (method 2). ^{1}H NMR (400 MHz, *CHLOROFORM-d*) d ppm 8.00 (d, *J*=7.78 Hz, 2 H), 7.37 (d, *J*=1.00 Hz, 1 H), 7.23 (d, *J*=7.78 Hz, 2 H), 6.33 (dd, *J*=3.14, 1.88 Hz, 1 H), 6.21 (d, *J*=2.76 Hz, 1 H), 5.53 (br. s., 1 H), 5.29 - 5.34 (m, 1 H), 4.72 (d, *J*=1.76 Hz, 1 H), 4.60 (s, 1 H), 3.67 (s, 2 H), 2.64 (td, *J*=10.85, 5.40 Hz, 1 H), 1.71 (s, 3 H), 1.10 - 1.15 (m, 3 H), 1.01 (s, 3 H), 1.00 (s, 3 H), 0.97 - 2.18 (m, 22 H), 0.96 (s, 6 H).

Example 156

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2,2-dimethoxyethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2,2-dimethoxyethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

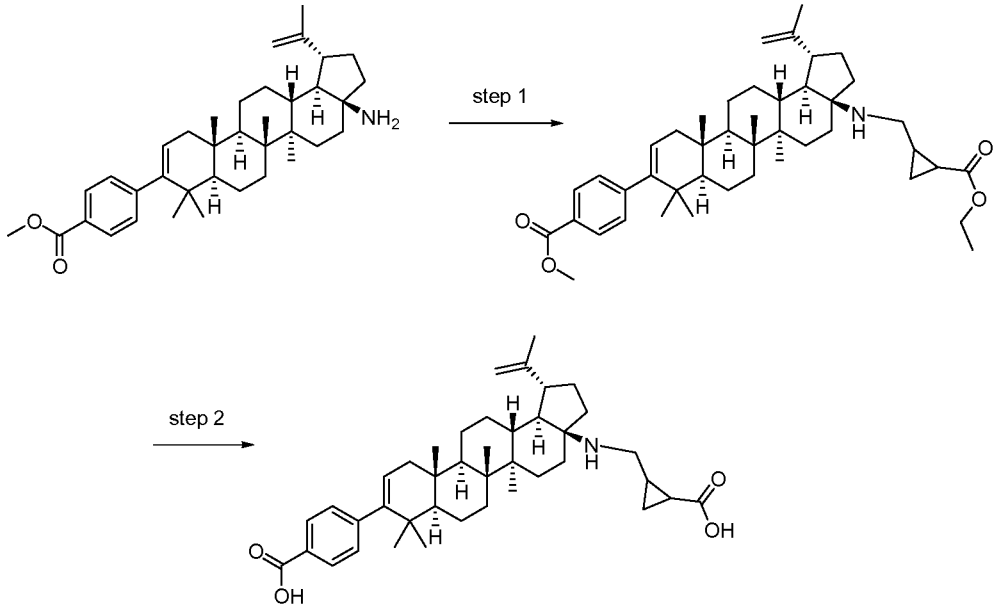
To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate, HCl (0.9 g, 1.551 mmol) in DCM (Volume: 15 mL) was added glyoxal 1,1-dimethyl acetal solution (45% in MTBE) (0.498 mL, 1.939 mmol), acetic acid (0.178 mL, 3.10 mmol), and sodium triacetoxyborohydride (0.493 g, 2.326 mmol). The mixture was stirred at rt. After 4 h of stirring, an additional 0.5 mL of glyoxal 1,1-dimethyl acetal solution (45% in MTBE) was added along with an additional 0.5 g of sodium triacetoxyborohydride. After a total of 7 h of stirring, the mixture was diluted with 25 mL of sat. $NaHCO_3$ and was extracted with dichloromethane (3 x 25 mL). The combined organic layers were dried with Na_2SO_4. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was adsorbed to silica gel and was purified by flash chromatography using a 0-10% EtOAc in hexanes gradient to give the title compound (0.67 g, 1.060 mmol, 68.4% yield) as a white foam. LCMS: m/e 632.75 $(M+H)^+$, 2.45 min (method 11).

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2,2-dimethoxyethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2,2-dimethoxyethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.025 g, 0.040 mmol) in 1,4-dioxane (1 mL) was added NaOH (1N) (0.198 mL, 0.198 mmol). The mixture was heated to 85 °C. After 6 h of heating, the mixture was cooled to rt, the reaction mixture was diluted with MeOH and was purified by prep HPLC. The fractions containing the expected product were combined and were concentrated under reduced pressure to give the title compound (17 mg, 0.026 mmol, 66.1% yield) as a clear film. LCMS: m/e 618.8 $(M+H)^+$, 2.28 min (method 11). ^{1}H NMR (500 MHz, *CHLOROFORM-d*) d ppm 7.99 (d, *J*=7.93 Hz, 2 H), 7.20 (d, *J*=7.93 Hz, 2 H), 5.28 (d, *J*=4.88 Hz, 1 H), 5.12 (br. s., 1 H), 4.72 (s, 1 H), 4.58 (s, 1 H), 4.53 (t, *J*=5.49 Hz, 1 H), 3.44 (s, 3 H), 3.41 (s, 3 H), 2.64 - 2.74 (m, 2 H), 2.60 (dd, *J*=11.44, 6.56 Hz, 1 H), 1.97 - 2.13 (m, 2 H), 1.86 - 1.95 (m, 2 H), 1.81 (dd, *J*=12.51, 8.24 Hz, 1 H), 1.68 (s, 3 H), 1.11 (s, 3 H), 0.98 (s, 3 H), 0.97 (br. s., 3 H), 0.95 - 1.72 (m, 17 H), 0.93 (br. s., 6 H).

Example 157

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-carboxycyclopropyl)methylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(ethoxycarbonyl)cyclopropyl)methylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (30 mg, 0.055 mmol) in DCE (0.5 mL) was added ethyl 2-formyl-1-cyclopropanecarboxylate (9.13 mL, 0.069 mmol) and titanium(IV) isopropoxide (0.020 mL, 0.069 mmol). The mixture was stirred at rt for 1 h and sodium triacetoxyborohydride (23.38 mg, 0.110 mmol) was added. After stirring the mixture for 16.25 h additional ethyl 2-formyl-1-cyclopropanecarboxylate (9.13 mL, 0.069 mmol) and sodium triacetoxyborohydride (23.38 mg, 0.110 mmol) were added and the mixture was again stirred at rt for 24 h. The reaction mixture was loaded directly onto a silica gel column and was purified by flash chromatography using a 0-25% EtOAc in hexanes gradient. The fractions containing the expected product were combined and concentrated under reduced pressure to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(ethoxycarbonyl)cyclopropyl)methylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

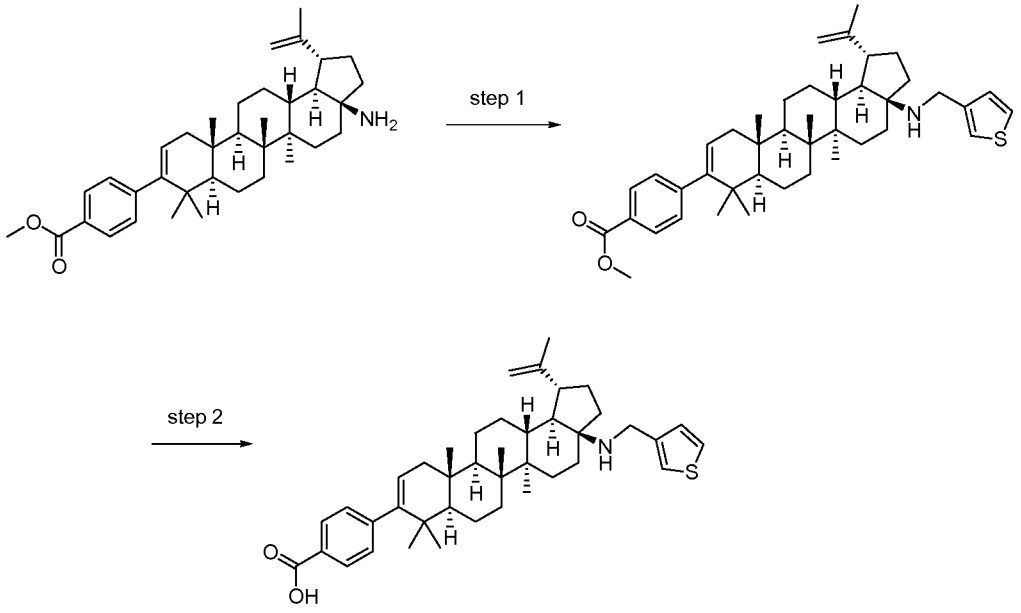
cyclopenta[a]chrysen-9-yl)benzoate (33 mg, 0.049 mmol, 89% yield). LCMS: m/e 670.8 $(M+H)^+$, 2.47 min (method 11).

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-carboxycyclopropyl)methylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(ethoxycarbonyl)cyclopropyl)methylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (33 mg, 0.049 mmol) in 1,4-dioxane (2 mL) was added NaOH (1N) (0.246 mL, 0.246 mmol). The mixture was heated to 85 °C for 22 h then was cooled to rt. An additional 0.25 mL of 1N NaOH was added to the mixture and it was again heated to 85 °C. After stirring the mixture over the weekend, the reaction mixture was purified by prep HPLC. The fractions containing the expected product were combined and concentrated under reduced pressure. 1H NMR still showed impurities present, so the mixture was purified a second time by prep HPLC. The fractions containing the product were combined and concentrated under reduced pressure to give the title compound (8.3 mg, 0.012 mmol, 24.15% yield) as a white solid. LCMS: m/e 628.6 $(M+H)^+$, 1.66 min (method 2).

Example 158

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(thiophen-3-ylmethylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(thiophen-3-ylmethylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (30 mg, 0.055 mmol) in DCE (0.5 mL) was added 3-thiophenecarboxaldehyde (7.73 mg, 0.069 mmol) and titanium(IV) isopropoxide (0.020 mL, 0.069 mmol). The mixture was stirred at rt for 1 h and sodium triacetoxyborohydride (23.38 mg, 0.110 mmol) was added. The mixture was stirred for 18 h at rt. The reaction mixture was loaded directly onto a silica gel column and was purified by flash chromatography using a 0-25% EtOAc in hexanes gradient. The fractions containing the expected product were combined and were concentrated under reduced pressure to give the title compound (32 mg, 0.05 mmol, 91% yield). LCMS: m/e 640.6 $(M+H)^+$, 2.13 min (method 2).

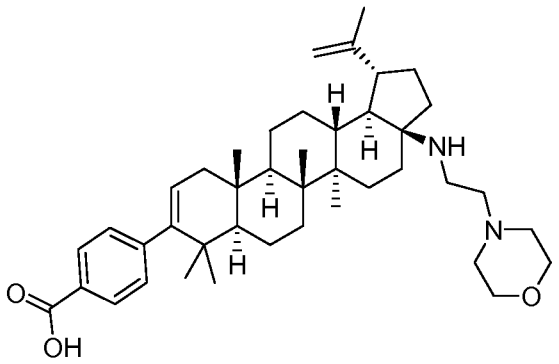
Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(thiophen-3-ylmethylamino)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(thiophen-3-ylmethylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (32 mg, 0.050 mmol) in dioxane (1 mL) was added NaOH (1N) (0.250 mL, 0.250 mmol). The mixture was heated to 85 °C for 15 h. The mixture was cooled to rt and was purified by prep HPLC to give the title compound (18 mg, 0.027 mmol, 53.5% yield) as a white solid. LCMS: m/e 626.5 $(M+H)^+$, 1.82 min (method 2). ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.00 (2 H, d, *J*=8.3 Hz), 7.30 (1 H, dd, *J*=4.8, 3.0 Hz), 7.24 (2 H, d, *J*=8.3 Hz), 7.20 (1 H, d, *J*=2.0 Hz), 7.12 (1 H, dd, *J*=5.0, 1.0 Hz), 5.30 - 5.34 (1 H, m), 4.72 (1 H, d, *J*=1.8 Hz), 4.61 (1 H, s), 2.61 (1 H, td, *J*=10.7, 5.4 Hz), 1.89 - 2.17 (5 H, m), 1.77 - 1.88 (1 H, m), 1.72 (3 H, s), 1.14 (3 H, s), 1.02 (3 H, s), 1.00 (3 H, s), 0.94 - 1.74 (18 H, m), 0.96 (6 H, s).

Example 159

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-morpholinoethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

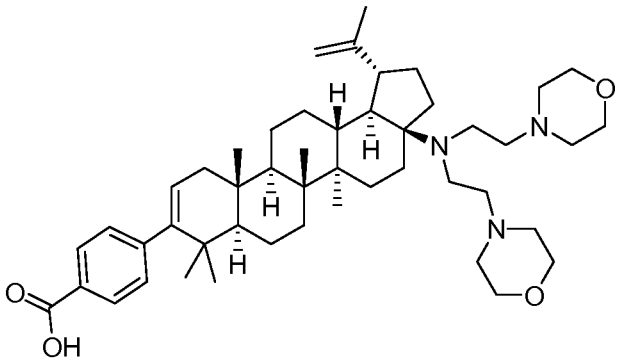


The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-

(dimethylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 4-(2-chloroethyl)morpholine hydrochloride as the alkylating agent in Step 1. The product was isolated as a white solid (65 mg, 49.4%). LCMS: m/e 643.6 (MH^+), 2.35 min (method 13). ^1H NMR (400 MHz, *MeOD*) δ ppm 7.95 (m, *J*=8.3 Hz, 2 H), 7.24 (m, *J*=8.3 Hz, 2 H), 5.31 (d, *J*=4.8 Hz, 1 H), 4.86 (s, 1 H), 4.74 (s, 1 H), 3.82 - 3.99 (m, 4 H), 3.37 - 3.58 (m, 4 H), 3.21 (d, *J*=4.5 Hz, 2 H), 3.19 (br. s., 2 H), 2.67 - 2.86 (m, 1 H), 2.02 - 2.26 (m, 5 H), 1.83 - 1.90 (m, 1 H), 1.64 - 1.81 (m, 8 H), 1.45 - 1.64 (m, 7 H), 1.34 - 1.45 (m, 2 H), 1.27 - 1.34 (m, 1 H), 1.15 - 1.27 (m, 4 H), 1.12 (s, 3 H), 1.04 (s, 3 H), 0.99 (s, 3 H), 0.93 (s, 3 H).

Example 160

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(bis(2-morpholinoethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

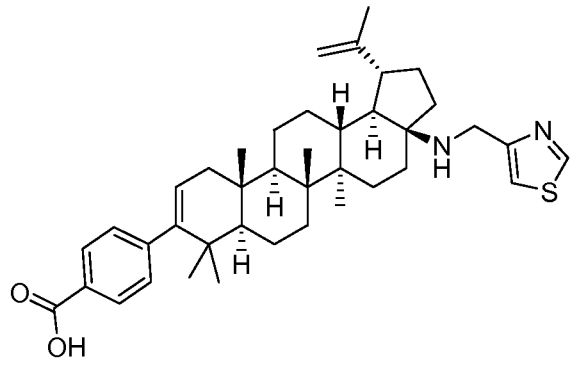


The title compound was obtained as a side product in the preparation 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-morpholinoethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid. The product was isolated as a white solid (20 mg, 12.2%). LCMS: m/e 756.7 (MH^+), 2.41 min (method 13). ^1H NMR (400 MHz,

MeOD) δ ppm 7.95 (m, *J*=8.3 Hz, 2 H), 7.24 (m, *J*=8.3 Hz, 2 H), 5.32 (d, *J*=4.8 Hz, 1 H), 4.86 (s, 1 H), 4.73 (s, 1 H), 4.19 (t, *J*=7.5 Hz, 2 H), 4.02 - 4.14 (m, 6 H), 3.88 (t, *J*=4.4 Hz, 4 H), 3.70 - 3.84 (m, 4 H), 3.57 (br. s., 2 H), 3.42 - 3.51 (m, 2 H), 2.96 - 3.19 (m, 4 H), 2.79 (br. s., 1 H), 2.01 - 2.26 (m, 5 H), 1.87 - 1.96 (m, 1 H), 1.68 - 1.82 (m, 6 H), 1.46 - 1.68 (m, 8 H), 1.26 - 1.45 (m, 4 H), 1.17 - 1.26 (m, 4 H), 1.13 (s, 3 H), 1.05 (s, 3 H), 0.99 (s, 3 H), 0.97 (s, 3 H).

Example 161

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(thiazol-4-ylmethylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

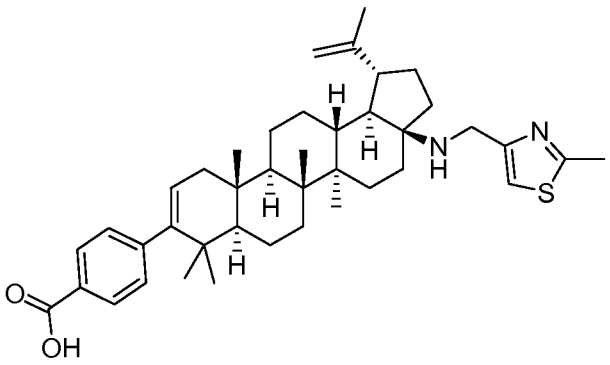


The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 4-(chloromethyl)thiazole as the alkylating agent in Step 1. MS: m/e 627.5 $(M+H)^+$, 1.56 min (method 12). ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 0.95 (s., 3 H) 0.96 (s, 3 H) 1.01 (s, 3 H) 1.10 (s, 3 H) 1.21 (s, 3 H) 1.72 (s, 3 H) 0.89 - 1. 83 (m, 16 H) 1.84 - 2.05 (m, 3 H) 2.07 - 2.22 (m, 1 H) 2.13 (dd, *J*=17.07, 6.53 Hz, 1 H) 2.22 - 2.32 (m, 1 H) 2.33 - 2.49 (m, 1 H) 4.24 (d, *J*=14.05 Hz, 1 H) 4.70 (s, 1 H) 4.72 (d, *J*=13.55 Hz, 1 H) 4.81 (s, 1 H)

5.31 (dd, *J*=6.02, 1.51 Hz, 1 H) 7.24 (d, *J*=8.28 Hz, 2 H) 7.59 (s, 1 H) 8.00 (d, *J*=8.28 Hz, 2 H) 8.83 (s, 1 H).

Example 162

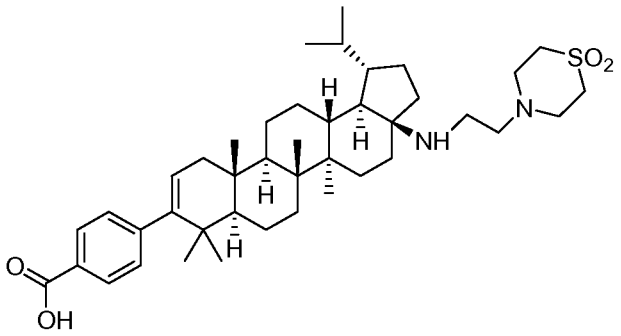
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-methylthiazol-4-yl)methylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 4-(chloromethyl)-2-methylthiazole hydrochloride as the alkylating agent in Step 1. MS: m/e 641.5 $(M+H)^+$, 1.56 min (method 12). ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 0.96 (s, 3 H) 0.97 (s, 3 H) 1.02 (s, 3 H) 1.10 (s, 3 H) 1.26 (s, 3 H) 1.71 (s, 3 H) 0.88 - 1.83 (m, 16 H) 1.89 - 2.04 (m, 3 H) 2.08 - 2.21 (m, 1 H) 2.14 (dd, *J*=17.19, 6.15 Hz, 1 H) 2.22 - 2.30 (m, 1 H) 2.33 - 2.45 (m, 1 H) 2.68 (s, 3 H) 4.09 (d, *J*=13.05 Hz, 1 H) 4.64 (d, *J*=12.80 Hz, 1 H) 4.69 (s, 1 H) 4.80 (s, 1 H) 5.32 (d, *J*=4.52 Hz, 1 H) 7.24 (d, *J*=8.28 Hz, 2 H) 7.28 (s, 1 H) 8.00 (d, *J*=8.28 Hz, 2 H).

Example 163

Preparation of 4-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

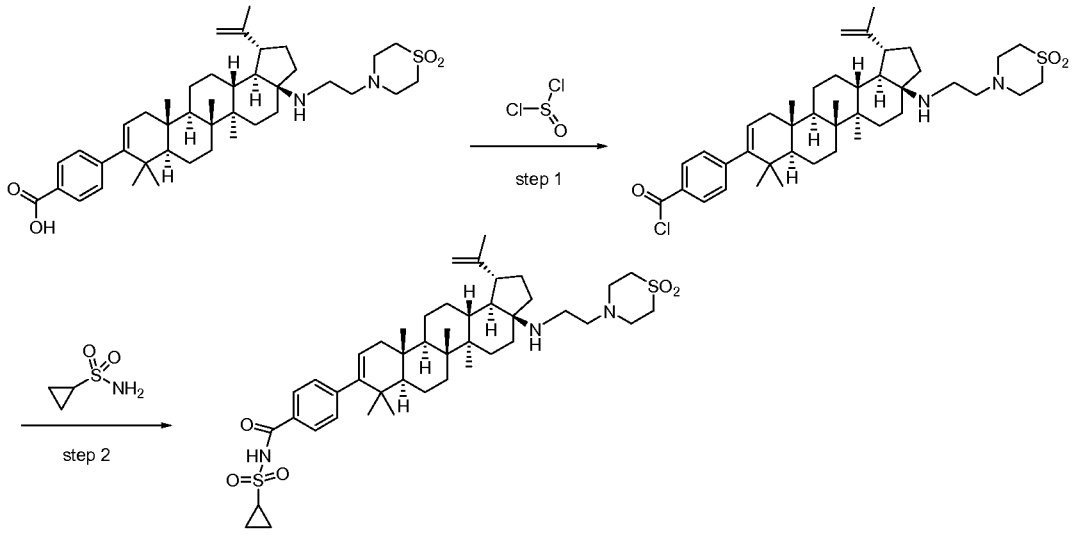


A mixture of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (100 mg, 0.145 mmol) and 10% Pd/C (90 mg, 0.087 mmol) in methanol (5 mL) and ethyl acetate (5 mL) was loaded onto a PARR shaker reactor and treated with hydrogen for 25 hours under 40 psi at room temperature. The reaction mixture was filtered through a celite pad to remove the catalyst. The filtrate was purified by HPLC to provide the title compound as a white solid (5.6 mg, 28%). LCMS: m/e 693.46 $(M+H)^+$, 2.46 min (method 10). ^{1}H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.04 (d, *J*=8.2 Hz, 2 H), 7.31 (d, *J*=8.2 Hz, 2 H), 5.39 (d, *J*=4.6 Hz, 1 H), 3.50 - 3.36 (m, 1 H), 3.36 - 3.21 (m, 6 H), 3.21 – 2.98 (m, 5 H), 2.31 – 1.29 (m, 24 H), 1.29 (s, 3 H), 1.13 (s, 6 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.94 (d, *J*=6.7 Hz, 3 H), 0.86 (d, *J*=6.7 Hz, 3 H).

Example 164

Preparation of *N*-(cyclopropylsulfonyl)-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzamide.



Step 1. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoyl chloride.

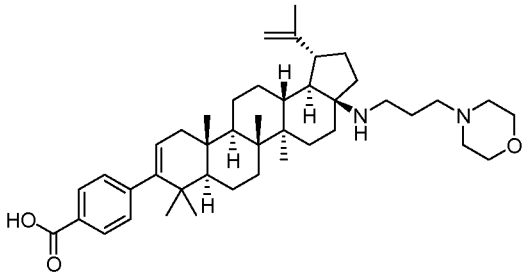
A mixture of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (200 mg, 0.289 mmol) and thionyl chloride (0.211 mL, 2.89 mmol) in dichloroethane (5 mL) was refluxed for 30 h. The reaction mixture was concentrated under reduced pressure to provide the title compound as a white solid (150 mg, 73%). LCMS: m/e 705.46 $(M\text{-}Cl+OMe+H)^+$, 3.0 min (method 10).

Step 2. Preparation of *N*-(cyclopropylsulfonyl)-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzamide

A mixture of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoyl chloride (30 mg, 0.042 mmol), cyclopropanesulfonamide (6.15 mg, 0.051 mmol), Hunig's Base (0.022 mL, 0.127 mmol) and DMAP (2.58 mg, 0.021 mmol) in dichloromethane (1 mL) was stirred for 16 h at room temperature. The crude reaction mixture was purified by prep HPLC to provide the title compound as a white solid (4 mg, 11%). LCMS: m/e 794.53 $(M+H)^+$, 2.44 min (method 10). ^{1}H NMR (500 MHz, *Acetic acid d4*) δ ppm 7.94 (d, *J*=8.5 Hz, 2 H), 7.32 (d, *J*=8.2 Hz, 2 H), 5.38 (d, *J*=4.6 Hz, 1 H), 4.84 (s, 1 H), 4.74 (s, 1 H), 3.56 - 3.39 (m, 1 H), 3.38 - 3.21 (m, 7 H), 3.21 - 3.11 (m, 3 H), 3.11 - 3.03 (m, 2 H), 3.01 – 2.89 (m, 1 H), 2.41 – 1.16 (m, 26 H), 1.76 (s, 3 H), 1.29 (s, 3 H), 1.15 (s, 3 H), 1.11 (s, 3 H), 1.03 (s, 3 H), 1.00 (s, 3 H).

Example 165

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-morpholinopropylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

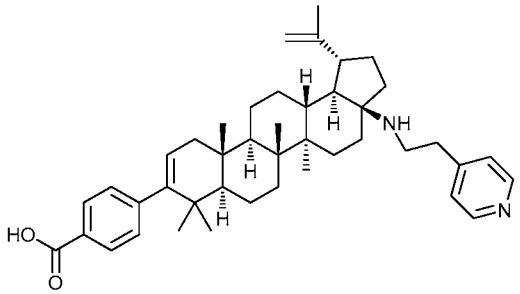


The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 4-(3-chloropropyl)morpholine hydrochloride as the alkylating reagent in Step 1. The product was isolated as a white solid (60 mg, 48.1%). LCMS: m/e 657.55 $(M+H)^+$, 2.24 min (method 13). ^{1}H NMR (400MHz, METHANOL-d_4) δ 7.95 (d, *J*=8.3 Hz, 2H), 7.26 (d, *J*=8.3 Hz , 2H), 5.33

(d, *J*=4.5 Hz, 1H), 4.88 (s, 1H), 4.75 (s, 1H), 3.97 (m, 4H), 3.30 - 3.04 (m, 8H), 2.85 - 2.66 (m, 1H), 2.46 - 2.24 (m, 2H), 2.24 - 1.85 (m, 7H), 1.82 - 1.65 (m, 7H), 1.65 - 1.45 (m, 7H), 1.45 - 1.26 (m, 4H), 1.22 (s, 3H), 1.14 (s, 3H), 1.08 (s, 3H), 1.00 (s, 3H), 0.98 (s, 3H)

Example 166

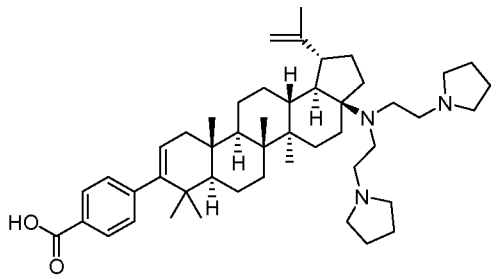
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((2-(pyridin-4-yl)ethyl)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 4-(2-chloroethyl)pyridine as the alkylating reagent in Step 1. The product was isolated as an off white solid (10 mg, 2.9%). LCMS: m/e 635.40 $(M+H)^+$, 2.31 min (method 13). ^{1}H NMR (400MHz, METHANOL-d_4) δ 8.83 (d, *J*=5.8 Hz, 2H), 8.06 (d, *J*=6.0 Hz, 2H), 7.95 (d, *J*=8.5 Hz, 2H), 7.25 (d, *J*=8.3 Hz, 2H), 5.33 (d, *J*=4.5 Hz, 1H), 4.90 (s, 1H), 4.76 (s, 1H), 3.57 - 3.46 (m, 4H), 2.86 - 2.75 (m, 1H), 2.27 - 2.08 (m, 5H), 2.05 - 1.89 (m, 2H), 1.79 (s, 3H), 1.85 - 1.67 (m, 4H), 1.66 - 1.49 (m, 7H), 1.45 - 1.23 (m, 4H), 1.21 (s, 3H), 1.14 (s, 3H), 1.09 (s, 3H), 1.00 (s, 3H), 0.98 (s, 3H).

Example 167

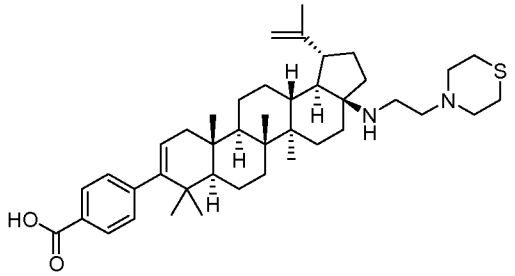
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(bis(2-(pyrrolidin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 1-(2-chloroethyl)pyrrolidine hydrochloride as the alkylating reagent in Step 1. The product was isolated as a white solid (10 mg, 2.57%). LCMS: m/e 724.52 $(M+H)^+$, 1.43 min (method 15). ^{1}H NMR (400MHz, METHANOL-d) δ 7.88 (d, *J*=8.0 Hz, 2H), 7.19 (d, *J*=8.0 Hz, 2H), 5.26 (d, *J*=4.8 Hz, 1H), 4.79 (s, 1H), 4.66 (s, 1H), 4.03 - 3.86 (m, 4H), 3.86 - 3.62 (m, 6H), 3.59 - 3.29 (m, 6H), 2.81 - 2.58 (m, 1H), 2.26 (br. s., 4H), 2.21 - 1.88 (m, 9H), 1.82 (d, *J*=13.1 Hz, 1H), 1.73 - 1.62 (m, 5H), 1.62 - 1.40 (m, 9H), 1.40 - 1.19 (m, 4H), 1.13 (s, 4H), 1.06 (s, 3H), 1.01 (s, 3H), 0.93 (s, 3H), 0.91 (s, 3H),

Example 168

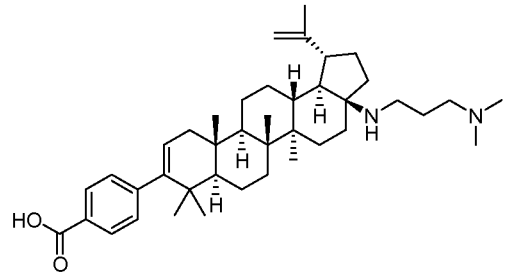
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-thiomorpholinoethylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 4-(2-chloroethyl)thiomorpholine hydrochloride (prepared as describe in WO 2009058859) as the alkylating reagent in Step 1. The product was isolated as a white solid (3 mg, 0.85%). LCMS: m/e 659.37 $(M+H)^+$, 2.38 min (method 13). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.00 (d, *J*=8.3 Hz, 2H), 7.21 (d, *J*=8.5 Hz, 2H), 5.32 - 5.19 (m, 1H), 4.77 (s, 1H), 4.65 (s, 1H), 3.11 - 2.98 (m, 1H), 2.89 (m, 5H), 2.75 (m, 5H), 2.67 - 2.57 (m, 1H), 2.31 - 2.16 (m, 1H), 2.14 - 1.85 (m, 6H), 1.71 (s, 7H), 1.59 - 1.40 (m, 6H), 1.38 - 1.15 (m, 8H), 1.08 - 0.96 (m, 10H), 0.94 (s, 3H)

Example 169

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimethylamino)propylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

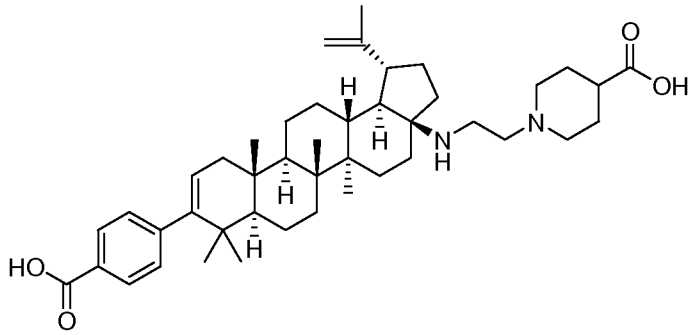


The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 3-chloro-N,N-dimethylpropan-1-amine hydrochloride as the alkylating reagent in Step 1. The product was isolated as a white solid (3 mg, 0.85%). LCMS: m/e 615.75 $(M+H)^+$, 2.24 min (method 13). ^1H NMR (400MHz, METHANOL-d_4) δ 7.95 (d, *J*=8.0 Hz, 2H), 7.25 (d, *J*=8.0 Hz, 2H), 5.34 (s, 1H), 4.89 (s, 1H), 4.75 (s, 1H), 3.58 - 3.36 (m, 2H), 3.26 (br. s., 8H), 2.78 (d, *J*=7.5 Hz, 1H), 2.51 - 2.26 (m, 3H), 2.26 - 1.97 (m, 7H), 1.92 (m, 1H), 1.78 (m, 6H), 1.63 - 1.47 (m, 6H), 1.45 - 1.36 (m, 2H), 1.32 - 1.18 (m, 5H), 1.14 (s, 3H), 1.08 (s, 3H), 1.00 (s, 3H), 0.98 (s, 3H)

Example 170

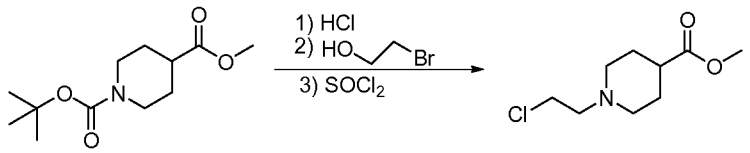
Preparation of 1-(2-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-carboxyphenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-yl)amino)ethyl)piperidine-4-carboxylic acid



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using methyl 1-(2-chloroethyl)piperidine-4-carboxylate hydrochloride (prepared as described below) as the alkylating reagent in Step 1. The product was isolated as a white solid (8 mg, 83%). LCMS: m/e 685.6 $(M+H)^+$, 2.33 min (method 10). ^1H NMR (400MHz, METHANOL-d_4) δ 7.94 (d, *J*=8.3 Hz, 2H), 7.23 (d, *J*=8.3 Hz, 2H), 5.31 (d, *J*=4.5 Hz, 1H), 4.86 (s, 1H), 4.74 (s,

1H), 3.48 - 3.36 (m, 5H), 3.12 - 2.88 (m, 2H), 2.79 - 2.69 (m 1H), 2.68 - 2.60 (m, 1H), 2.24 - 2.11 (m, 4H), 2.11 - 2.00 (m, 4H), 1.97 - 1.81 (m, 3H), 1.77 (s, 3H), 1.81 - 1.71 (m, 2H), 1.70 - 1.46 (m, 10H), 1.45 - 1.27 (m, 4H), 1.21 (s, 3H), 1.12 (s, 3H), 1.06 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H).

Preparation of methyl 1-(2-chloroethyl)piperidine-4-carboxylate

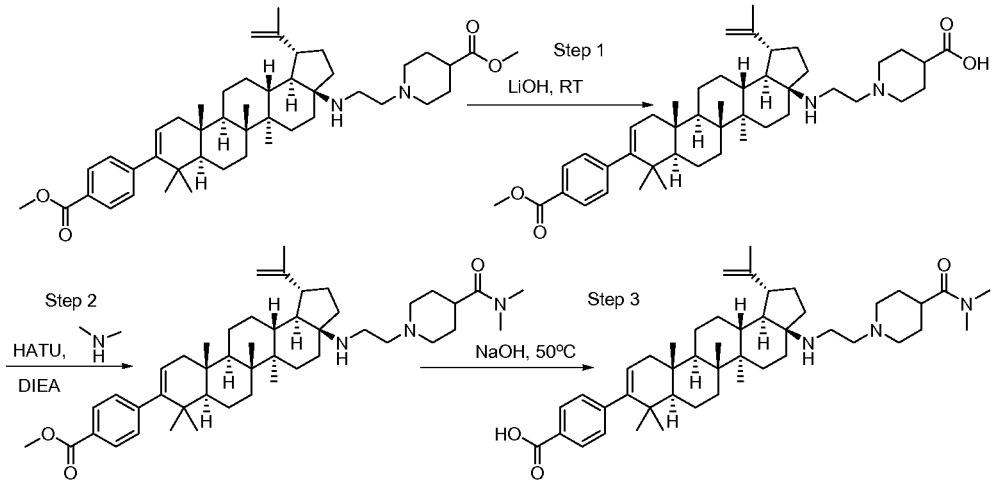


To a solution of 1-tert-butyl 4-methyl piperidine-1,4-dicarboxylate (5.4 g, 22.19 mmol) in ether was added hydrogen chloride (27.7 mL, 111 mmol) in dioxane. The resulted clear solution was stirred for 4 hours. Bubbles and white precipitates were observed. Then the solvent was removed and dried in vacuo. The residue was suspended in acetonitrile (50 mL), and 2-bromoethanol (1.567 mL, 22.19 mmol) was added followed by powdered K_2CO_3 (14.72 g, 107 mmol). After the reaction mixture was refluxed for 18 hours, it was filtered and concentrated. The residue was redissolved in water (50.0 mL) and extracted with ethyl acetate (50.0 mL). The organic layer was dried over sodium sulfate. After filtration the solvent was removed in vacuo. The residue was dissolved in DCE (50.0 mL) before sulfurous dichloride (2.428 mL, 33.3 mmol) was added. The reaction mixture was reflux for 3 hours, then all volatile was removed in vacuo, the resulting solid was suspended in ether, then filtered and washed with ether (50.0 mL), resuspended in ethyl acetate and neutralized with sodium bicarbonate. The organic layer was collected and dried with sodium sulfate to afford methyl 1-(2-chloroethyl)piperidine-4-carboxylate (1 g, 4.86 mmol, 21.91 % yield) as a brown oil. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 3.70 (s, 3H), 3.61 (t, *J*=7.0 Hz, 2H), 2.97 - 2.86 (m, 2H), 2.75 (t, *J*=7.2 Hz, 2H), 2.40 - 2.27 (m, 1H), 2.19 (m, 2H), 2.01 - 1.88 (m, 2H), 1.87 - 1.72 (m, 2H).

Example 171

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4-(dimethylcarbamoyl)piperidin-1-yl)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-

(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



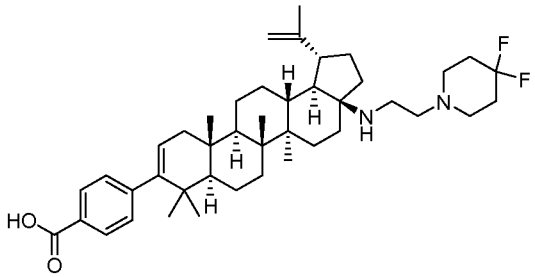
Step 1. To a solution of methyl 1-(2-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-ylamino)ethyl)piperidine-4-carboxylate (40 mg) in dioxane (1 mL) was added lithium hydroxide (2.7 mg, 0.112 mmol) in water (1 mL). A white precipitate was observed. The mixture was stirred at 25°C for 3 hours. The desired product was observed at m/e 699.7 $(M+H)^+$, 2.703 min, method 10. The reaction mixture was neutralized with 1 N HCl to pH~4 and diluted with methlylene chloride (10 mL). The organic layer was then collected, dried over sodium sulfate and filtered. After removal of solvent, the crude product was obtained as an oil (40 mg, ~ 100%) which was used without further purification.

Step 2. To a solution of 1-(2-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-yl)amino)ethyl)piperidine-4-carboxylic acid (40 mg, 0.057 mmol) in CH_2Cl_2 (5 ml) at rt was added dimethylamine (7.6 mg, 0.17 mmol) and HATU (65 mg, 0.18 mmol) followed by DIEA (29 mg, 0.23mmol) . The mixture was stirred for 3 hour at rt. The resulted mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over sodium sulfate. The crude product was obtained after removal of solvent as a white solid (40 mg, ~ 100%) which was used without further purification

Step 3. 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4-(dimethylcarbamoyl)piperidin-1-yl)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid was prepared following step 2 of the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimethylamino)-2-oxoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid. The product was isolated as a white solid (9 mg, 23.0%). LCMS: m/e 712.64 $(M+H)^+$, 2.265 min (method 11). ^{1}H NMR (400MHz, METHANOL-d_4) δ 7.95 (d, *J*=8.3 Hz, 2H), 7.25 (d, *J*=8.3 Hz, 2H), 5.33 (d, *J*=4.5 Hz, 1H), 4.87 (s, 1H), 4.74 (s, 1H), 3.65 - 3.38 (m, 6H), 3.16 (s, 3H), 3.05 (m, 2H), 2.96 (s, 3H), 2.75 (m, 1H), 2.23 - 1.85 (m, 11H), 1.82 - 1.74 (m, 6H), 1.70 - 1.48 (m, 9H), 1.44 - 1.28 (m, 3H), 1.22 (m, 4H), 1.13 (s, 3H), 1.08 (s, 3H), 1.00 (s, 3H), 0.98 (s, 3H),

Example 172

Preparation of 4-(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4,4-difluoropiperidin-1-yl)ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

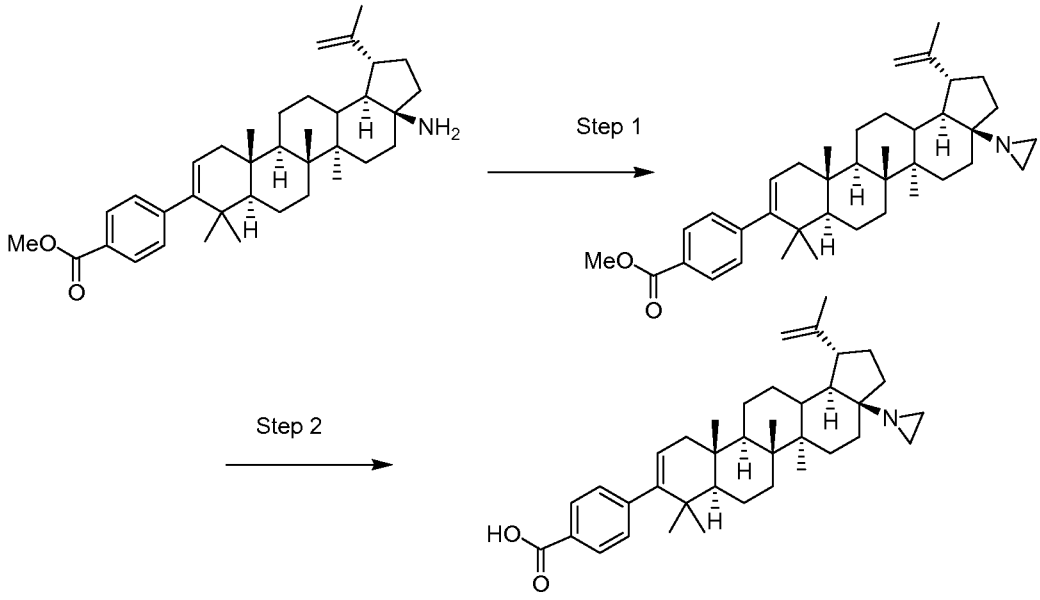


The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(tert-butoxycarbonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 4,4-difluoropiperidine hydrochloride as

the alkylating reagent in Step 3. The product was isolated as a white solid (20 mg, 58.3%). LCMS: m/e 677.57 $(M+H)^+$, 2.30 min (method 11). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.97 (d, *J*=8.3 Hz, 2H), 7.22 (d, *J*=8.3 Hz, 2H), 5.27 (d, *J*=4.8 Hz, 1H), 4.82 (s, 1H), 4.70 (s, 1H), 3.32 (m, 1H), 3.19 - 3.05 (m, 1H), 2.94 (m, 2H), 2.83 - 2.68 (m, 5H), 2.36 - 2.21 (m, 2H), 2.15 - 1.90 (m, 7H), 1.74 (br. s., 7H), 1.60 - 1.45 (m, 6H), 1.44 - 1.30 (m, 4H), 1.26 (s, 2H), 1.18 (s, 3H), 1.06 (s, 4H) 0.98 (s, 3H), 0.97 (s, 3H), 0.95 (s, 3H). ^{19}F NMR (376MHz, CHLOROFORM-d) δ -98.39 (br. s., 2F)

Example 173

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13bR)-3a-(aziridin-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



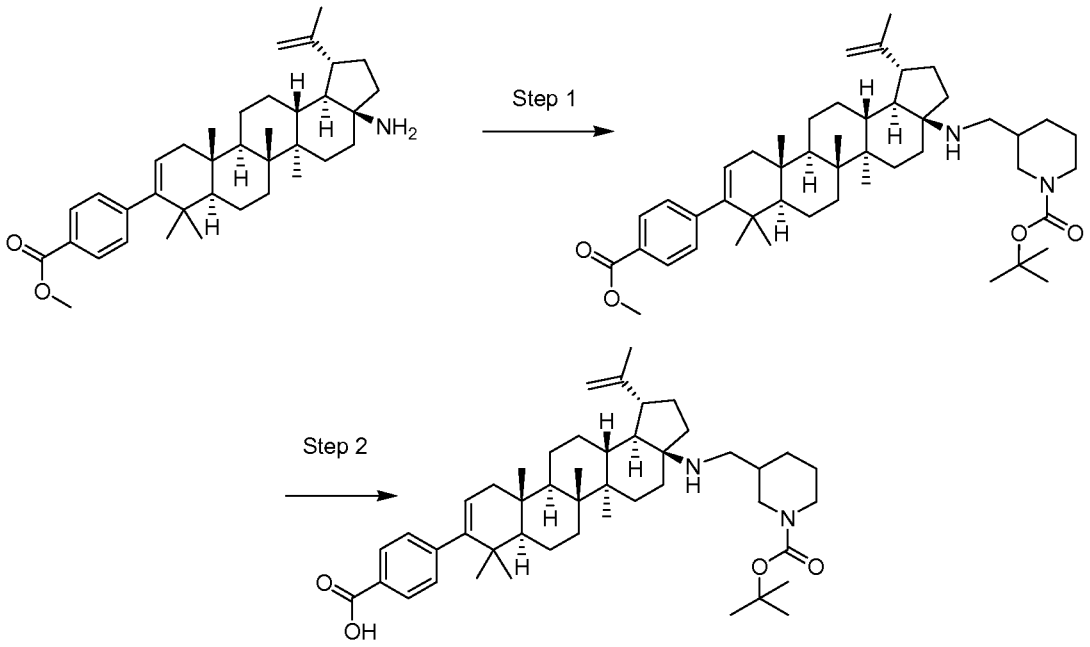
Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13bR)-3a-(aziridin-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate. To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.160 g, 0.276 mmol) in a

mixture of acetonitrile (25 mL) and dichloroethane (5 mL) was added anhydrous potassium phosphate (0.25 gm, 1.18 mmol). The resulting suspension was heated to 120 °C under nitrogen in a thick-walled tube for 24 hours. The cooled reaction suspension was filtered through a short bed of silica gel (Type-H), washed with ethyl acetate (60 mL). The clear filtrate was concentrated in vacuo to give a white solid (0.150 g, 96%). LCMS: m/e 570.5 $(M+H)^+$, 3.32 min (method 12, but modified to gradient over 3 minutes). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.95 (d, *J*=8.3 Hz, 2H), 7.22 (d, *J*=8.5 Hz, 2H), 5.31 (dd, *J*=6.1, 1.6 Hz, 1H), 4.81 - 4.73 (m, 1H), 4.67 - 4.59 (m, 1H), 3.93 (s, 3H), 2.82 - 2.45 (m, 1H), 2.19 - 2.04 (m, 1H), 1.88 - 1.74 (m, 1H), 1.71 (s, 3H), 1.68 (br. s., 1H), 1.63 - 1.21 (m, 7H), 1.11 (s, 3H), 1.01 (s,3H), 1.00 (s, 3H), 0.95 (s, 6H).

Step 2. To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13bR)-3a-(aziridin-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.150 g, 0.264 mmol) in a mixture of methanol (2 mL) and THF (6 mL) at rt was added a stock solution of lithium hydroxide (1.0 Molar, 2 mL, 2.0 mmol) forming a thick suspension. The mixture was kept at 50 °C under nitrogen for 60 hours. The reaction mixture was neutralized with HCl (0.5 Molar, 10 mL), the organic material was extracted into ethyl acetate (30 mL). While the 2-phase mixture was stirred at rt, a white precipitate slowly separated out. It was filtered to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13bR)-3a-(aziridin-1-yl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid as a white solid (99 mg, 68 %). LCMS: m/e 592.5 $(M+MeOH+Na)^+$, 3.03 min (method 12, but modified to gradient over 3 minutes). Selected ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.01 (d, *J*=8.3 Hz, 2H), 7.24 (d, *J*=8.3 Hz, 2H), 5.28 (m, 1H), 4.94 (br. s, 1H), 4.73 (br. s, 1H), 1.74 (s, 3H), 1.20 (s, 3H), 1.09 (s, 3H), 1.01 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H).

Example 174

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1-(tert-butoxycarbonyl)piperidin-3-yl)methylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



Step 1. Preparation of tert-butyl 3-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-ylamino)methyl)piperidine-1-carboxylate.

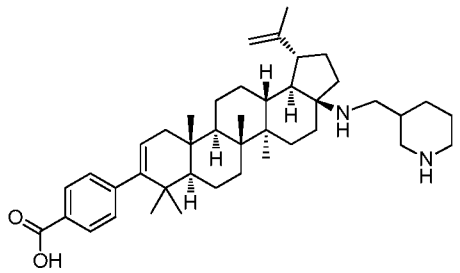
To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (30 mg, 0.055 mmol) in dichloroethane (0.5 mL) was added 3-formyl-piperidine-1-carboxylic acid tert-butyl ester (14.71 mg, 0.069 mmol) and titanium (IV) isopropoxide (0.020 mL, 0.069 mmol). The mixture was stirred at rt for 1h and sodium triacetoxyborohydride (23.38 mg, 0.110 mmol) was added. The mixture was stirred at rt for 16.5h, then was diluted with 3 mL of sat. $NaHCO_3$ and was extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried with Na_2SO_4, were filtered and were concentrated under reduced pressure. The residue was adsorbed to silica gel and was purified by flash

chromatography using a 0-10% ethyl acetate in hexanes gradient and a Thomson 12g silica gel column. The fractions containing the expected product were combined and concentrated under reduced pressure to give the title compound as an off-white foam. LCMS: m/e 741.7 $(M+H)^+$, 3.76 min (method 2).

Step 2. To a solution of tert-butyl 3-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-ylamino)methyl)piperidine-1-carboxylate (0.029 g, 0.039 mmol) in 1,4-dioxane (2 mL) was added NaOH (1N) (0.196 mL, 0.196 mmol). The mixture was heated to 85°C for 22h, then was cooled to rt, was diluted with MeOH, and was purified by prep HPLC. The fractions containing the expected product were combined and concentrated under reduced pressure to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1-(tert-butoxycarbonyl)piperidin-3-yl)methylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (24 mg, 0.031 mmol, 56 % yield over 2 steps) as a clear, colorless film. LCMS: m/e 727.7 $(M+H)^+$, 2.00 min (method 2). ^{1}H NMR (500 MHz, *Chloroform-d*) δppm 7.98 (d, *J*=7.93 Hz, 2 H), 7.21 (d, *J*=7.93 Hz, 2 H), 5.29 (d, *J*=5.49 Hz, 1 H), 4.70 (br. s., 1 H), 4.58 (br. s., 1 H), 3.82 - 4.51 (m, 5 H), 1.68 (s, 3 H), 1.47 (d, *J*=4.58 Hz, 9 H), 1.10 (d, *J*=7.93 Hz, 3 H), 0.98 (br. s., 6 H), 0.93 (s, 3 H), 0.92 (s, 3 H), 0.90 - 2.85 (m, 30 H).

Example 175

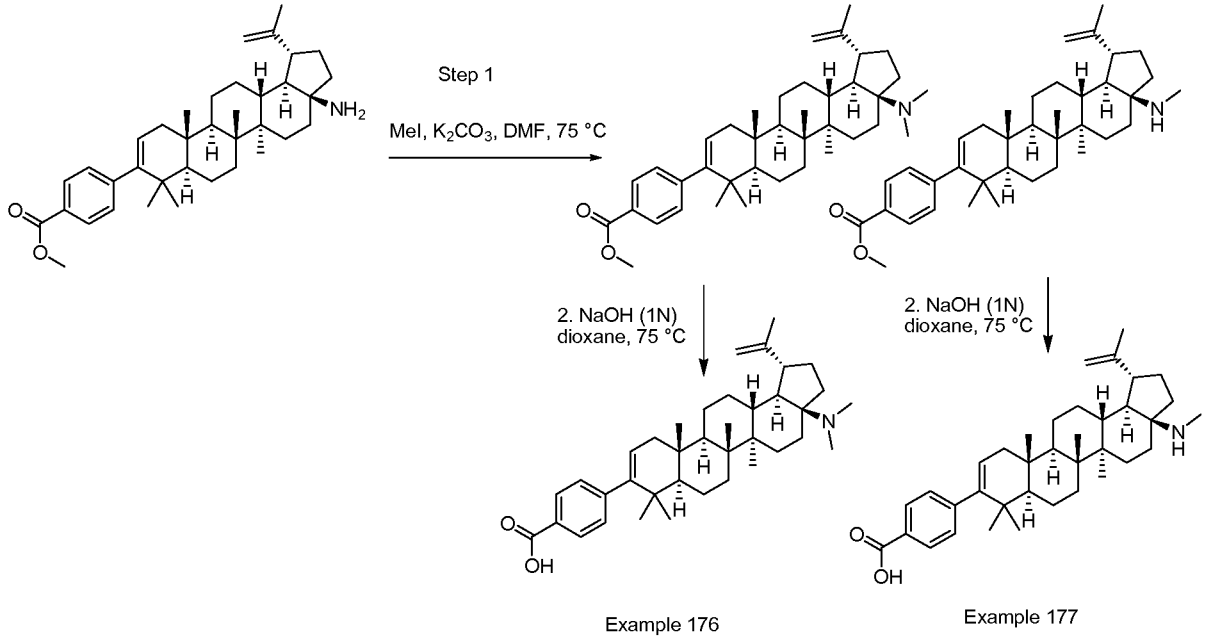
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(piperidin-3-ylmethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



To a solution of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1-(tert-butoxycarbonyl)piperidin-3-yl)methylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (0.019 g, 0.026 mmol) in dichloromethane (1 mL) was added TFA (0.25 mL, 3.24 mmol). The mixture was stirred at rt for 1.75h then was concentrated under reduced pressure. The residue was purified by prep HPLC. The fractions containing the expected product were combined and were concentrated under reduced pressure to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(piperidin-3-ylmethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (14.2 mg, 0.021 mmol, 81 % yield) as a white solid. LCMS: m/e 627.6 $(M+H)^+$, 1.50 min (method 2).

Examples 176 and 177

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(methylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid and 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(dimethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



Step 1. To a sealable vial containing methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate, HCl (1.0 g, 1.72 mmol) was added potassium carbonate (0.48 g, 3.45 mmol). The mixture was diluted with DMF (15 mL) and methyl iodide (323 mL, 3.45 mmol) was added. The vial was sealed and the mixture was heated to 75 °C for 4 h then was cooled to rt. The vial was opened to the air and was stirred at rt overnight. The mixture was diluted with 20 mL of saturated aqueous sodium thiosulfate. Solids formed and were collected by filtration and were washed with water. The residue was purified by flash chromatography in silica gel using a 0-25% ethyl acetate in hexanes gradient with 0.1% ammonium hydroxide added to the mixture. Two main isolates were recovered from the column. The less polar product, methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(dimethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.247 g, 0.405 mmol, 23.5 % yield) was recovered as a white foam. The more polar isolate, methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(methylamino)-1-(prop-1-en-2-yl)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.5 g, 0.807 mmol, 46.8 % yield), was recovered as a white solid. LCMS of the less polar isolate: m/e 572.6 $(M+H)^+$, 2.03 min (method 2). ^{1}H NMR (400MHz, *Chloroform-d*) δ = 7.96 - 7.92 (m, 2H), 7.23 - 7.19 (m, 2H), 5.31 - 5.29 (m, 1H), 4.71 (d, *J*=2.0 Hz, 1H), 4.61 (dd, *J*=2.3, 1.3 Hz, 1H), 3.92 (s, 3H), 2.86 (td, *J*=11.2, 6.1 Hz, 1H), 2.34 - 2.24 (m, 7H), 2.12 (dd, *J*=17.1, 6.5 Hz, 1H), 2.04 - 1.80 (m, 5H), 1.70 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H), 0.94 (s, 3H), 0.94 (s, 3H), 1.74 - 0.85 (m, 15H). LCMS of the more polar isolate: m/e 558.6 $(M+H)^+$, 2.04 min (method 2). ^{1}H NMR (400MHz, *Chloroform-d*) = 7.93 (d, *J*=8.0 Hz, 2H), 7.20 (d, *J*=8.3 Hz, 2H), 5.30 (dd, *J*=6.1, 1.6 Hz, 1H), 4.72 (d, *J*=2.0 Hz, 1H), 4.59 (s, 1H), 3.92 (s, 3H), 2.60 (td, *J*=10.9, 5.8 Hz, 1H), 2.24 (s, 3H), 2.11 (dd, *J*=17.2, 6.1 Hz, 1H), 2.03 - 1.91 (m, 2H), 1.88 - 1.79 (m, 2H), 1.09 (s, 3H), 1.00 (s, 3H), 0.99 (s, 3H), 0.94 (s, 3H), 0.93 (s, 3H), 1.69 - 0.91 (m, 20H).

Step 2. The saponification of the isolates were carried out independently:

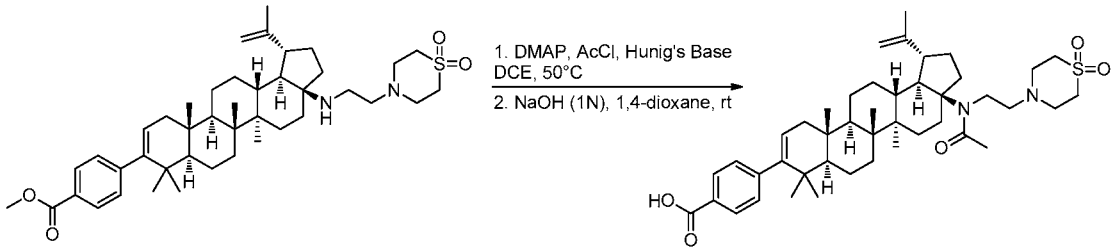
Example 176: Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(methylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, HCl. To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(methylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (88 mg, 0.158 mmol) in 1,4-dioxane (3 mL) was added NaOH (1M) (1 mL, 1.000 mmol). The mixture was heated to 75 °C for 17h then was cooled to rt and was acidified with 3 mL of 1N HCl. Solids formed upon standing and were collected by filtration and were washed with water. The solids were dissolved and were purified by flash chromatography using a 0-40% methanol in ethyl acetate gradient and a Thomson 25g silica gel column. The fractions containing the expected product were combined and were concentrated under reduced pressure then were redissolved in dichloromethane and methanol and were filtered through a plug of celite. The filtrate was concentrated under reduced pressure to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-

(methylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, HCl (40 mg, 0.065 mmol, 41% yield) as a white solid. LCMS: m/e 544.5 $(M+H)^+$, 1.79 min (method 2). ^{1}H NMR (500MHz, *Acetic acid d4*) δ = 8.01 (d, *J*=8.2 Hz, 2H), 7.27 (d, *J*=8.2 Hz, 2H), 5.34 (d, *J*=4.6 Hz, 1H), 4.84 (s, 1H), 4.71 (s, 1H), 2.85 - 2.77 (m, 1H), 2.74 (s, 3H), 1.75 (s, 3H), 1.16 (s, 3H), 1.10 (s, 3H), 1.06 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 2.24 - 0.95 (m, 22H).

Example 177: Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(dimethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid. To a suspension of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(dimethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate, HCl (100 mg, 0.164 mmol) in 1,4-dioxane (3 mL) was added 1N NaOH (1 mL, 1.000 mmol) and the mixture was heated to 70 °C. After 3.75h the mixture was cooled to rt and was diluted with 2 mL of MeOH and then 1N HCl (6 mL) was added. The solids that formed were collected by filtration and were washed with water. The solids were dissolved in dioxane and methanol and were purified by prep HPLC. The fractions containing the expected product were combined and concentrated under reduced pressure to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(dimethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (45 mg, 0.077 mmol, 46.6 % yield) as a white solid. LCMS: m/e 558.3 $(M+H)^+$, 2.28 min (method 11). ^{1}H NMR (500 MHz, *Acetic acid d4*) δ ppm 8.04 (2 H, d, *J*=8.2 Hz), 7.30 (2 H, d, *J*=8.2 Hz), 5.37 (1 H, d, *J*=4.9 Hz), 4.92 (1 H, s), 4.77 (1 H, s), 3.08 (7 H, br. s.), 1.80 (3 H, s), 1.22 (3 H, s), 1.18 (3 H, s), 1.09 (3 H, s), 1.02 (3 H, s), 1.00 (3 H, s), 0.98 - 2.46 (22 H, m).

Example 178

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(acetyl(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(acetyl(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

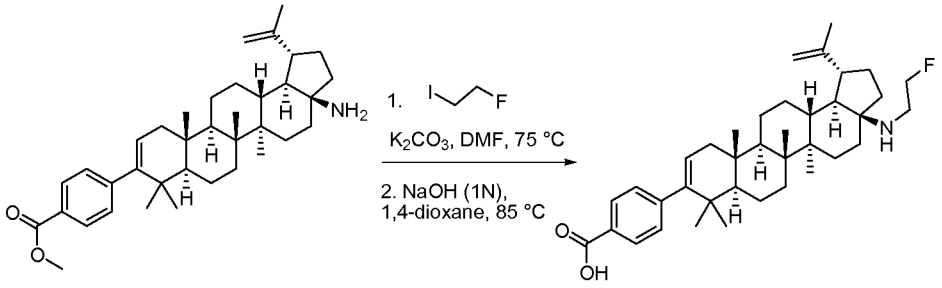
To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((1,1-dioxido-4-thiomorpholinyl)acetyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.05 g, 0.071 mmol) in dichloroethane (1 mL) and Hunig's base (0.062 mL, 0.355 mmol) was added acetyl chloride (0.020 mL, 0.284 mmol). The mixture was heated to 50 °C. After heating the mixture for 71.25h, the mixture was cooled to rt and was directly loaded onto a 12g Thomson silica gel column and was purified by Biotage flash chromatography using a 0-5% MeOH in dichloromethane gradient. The fractions containing the expected product were combined and were concentrated under reduced pressure to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(acetyl(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (40 mg, 0.054 mmol, 75%) as a clear, colorless film. LCMS: m/e 747.5 $(M+H)^+$, 2.26 min (method 2).

Step 2. To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(acetyl(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (40 mg, 0.054 mmol) in 1,4-dioxane (1 mL) was

added NaOH (1N) (0.27 mL, 0.27 mmol). The mixture was stirred at rt for 16.5h then was purified directly by prep HPLC. The fractions containing the expected product were combined and concentrated under reduced pressure to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(acetyl(2-(1,1-dioxido-4-thiomorpholinyl)ethyl)amino)-1-isopropenyl-5a,5b,8,8,11a-pentamethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (14 mg, 0.018 mmol, 33%) as a white solid. LCMS: m/e 733.5 $(M+H)^+$, 1.96 min (method 2). ^{1}H NMR (400MHz, *Chloroform-d*) δ = 7.99 (d, *J*=7.8 Hz, 2H), 7.22 (d, *J*=7.8 Hz, 2H), 5.23 (d, *J*=4.0 Hz, 1H), 4.85 (br. s., 1H), 4.68 (br. s., 1H), 3.65 (br. s., 2H), 3.40 - 3.04 (m, 8H), 2.97 - 2.46 (m, 4H), 1.74 (s, 3H), 1.27 (s, 3H), 1.03 - 0.98 (m, 9H), 0.95 (br. s., 3H), 0.89 (br. s., 3H), 2.20 - 0.71 (m, 21H).

Example 179

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoroethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoroethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

To a sealable vial containing methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

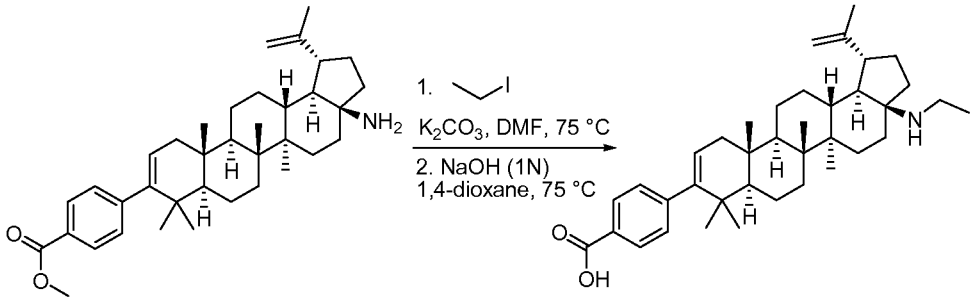
octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate, HCl (0.075 g, 0.129 mmol) was added potassium carbonate (0.036 g, 0.258 mmol). The mixture was diluted with DMF (1 mL) and 1-fluoro-2-iodoethane (0.032 ml, 0.388 mmol) was added. The vial was sealed and the mixture was heated to 75 °C for 26h then was cooled to rt. The mixture was diluted with 3 mL of sat. aq. sodium thiosulfate and was extracted with dichloromethane (3 x 4 mL). The combined organic layers were dried with sodium sulfate, the drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in toluene and was loaded onto a Thomson 12g silica gel column and was purified by Biotage flash chromatography using a 0-15% ethyl acetate in hexanes gradient with 0.1% ammonium hydroxide added to the mixture. The fractions containing the expected product were combined and concentrated under reduced pressure to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoroethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.062 g, 0.103 mmol, 80 % yield) as a white foam. LCMS: m/e 590.6 $(M+H)^+$, 2.05 min (method 2). ^{1}H NMR (400 MHz, *chloroform-d*) 7.94 (d, *J*=8.53 Hz, 2H), 7.21 (d, *J*=8.28 Hz, 2H), 5.30 (dd, *J*=2.01, 6.27 Hz, 1H), 4.73 (d, *J*=2.01 Hz, 1H), 4.58-4.64 (m, 2H), 4.50 (t, *J*=4.89 Hz, 1H), 3.92 (s, 3H), 2.57-2.85 (m, 3H), 2.11 (dd, *J*=6.40, 17.19 Hz, 1H), 1.71 (s, 3H), 1.10 (s, 3H), 1.00 (s, 3H), 0.99 (s, 3H), 0.94 (s, 3H), 0.94 (s, 3H), 0.86-2.05 (m, 21H).

Step 2. To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoroethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.059 g, 0.100 mmol) in 1,4-dioxane (2 mL) was added NaOH (1N) (0.5 mL, 0.500 mmol). The mixture was heated to 85 °C for 15.25h, was cooled to rt, then was diluted with methanol and 1,4-dioxane and was purified by prep HPLC. The fractions containing the expected product were combined and concentrated under reduced pressure to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoroethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (29.2 mg, 0.048 mmol, 48.2 % yield) as a

white solid. LCMS: m/e 576.6 $(M+H)^+$, 1.74 min (method 2). ^1H NMR (400 MHz, *Acetic acid* d_4) δ 7.99 (d, *J*=8.53 Hz, 2H), 7.26 (d, *J*=8.28 Hz, 2H), 5.33 (d, *J*=4.77 Hz, 1H), 4.73-4.99 (m, 3H), 4.70 (s, 1H), 3.41-3.73 (m, 2H), 2.83-2.94 (m, 1H), 1.73 (s, 3H), 1.19 (s, 3H), 1.11 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.82-2.27 (m, 22H).

Example 180

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

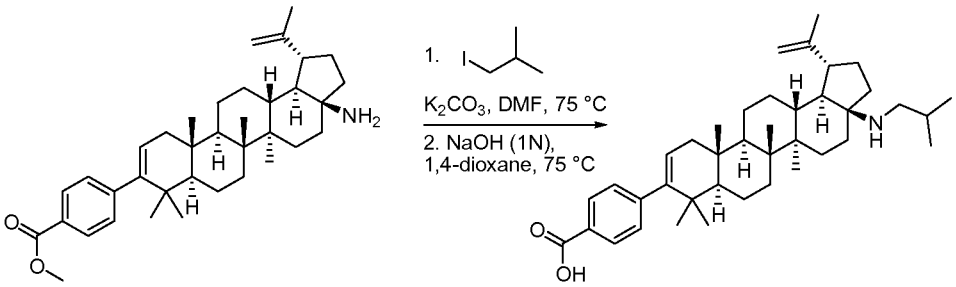
To a sealable vial containing methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate, HCl (0.075 g, 0.129 mmol) was added potassium carbonate (0.036 g, 0.258 mmol). The mixture was diluted with DMF (1 mL) and iodoethane (0.031 mL, 0.388 mmol) was added. The mixture was heated to 75 °C for 23h then was cooled to rt. The mixture was diluted with 1mL of DMF and additional iodoethane (0.031 mL, 0.388 mmol) was added to the mixture. The vial was sealed and heated to 75 °C for 24h, then was concentrated under reduced pressure and was adsorbed to silica gel. The mixture was purified by flash

chromatography using a 0-25% EtOAc in hexanes gradient with 0.1% ammonium hydroxide added and a Thomson 12g silica gel column. The fractions containing the expected product were combined and were concentrated under reduced pressure to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.039 g, 0.065 mmol, 50.1 % yield) as a white foam. LCMS: m/e 572.7 $(M+H)^+$, 2.16 min (method 2). ^{1}H NMR (400 MHz, *chloroform-d*) δ 7.94 (d, *J*=8.28 Hz, 2H), 7.21 (d, *J*=8.53 Hz, 2H), 5.30 (dd, *J*=1.76, 6.27 Hz, 1H), 4.73 (d, *J*=2.51 Hz, 1H), 4.59 (dd, *J*=1.38, 2.38 Hz, 1H), 3.92 (s, 3H), 2.62 (dt, *J*=5.40, 10.98 Hz, 1H), 2.38-2.53 (m, 2H), 2.11 (dd, *J*=6.40, 17.19 Hz, 1H), 1.88-2.03 (m, 3H), 1.83 (dd, *J*=7.78, 12.55 Hz, 1H), 1.70 (s, 3H), 1.10 (s, 3H), 1.11 (t, *J*=7.03 Hz, 3H), 0.99 (s, 6H), 0.94 (s, 3H), 0.94 (s, 3H), 0.91-1.74 (m, 17H).

Step 2. To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.037 g, 0.065 mmol) in 1,4-dioxane (1.5 mL) was added NaOH (1N) (0.3 mL, 0.300 mmol). The mixture was heated to 75 °C for 18.5h then was cooled to rt, was diluted with methanol and 1,4-dioxane, was filtered through a plug of glass wool and was purified by prep HPLC. The fractions containing the expected product were combined and were concentrated under reduced pressure to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(ethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (0.023 g, 0.040 mmol, 61.2 % yield) as a white solid. LCMS: m/e 558.6 $(M+H)^+$, 1.77 min (method 2). ^{1}H NMR (400 MHz, *Acetic acid d$_4$*) δ 7.99 (d, *J*=8.53 Hz, 2H), 7.26 (d, *J*=8.28 Hz, 2H), 5.33 (d, *J*=4.52 Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 3.23 (q, *J*=7.11 Hz, 2H), 2.81-2.92 (m, 1H), 1.72 (s, 3H), 1.40 (t, *J*=7.15 Hz, 3H), 1.19 (s, 3H), 1.09 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.83-2.24 (m, 22H).

Example 181

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(isobutylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

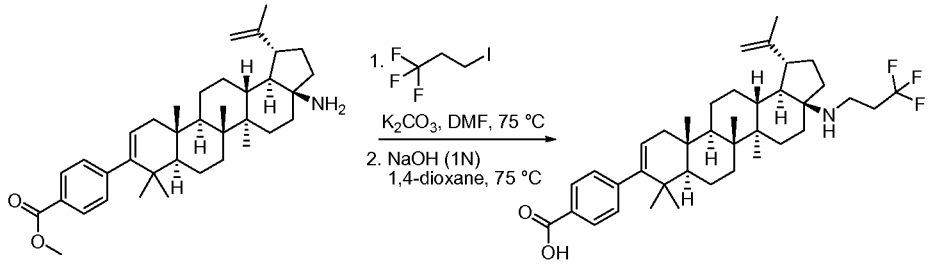


Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(isobutylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate. To a sealable vial containing methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate, HCl (0.075 g, 0.129 mmol) was added potassium carbonate (0.036 g, 0.258 mmol). The mixture was diluted with DMF (1 mL) and isobutyl iodide (0.045 mL, 0.388 mmol) was added. The vial was sealed and the mixture was heated to 75 °C for 23h, then the mixture was cooled to rt. LC/MS showed formation of the expected product, but starting material still remained. To the mixture was added additional isobutyl iodide (0.045 mL, 0.388 mmol) and the vial was sealed and heated to 75 °C for 48h. The mixture was cooled to rt then was diluted with 5 mL of water. The solids that formed were collected by filtration then were washed with water to give the expected product, methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(isobutylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (53 mg, 0.075 mmol, 58.1 % yield) as a light-yellow solid. The crude product was used in the next step with no additional purification. LCMS: m/e 600.6 $(M+H)^+$, 2.14 min (method 2).

Step 2. To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(isobutylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (52 mg, 0.087 mmol) in 1,4-dioxane (1.5 mL) was added NaOH (1N) (0.3 mL, 0.300 mmol). The mixture was heated to 75 °C for 67h then was cooled to rt. The mixture was diluted with 1,4-dioxane and methanol, was filtered through a plug of glass wool, and was purified by prep HPLC. The fractions containing the expected product were combined and concentrated under reduced pressure to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(isobutylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (25.2 mg, 0.041 mmol, 47.1 % yield) as a white solid. LCMS: m/e 586.6 $(M+H)^+$, 1.85 min (method 2). ^{1}H NMR (400 MHz, *Acetic acid* d_4) δ 8.00 (d, *J*=8.28 Hz, 2H), 7.26 (d, *J*=8.28 Hz, 2H), 5.33 (d, *J*=4.52 Hz, 1H), 4.81 (s, 1H), 4.69 (s, 1H), 3.15 (dd, *J*=5.02, 12.05 Hz, 1H), 2.88-2.98 (m, 1H), 2.78 (dd, *J*=9.03, 11.80 Hz, 1H), 1.72 (s, 3H), 1.22 (s, 3H), 1.10 (s, 3H), 1.09 (d, *J*=6.78 Hz, 3H), 1.06 (s, 3H), 1.01 (d, *J*=6.78 Hz, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.83-2.31 (m, 23H).

Example 182

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((3,3,3-trifluoropropyl)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



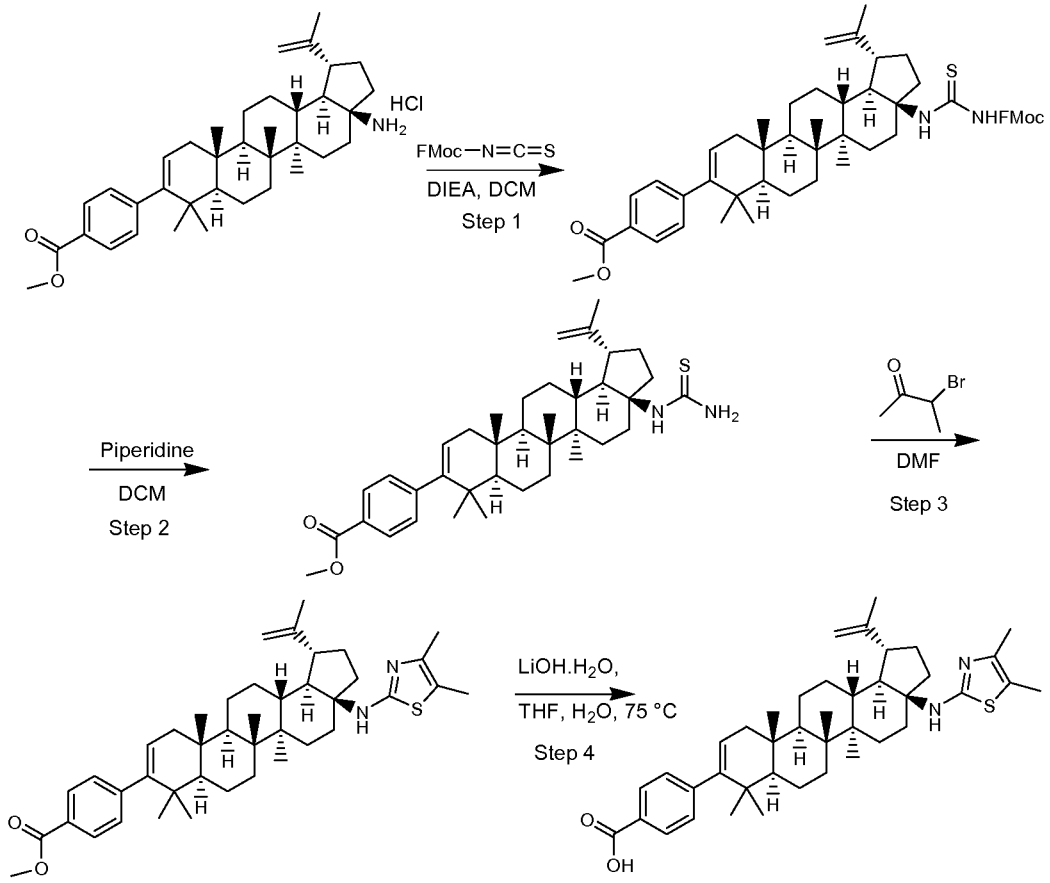
Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((3,3,3-trifluoropropyl)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

To a sealable vial containing methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate, HCl (0.075 g, 0.129 mmol) was added potassium carbonate (0.036 g, 0.258 mmol). The mixture was diluted with DMF (1 mL) and 1-iodo-3,3,3-trifluoropropane (0.045 mL, 0.388 mmol) was added. The vial was sealed and the mixture was heated to 75 °C for 23h then was cooled to rt. LC/MS showed a mixture of starting material and product. An additional 0.045 mL of 1-Iodo-3,3,3-trifluoropropane was added and the mixture and was heated to 75 °C for 48h then was cooled to rt. LC/MS showed further progression, but the reaction was still not complete. An additional 0.045 mL of 1-iodo-3,3,3-trifluoropropane was added and the mixture was heated to 75 °C for 71h, then was cooled to rt and was concentrated under reduced pressure. The mixture was adsorbed to silica gel and was purified by flash chromatography using a 0-15% EtOAc in hexanes gradient with 0.1% ammonium hydroxide added to the mixture and a Thomson 12g silica gel column. The fractions containing the expected product were combined and were concentrated under reduced pressure to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((3,3,3-trifluoropropyl)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.032 g, 0.044 mmol, 34.1 % yield) as a white foam. LCMS: m/e 640.6 $(M+H)^+$, 2.15 min (method 2). ^{1}H NMR (500 MHz, *chloroform-d*) δ 7.92 (d, *J*=8.24 Hz, 2H), 7.19 (d, *J*=8.24 Hz, 2H), 5.28 (dd, *J*=1.53, 6.10 Hz, 1H), 4.70 (d, *J*=1.83 Hz, 1H), 4.59 (s, 1H), 3.90 (s, 3H), 2.60-2.73 (m, 2H), 2.56 (dt, *J*=5.34, 10.91 Hz, 1H), 2.21-2.32 (m, 2H), 2.09 (dd, *J*=6.41, 17.09 Hz, 1H), 1.68 (s, 3H), 1.07 (s, 3H), 0.98 (s, 6H), 0.92 (s, 3H), 0.92 (br. s., 3H), 0.84-2.01 (m, 21H).

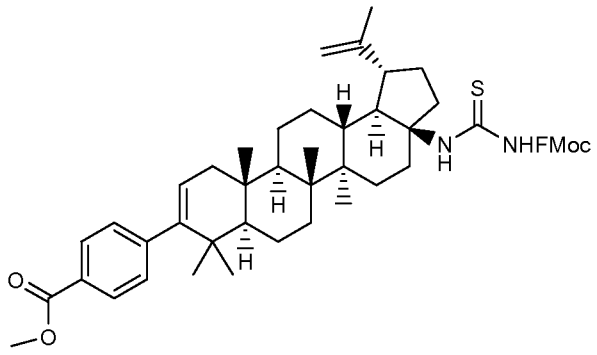
Step 2. To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((3,3,3-trifluoropropyl)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.032 g, 0.050 mmol) in 1,4-dioxane (1 mL) was added NaOH (1N) (0.2 mL, 0.200 mmol). The mixture was heated to 75 °C for 22.5h then was cooled to rt. The mixture was diluted with methanol, was filtered through a plug of glass wool and was purified by Prep HPLC. The fractions containing the expected product were combined and concentrated under reduced pressure to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((3,3,3-trifluoropropyl)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (0.022 g, 0.033 mmol, 66.8 % yield) as a white solid. LCMS: m/e 626.6 $(M+H)^+$, 1.87 min (method 2). ^{1}H NMR (400 MHz, *Acetic acid* d_4) δ7.99 (d, *J*=8.28 Hz, 2H), 7.25 (d, *J*=8.28 Hz, 2H), 5.33 (d, *J*=4.77 Hz, 1H), 4.82 (s, 1H), 4.70 (s, 1H), 3.36-3.51 (m, 2H), 2.81-2.97 (m, 3H), 2.12-2.28 (m, 4H), 1.72 (s, 3H), 1.17 (s, 3H), 1.09 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.82-2.11 (m, 18H).

Example 183

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4,5-dimethylthiazol-2-ylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



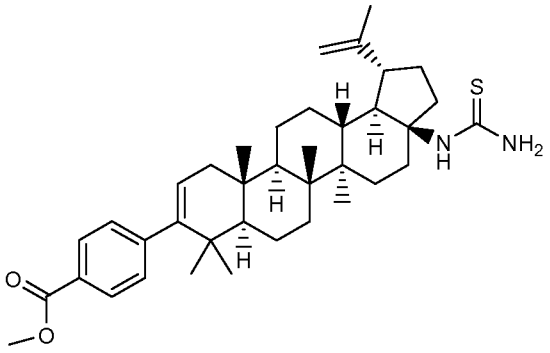
Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(((9H-fluoren-9-yl)methoxy)carbonyl)thioureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.



To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate, HCl (2 g, 3.45 mmol) in DCM (50 mL) was added *N,N*-diisopropylethylamine (3.00 mL, 17.23 mmol) and Fmoc-isothioisocyanate (1.939 g, 6.89 mmol). The reaction mixture was stirred at rt. After 3h, the reaction was washed with 0.1 N HCl (50 mL). The aqueous layer was extracted with DCM (50 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to about 30 mL of DCM and treated with MeOH (100 mL). The mixture was concentrated to remove all DCM until approximately 50 mL of MeOH remained. The resulting yellow precipitate was filtered and washed with MeOH. The solid product was saved and the liquid filtrate was concentrated to effect more precipitation. The resulting solid was isolated by filtration and washed with MeOH. The combined solid product was dried in a 50 °C vacuum oven to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(((9H-fluoren-9-yl)methoxy)carbonyl)thioureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (2.52 g, 3.05 mmol, 89 % yield) as a yellow solid. ^{1}H NMR (500MHz , *CHLOROFORM-d*) δ 9.84 (s, 1 H), 8.00 (s, 1 H), 7.95 (d, *J* = 8.2 Hz, 2 H), 7.82 (d, *J* = 7.6 Hz, 2 H), 7.64 (t, *J* = 8.2 Hz, 2 H), 7.49 - 7.44 (m, 2 H), 7.38 (tt, *J* = 1.5, 7.4 Hz, 2 H), 7.21 (d, *J* = 8.5 Hz, 2 H), 5.33 - 5.27 (m, 1 H), 4.79 (s, 1 H), 4.67 (s, 1 H), 4.58 - 4.53 (m, 2 H), 4.29 (t, *J* = 6.9 Hz, 1 H), 3.93 (s, 3 H), 3.39 (d, *J* = 13.7 Hz, 1 H), 3.23 (dd, *J* = 8.2, 12.8 Hz, 1 H), 2.50 (dt, *J* = 5.3, 10.8 Hz, 1 H), 2.13 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.98 - 1.88 (m, 1 H), 1.87 - 1.77 (m, 3 H), 1.74 (s, 3 H), 1.70 (d, *J* = 17.4 Hz, 1 H), 1.54 - 1.42 (m, 8 H), 1.41 - 1.29 (m, 3 H), 1.24 (d, *J* = 10.4 Hz, 1 H), 1.19 - 1.10 (m, 2 H), 1.05 (s, 3 H), 1.00 (s, 6 H), 0.94 (s, 6 H).

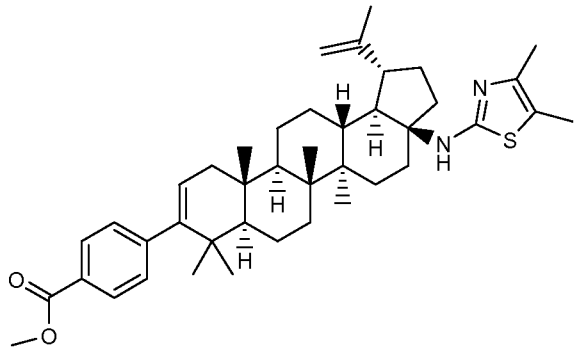
Step 2. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-thioureido-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.



To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(((9H-fluoren-9-yl)methoxy)carbonyl)thioureido)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (2.51 g, 3.04 mmol) in DCM (30 mL) was added piperidine (1.502 mL, 15.21 mmol). The resulting brown reaction mixture was stirred at rt for 5 h. The reaction was concentrated and triturated with MeOH to give white solid product and fulvene adduct. This material was then re-dissolved in hot DCM and allowed to cool to rt. The resulting white precipitate was filtered and washed with cold DCM. The liquid filtrate was concentrated and more white precipitate was filtered. The combined white solid product was dried in a vacuum oven. The liquid filtrate was concentrated and loaded onto a column of SiO_2 (90 g) and eluted with DCM (1L) to remove top spot by-product then the desired product was eluted with 97:3 DCM:MeOH. After drying in a vacuum oven all solid product was combined to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-thioureido-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (1.7 g, 2.82 mmol, 93 % yield) as a white solid. LCMS: m/e 603.5 $(M+H)^+$, 2.51min (method 1). ^{1}H NMR (500MHz , *CHLOROFORM-d*) δ 7.94 (d, *J* = 7.9 Hz, 2 H), 7.28 (s, 1 H), 7.21 (d, *J* = 7.9 Hz, 2 H), 6.07 (br. s., 1 H), 5.94 (br. s., 1 H), 5.34 - 5.28 (m, 2 H), 4.78 (s, 1 H), 4.68 (br. s., 1 H), 3.92 (s, 3 H), 2.64 - 2.55 (m, 1 H), 2.17 - 2.02 (m, 2 H), 1.85 - 1.74 (m, 3 H), 1.71 (s, 3 H), 1.67 (br. s., 1 H), 1.60 - 1.38 (m, 10 H), 1.35 - 1.35 (m, 1 H), 1.27 - 1.17 (m, 2 H), 1.13 (s, 4 H), 1.02 (s, 3 H), 1.00 (s, 3 H), 0.95 (br. s., 3 H), 0.94 (br. s., 3 H), 0.91 - 0.90 (m, 1 H). ^{13}C NMR (126MHz , *CHLOROFORM-d*) δ 182.0, 167.4, 148.8, 148.4, 146.4, 130.2, 128.6, 128.0, 124.0, 111.0, 66.8, 53.5, 53.0, 52.1, 50.3,

49.5, 46.8, 42.0, 41.8, 40.6, 37.9, 37.6, 36.4, 34.2, 33.5, 29.7, 29.5, 29.5, 27.6, 25.1, 21.3, 21.1, 19.8, 19.4, 16.5, 15.9, 14.6.

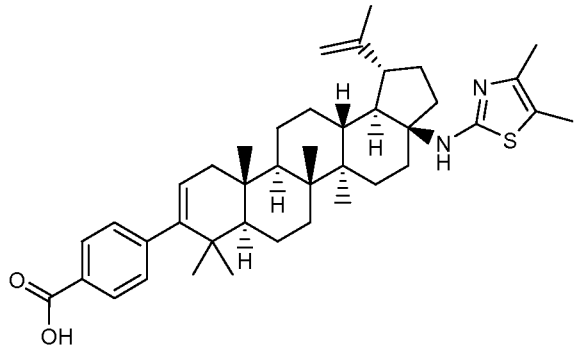
Step 3. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4,5-dimethylthiazol-2-ylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.



To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-thioureido-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (150 mg, 0.249 mmol) in DMF (5 mL) was added *N,N*-diisopropylethylamine (0.173 mL, 0.995 mmol) and 3-bromobutan-2-one (56.4 mg, 0.373 mmol). The reaction mixture was stirred at rt. After 18 h, the reaction mixture was poured into a separatory funnel containing H_2O (10 mL) and extracted with EtOAc (50 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to white solid. The material was redissolved in DCM (5 mL) and MeOH was added to effect precipitation. The mixture was concentrated to remove most of DCM and the resulting white precipitate was filtered, washed with cold MeOH, and dried in a vacuum oven to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4,5-dimethylthiazol-2-ylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (121 mg, 0.175 mmol, 70.5 % yield) as a white solid. LCMS: m/e 655.3 $(M+H)^+$, 2.72 min (method 2). ^1H NMR (500MHz ,

CHLOROFORM-d) δ 7.95 (d, J = 8.2 Hz, 2 H), 7.21 (d, J = 8.2 Hz, 2 H), 5.31 (d, J = 4.6 Hz, 1 H), 4.76 (br. s., 1 H), 4.65 (s, 1 H), 3.93 (s, 3 H), 2.43 (d, J = 10.4 Hz, 1 H), 2.21 (s, 3 H), 2.15 (s, 3 H), 2.11 (d, J = 6.7 Hz, 1 H), 2.07 - 1.96 (m, 1 H), 1.80 - 1.65 (m, 6 H), 1.57 - 1.36 (m, 8 H), 1.35 - 1.27 (m, 2 H), 1.23 (d, J = 10.1 Hz, 1 H), 1.17 - 1.11 (m, 1 H), 1.09 (s, 3 H), 1.03 (s, 3 H), 1.00 (s, 3 H), 0.94 (s, 6 H).

Step 4. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4,5-dimethylthiazol-2-ylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, TFA.

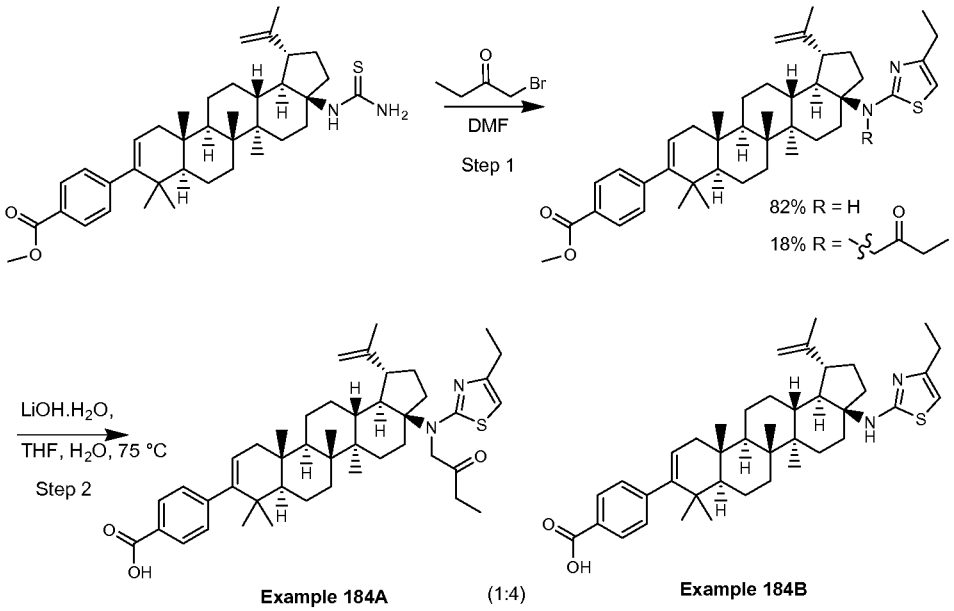


To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4,5-dimethylthiazol-2-ylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (107 mg, 0.163 mmol) in THF (3 mL) was added a solution of lithium hydroxide monohydrate (20.57 mg, 0.490 mmol) in water (1.000 mL). The reaction was heated to 75 °C for 6 h. The reaction mixture was concentrated, redissolved in MeOH (2 mL) and THF (1 mL) filtered and was then injected (2 injections) into reverse phase HPLC for purification using Prep HPLC method 3 to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4,5-dimethylthiazol-2-ylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, TFA (58.3 mg, 0.073 mmol, 44.4 % yield) as a white solid. LCMS: m/e 641.3 $(M+H)^+$, 2.51 min (method 2). ^{1}H NMR (500MHz , *CHLOROFORM-d*) δ 10.10 (s, 1 H), 8.02 (d, *J* = 8.2 Hz, 2 H), 7.25 (d, *J* = 8.2 Hz, 2 H), 5.33 (d, *J* = 4.6 Hz, 1 H), 4.84 (s, 1 H), 4.69 (s, 1 H), 2.97 (dt, *J* = 5.2,

11.0 Hz, 1 H), 2.48 (d, *J* = 13.7 Hz, 1 H), 2.32 - 2.25 (m, 2 H), 2.23 (s, 3 H), 2.20 (s, 3 H), 2.16 (dd, *J* = 6.4, 17.1 Hz, 1 H), 2.03 - 1.89 (m, 1 H), 1.89 - 1.79 (m, 2 H), 1.74 (s, 3 H), 1.71 (br. s., 1 H), 1.60 - 1.34 (m, 11 H), 1.26 - 1.19 (m, 1 H), 1.12 (d, *J* = 13.4 Hz, 1 H), 1.06 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.96 (s, 3 H), 0.94 (s, 3 H). ^{13}C NMR (126MHz , *CHLOROFORM-d*) δ 171.0, 164.9, 149.8, 148.9, 146.2, 132.4, 130.3, 129.2, 127.0, 124.4, 117.7, 111.4, 110.7, 68.1, 53.1, 50.3, 49.8, 45.4, 41.9, 40.8, 37.6, 36.5, 36.4, 33.8, 33.1, 29.6, 27.3, 25.3, 21.2, 19.9, 19.6, 16.5, 15.7, 14.5, 11.4, 10.8.

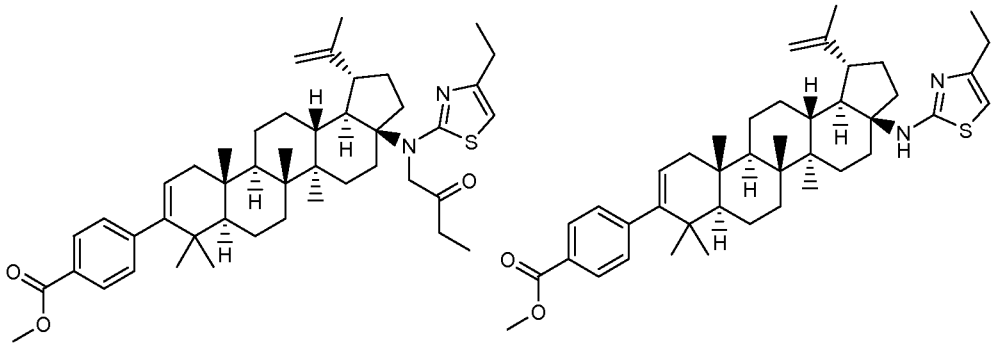
Examples 184A and 184B

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((4-ethylthiazol-2-yl)(2-oxobutyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid and 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-ethylthiazol-2-ylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((4-ethylthiazol-2-yl)(2-oxobutyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-

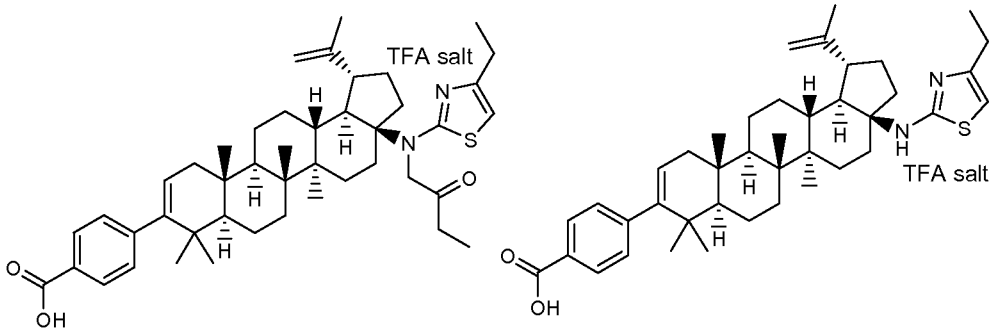
yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate and methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-ethylthiazol-2-ylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.



To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-thioureido-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (158 mg, 0.262 mmol) in DMF (3 mL) was added *N,N*-diisopropylethylamine (0.183 mL, 1.048 mmol) and 1-bromobutan-2-one (0.042 mL, 0.393 mmol). The reaction mixture was stirred at rt. After 16 h, the reaction mixture was poured into H_2O (5 mL) and extracted with EtOAc (50 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude material was dissolved in DCM and treated with MeOH to effect precipitation. The mixture was concentrated to remove all DCM and the resulting white precipitate was filtered and washed with MeOH. The product was dried in a vacuum oven to give a mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((4-ethylthiazol-2-yl)(2-oxobutyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate and methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-ethylthiazol-2-ylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate as a white solid in quantitative yield (173 mg, 0.264 mmol). LC/MS: m/e 725.4 $(M+H)^+$, 2.70 min and m/e 655.3 $(M+H)^+$, 2.95 min

(method 9), respectively. Reversed phased analytical HPLC showed ratio of major product with rt = 23.45 min (m/e 655.3 $(M+H)^+$) to minor product with rt = 26.86 min (m/e 725.4 $(M+H)^+$) of 82%:18% (using analytical HPLC method 1).

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((4-ethylthiazol-2-yl)(2-oxobutyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, TFA and 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-ethylthiazol-2-ylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, TFA.



To a mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((4-ethylthiazol-2-yl)(2-oxobutyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate and methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-ethylthiazol-2-ylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate in THF (3 mL) was added a solution of Li . H O . H_2O (32.7 mg, 0.779 mmol) in water (1.50 mL). The reaction was heated to 75 °C for 6 h. The reaction mixture was concentrated, redissolved in MeOH (2 mL) and THF (1 mL) filtered and was then injected (2 injections) into reverse phase HPLC for purification using Prep HPLC method 3 to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((4-ethylthiazol-2-yl)(2-oxobutyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

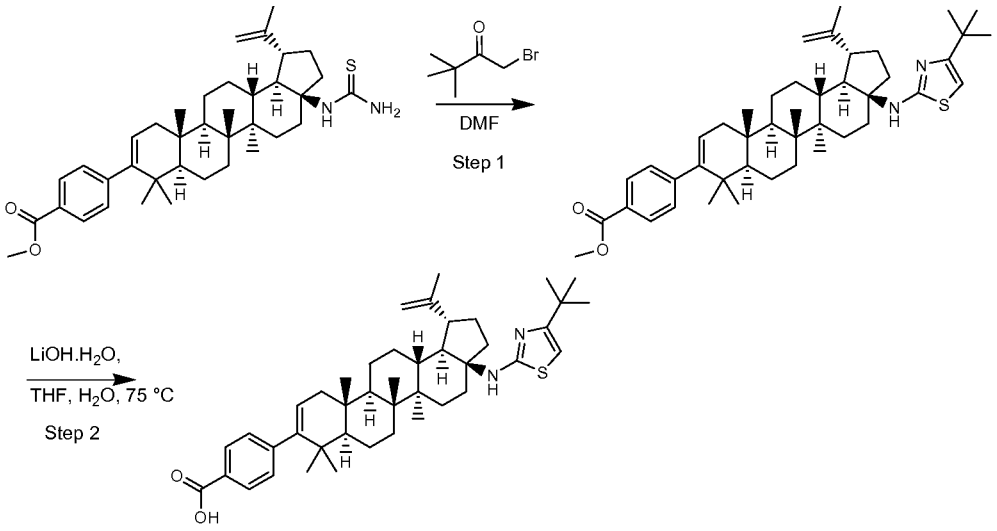
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, TFA (22.3 mg, 0.027 mmol, 10.31 % yield) and 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-ethylthiazol-2-ylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, TFA (91.7 mg, 0.118 mmol, 45.4 % yield) both as a white solid.

Example 184A: LC/MS: m/e 711.4 $(M+H)^+$, 2.45 min (method 11), ^{1}H NMR (500MHz , *CHLOROFORM-d*) δ 8.14 (br. s., 1 H), 7.97 (d, *J* = 7.9 Hz, 2 H), 7.21 (d, *J* = 8.2 Hz, 2 H), 6.56 - 6.45 (m, 1 H), 6.32 (s, 1 H), 5.26 (d, *J* = 5.2 Hz, 1 H), 5.16 (d, *J* = 19.5 Hz, 1 H), 4.84 (s, 1 H), 4.67 (br. s., 1 H), 3.11 - 2.98 (m, 1 H), 2.89 - 2.77 (m, 1 H), 2.73 - 2.61 (m, 2 H), 2.54 - 2.47 (m, 1 H), 2.43 (dd, *J* = 7.6, 16.2 Hz, 1 H), 2.30 - 2.22 (m, 1 H), 2.21 - 2.11 (m, 1 H), 2.11 - 1.98 (m, 2 H), 1.95 - 1.87 (m, 1 H), 1.71 (s, 3 H), 1.63 (d, *J* = 16.2 Hz, 2 H), 1.51 (d, *J* = 11.0 Hz, 2 H), 1.48 - 1.37 (m, 6 H), 1.34 - 1.25 (m, 6 H), 1.23 - 1.19 (m, 1 H), 1.16 (t, *J* = 7.2 Hz, 3 H), 1.11 (d, *J* = 10.7 Hz, 1 H), 1.00 (br. s., 3 H), 0.99 (br. s., 3 H), 0.96 (br. s., 6 H), 0.95 (br. s., 2 H). ^{13}C NMR (126MHz , *CHLOROFORM-d*) δ 203.2, 170.6, 167.1, 149.4, 148.6, 146.3, 144.3, 130.2, 129.1, 127.8, 124.6, 110.7, 100.1, 70.7, 55.2, 53.0, 50.7, 49.4, 44.3, 42.0, 41.8, 40.7, 37.6, 36.4, 36.3, 33.6, 33.4, 32.7, 29.6, 29.4, 27.3, 27.2, 25.2, 21.5, 21.2, 20.7, 19.8, 19.7, 16.5, 15.5, 14.5, 10.8, 7.3.

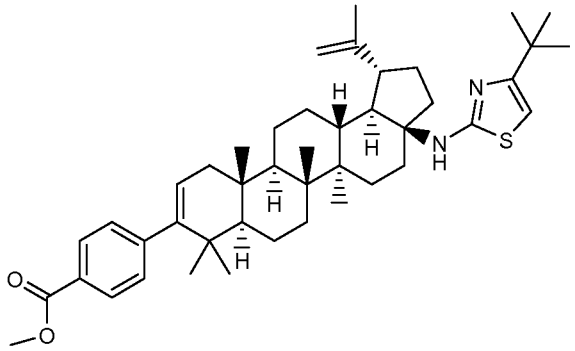
Example 184B: LC/MS: m/e 641.3 $(M+H)^+$, 2.51 min (method 11), ^{1}H NMR (500MHz , *CHLOROFORM-d*) δ 10.17 (s, 1 H), 8.02 (d, *J* = 8.2 Hz, 2 H), 7.25 (d, *J* = 8.2 Hz, 2 H), 6.07 (s, 1 H), 5.33 (d, *J* = 4.6 Hz, 1 H), 4.85 (s, 1 H), 4.70 (s, 1 H), 2.97 (dt, *J* = 5.0, 11.1 Hz, 1 H), 2.71 (dq, *J* = 0.9, 7.5 Hz, 2 H), 2.53 - 2.45 (m, 1 H), 2.32 (dd, *J* = 7.8, 13.0 Hz, 1 H), 2.26 (dt, *J* = 2.9, 12.1 Hz, 1 H), 2.16 (dd, *J* = 6.3, 17.2 Hz, 1 H), 2.05 - 1.92 (m, 1 H), 1.90 - 1.79 (m, 2 H), 1.74 (s, 3 H), 1.69 (d, *J* = 16.8 Hz, 1 H), 1.60 - 1.35 (m, 11 H), 1.30 (t, *J* = 7.6 Hz, 3 H), 1.23 (dd, *J* = 4.1, 9.6 Hz, 1 H), 1.13 (d, *J* = 13.1 Hz, 1 H), 1.06 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.96 (s, 3 H), 0.95 (s, 3 H). ^{13}C NMR (126MHz , *CHLOROFORM-d*) δ 171.5, 167.1, 163.3, 163.0, 149.8, 148.8, 146.2, 144.6, 130.3, 129.3, 127.1, 124.4, 117.5, 115.2, 110.8, 98.3, 68.3, 53.1, 50.3, 49.7, 45.4, 41.9, 40.8, 37.6, 36.5, 36.4, 33.8, 32.8, 29.6, 27.3, 27.1, 25.3, 21.7, 21.2, 19.8, 19.6, 16.5, 15.7, 14.5, 11.8.

Example 185

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-tert-butylthiazol-2-ylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



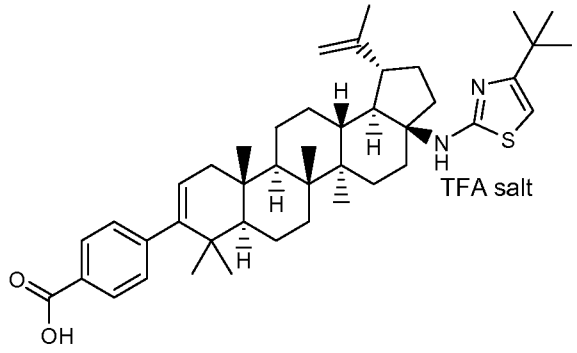
Step 1. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-tert-butylthiazol-2-ylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.



To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-thioureido-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (150 mg, 0.249 mmol) in DMF (3 mL) was added

N,N-diisopropylethylamine (0.217 mL, 1.244 mmol) and 1-bromopinacolone (0.056 mL, 0.373 mmol). The reaction mixture was stirred at rt overnight. After 18 h, the reaction mixture was poured into a separatory funnel containing H_2O (5 mL) and extracted with EtOAc (50 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to white solid. The material was redissolved in DCM (3 mL), MeOH wash added and concentrated to remove most of the DCM. The resulting white precipitate was filtered, washed with cold MeOH, and dried in a vacuum oven to give methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-tert-butylthiazol-2-ylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (154.0 mg, 0.225 mmol, 91 % yield) as a white solid. LC/MS: m/e 683.4 $(M+H)^+$, 2.88 min (method 11). ^1H NMR (500MHz , *CHLOROFORM-d*) δ 7.95 (d, *J* = 8.2 Hz, 2 H), 7.22 (d, *J* = 8.2 Hz, 2 H), 6.06 (s, 1 H), 5.31 (d, *J* = 4.6 Hz, 1 H), 4.88 (s, 1 H), 4.77 (s, 1 H), 4.66 (s, 1 H), 3.93 (s, 3 H), 2.72 (d, *J* = 13.7 Hz, 1 H), 2.68 - 2.62 (m, 1 H), 2.55 (dd, *J* = 8.1, 12.7 Hz, 1 H), 2.13 (dd, *J* = 6.4, 17.1 Hz, 1 H), 2.07 - 1.98 (m, 1 H), 1.92 - 1.83 (m, 1 H), 1.82 - 1.76 (m, 1 H), 1.74 (s, 3 H), 1.73 - 1.66 (m, 2 H), 1.61 (s, 1 H), 1.57 - 1.49 (m, 3 H), 1.49 - 1.40 (m, 4 H), 1.40 - 1.31 (m, 3 H), 1.29 (s, 9 H), 1.27 - 1.21 (m, 1 H), 1.18 - 1.12 (m, 1 H), 1.10 (s, 3 H), 1.04 (s, 3 H), 1.01 (s, 3 H), 0.95 (s, 6 H).

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-tert-butylthiazol-2-ylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, TFA.

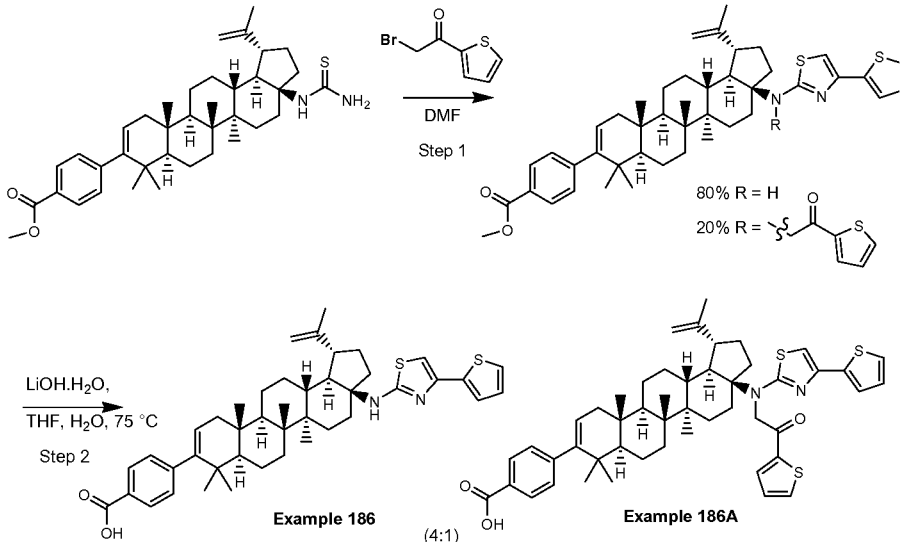


To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-tert-butylthiazol-2-ylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (139 mg, 0.204 mmol) in THF (3 mL) was added a solution of lithium hydroxide monohydrate (25.6 mg, 0.611 mmol) in water (1 mL). The reaction was heated to 75 °C for 6 h. The reaction mixture was concentrated, redissolved in MeOH (2 mL) and THF (1 mL) filtered and was then injected (2 injections) into reverse phase HPLC for purification using Prep HPLC method 3 to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-tert-butylthiazol-2-ylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, TFA (49.3 mg, 0.059 mmol, 28.8 % yield) as a white solid. LC/MS: m/e 669.4 $(M+H)^+$, 2.61 min (method 11). ^{1}H NMR (500MHz, *CHLOROFORM-d*) δ 8.02 (d, *J* = 7.9 Hz, 2 H), 7.25 (d, *J* = 8.2 Hz, 2 H), 6.05 (s, 1 H), 5.33 (d, *J* = 4.9 Hz, 1 H), 4.86 (s, 1 H), 4.70 (s, 1 H), 3.52 (s, 1 H), 3.03 (dt, *J* = 5.0, 10.9 Hz, 1 H), 2.54 (d, *J* = 14.0 Hz, 1 H), 2.34 (dd, *J* = 8.1, 12.7 Hz, 1 H), 2.31 – 2.22 (m, 1 H), 2.16 (dd, *J* = 6.3, 17.2 Hz, 1 H), 2.09 – 1.96 (m, 1 H), 1.92 – 1.80 (m, 2 H), 1.75 (s, 3 H), 1.69 (d, *J* = 16.8 Hz, 1 H), 1.58 (br. S., 1 H), 1.53 – 1.42 (m, 8 H), 1.39 (s, 9 H), 1.28 (s, 2 H), 1.23 (d, *J* = 9.2 Hz, 2 H), 1.13 (d, *J* = 13.7 Hz, 1 H), 1.08 (s, 4 H), 1.04 (s, 3 H), 1.01 (s, 3 H), 0.95 (br. S., 3 H), 0.95 (br. S., 3 H). ^{13}C NMR (126MHz , *CHLOROFORM-d*) δ 170.9, 167.4, 151.7, 149.5, 148.3, 145.6, 129.9, 128.8, 126.5, 124.0, 110.5, 96.6, 68.0, 52.7, 50.0, 49.3, 44.9, 41.5, 41.5, 40.3, 37.2, 36.1, 36.0, 33.5, 33.4, 32.3, 29.2, 29.2, 28.5, 27.0, 26.8, 24.9, 20.8, 20.7, 19.4, 19.3, 16.1, 15.4, 14.1.

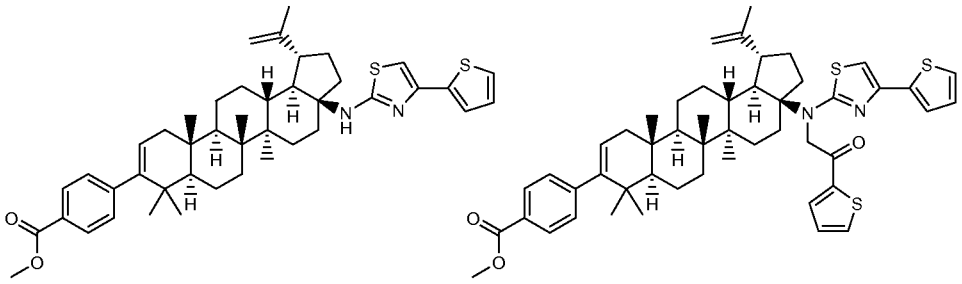
Example 186

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(4-(thiophen-3-yl)thiazol-2-ylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid and 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-oxo-2-(thiophen-3-yl)ethyl)(4-(thiophen-3-yl)thiazol-2-yl)amino)-1-(prop-1-en-2-yl)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



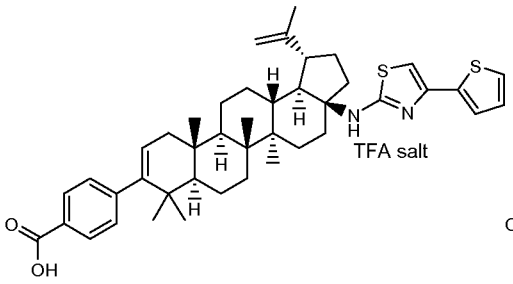
Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(4-(thiophen-3-yl)thiazol-2-ylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate and methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-oxo-2-(thiophen-3-yl)ethyl)(4-(thiophen-3-yl)thiazol-2-yl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

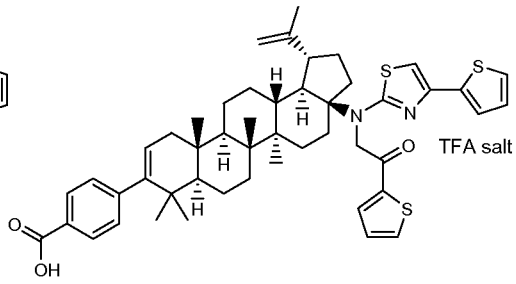


To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-thioureido-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (150 mg, 0.249 mmol) in DMF (3 mL) was added

N,N-diisopropylethylamine (0.217 mL, 1.244 mmol) and 2-bromo-1-(thiophen-3-yl)ethanone (77 mg, 0.373 mmol). The reaction mixture was stirred at rt overnight. After 18 h, the reaction mixture was poured into a separatory funnel containing H_2O (5 mL) and extracted with EtOAc (50 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to white solid. The material was redissolved in DCM (3 mL). MeOH was added and the mixture was concentrated to remove most of DCM. The resulting white precipitate was filtered, washed with cold MeOH, and dried in a vacuum oven to give a 4:1 mixture of (as determined by HPLC integration) methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(4-(thiophen-3-yl)thiazol-2-ylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate and methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-oxo-2-(thiophen-3-yl)ethyl)(4-(thiophen-3-yl)thiazol-2-yl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (134 mg, 82 % yield) as white solid. LC/MS: m/e 709.3 $(M+H)^+$, 3.62 min and m/e 833.3 $(M+H)^+$, 2.63 min (method 9), respectively. Reverse phased analytical HPLC showed ratio of major product with rt = 16.04 min (m/e 709.3 $(M+H)^+$) to minor product with rt = 15.42 min (m/e 833.3 $(M+H)^+$) product of 80%:20% (using analytical HPLC method 2).

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(4-(thiophen-3-yl)thiazol-2-ylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, TFA and 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-oxo-2-(thiophen-3-yl)ethyl)(4-(thiophen-3-yl)thiazol-2-yl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, TFA.





To a mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(4-(thiophen-3-yl)thiazol-2-ylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (119.36 mg, 0.168 mmol) and methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-oxo-2-(thiophen-3-yl)ethyl)(4-(thiophen-3-yl)thiazol-2-yl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (29.84 mg, 0.036 mmol) in THF (3 mL) was added a solution of lithium hydroxide monohydrate (25.4 mg, 0.606 mmol) in water (1 mL). The reaction was heated to 75 °C for 6 h. The reaction mixture was concentrated, redissolved in MeOH (2 mL) and THF (1 mL) filtered and was then injected (2 injections) onto reverse phase HPLC for purification using Prep HPLC method 3 to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(4-(thiophen-3-yl)thiazol-2-ylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, TFA (110.7 mg, 0.134 mmol, 80 % yield) and 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-oxo-2-(thiophen-3-yl)ethyl)(4-(thiophen-3-yl)thiazol-2-yl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, TFA (13.4 mg, 0.016 mmol, 9.52 % yield).

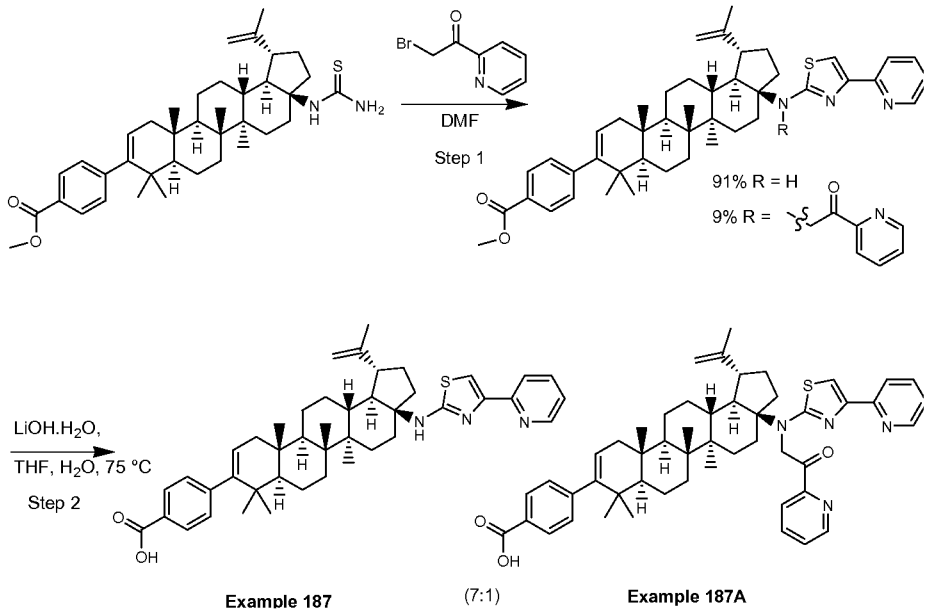
Example 186: LC/MS: m/e 695.3 $(M+H)^+$, 2.92 min (method 11). ^{1}H NMR (500MHz , *CHLOROFORM-d*) δ 8.12 (br. s., 1 H), 8.03 (d, J = 8.2 Hz, 2 H), 7.42 - 7.39 (m, 1 H), 7.38 - 7.36 (m, 1 H), 7.25 (d, J = 8.2 Hz, 2 H), 6.52 (s, 1 H), 5.33 (d, J = 4.6 Hz, 1 H), 4.86 (s, 1 H), 4.71 (s, 1 H), 3.04 (dt, J = 5.0, 11.1 Hz, 1 H), 2.58 (d, J = 14.0 Hz, 1 H), 2.39 (dd, J = 7.9, 12.8 Hz, 1 H), 2.33 - 2.25 (m, 1 H), 2.15 (dd, J = 6.4, 17.1 Hz, 1 H), 2.06 - 1.98 (m, 1 H), 1.92 - 1.82 (m, 2 H), 1.76 (s, 3 H), 1.70 (d, J = 17.1 Hz, 1 H), 1.64 - 1.56 (m, 1 H), 1.55 - 1.47 (m, 5 H), 1.46 - 1.37 (m, 5 H), 1.23 (d, J = 10.1 Hz, 1 H), 1.15 (d, J = 13.1 Hz, 1 H), 1.06 (s, 3 H), 1.05 (s, 3 H), 0.99 (s, 3

H), 0.95 (s, 3 H), 0.94 (s, 3 H). ^{13}C NMR (126MHz , *CHLOROFORM-d*) δ 171.2, 167.1, 163.3, 149.3, 148.5, 145.9, 129.9, 128.8, 127.0, 126.9, 124.7, 124.4, 123.9, 117.4, 115.1, 110.4, 98.1, 68.0, 52.6, 50.0, 49.3, 45.0, 41.6, 41.5, 40.4, 37.2, 36.2, 36.0, 33.4, 32.6, 29.2, 29.2, 27.0, 26.9, 24.9, 20.8, 19.5, 19.2, 16.1, 15.3, 14.1.

Example 186A: LC/MS: m/e 818.4 $(M+H)^+$, 2.50 min (method 11).

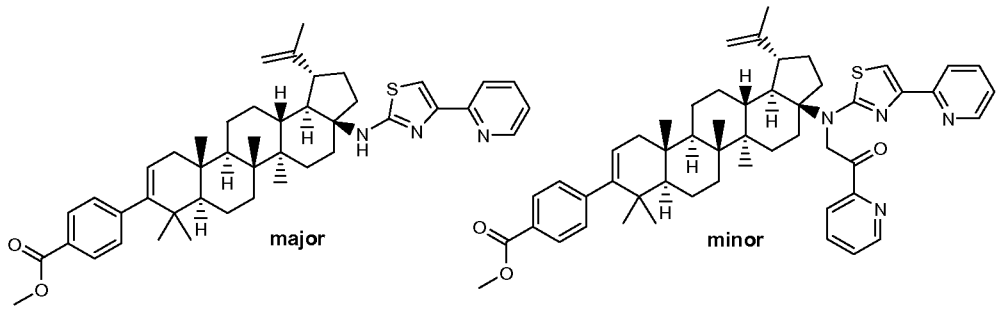
Examples 187 and 187A

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(4-(pyridin-2-yl)thiazol-2-ylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid and 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-oxo-2-(pyridin-2-yl)ethyl)(4-(pyridin-2-yl)thiazol-2-yl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(4-(pyridin-2-yl)thiazol-2-ylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate and methyl 4-

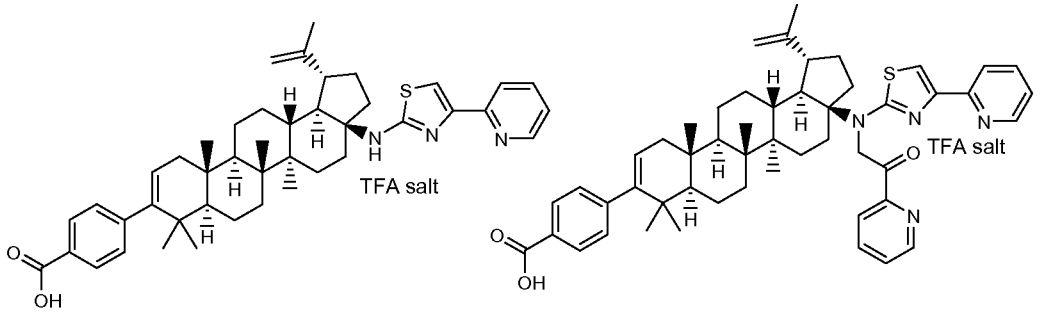
((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-oxo-2-(pyridin-2-yl)ethyl)(4-(pyridin-2-yl)thiazol-2-yl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.



To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-thioureido-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (150 mg, 0.249 mmol) was added *N,N*-diisopropylethylamine (0.217 mL, 1.244 mmol) and 2-bromo-1-(pyridin-2-yl)ethanone, hydrobromide (116 mg, 0.373 mmol). The reaction mixture was stirred at rt overnight. After 18 h, the reaction mixture was poured into a separatory funnel containing H_2O (5 mL) and extracted with EtOAc (50 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to brown solid. The material was redissolved in DCM (3 mL), MeOH was added and the resulting mixture was concentrated to remove most of DCM. The resulting white precipitate was filtered, washed with cold MeOH, and dried in a vacuum oven to give a 91:9 mixture (as determined by HPLC integration) of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(4-(pyridin-2-yl)thiazol-2-ylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate and methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-oxo-2-(pyridin-2-yl)ethyl)(4-(pyridin-2-yl)thiazol-2-yl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (137 mg, 76.57 % yield) as brown solid. LC/MS: m/e 704.3 $(M+H)^+$, 3.72 min and m/e 823.4 $(M+H)^+$, 2.56 min (method 9),

respectively. Reversed phased analytical HPLC showed ratio of major product with rt = 22.43 min (m/e 704.3 $(M+H)^+$) to minor product with rt = 23.61 min (m/e 823.4 $(M+H)^+$) product of 91%:9% (using analytical HPLC method 1).

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(4-(pyridin-2-yl)thiazol-2-ylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, TFA and 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-oxo-2-(pyridin-2-yl)ethyl)(4-(pyridin-2-yl)thiazol-2-yl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, TFA.



To a mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(4-(pyridin-2-yl)thiazol-2-ylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (117.66 mg, 0.167 mmol) and methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-oxo-2-(pyridin-2-yl)ethyl)(4-(pyridin-2-yl)thiazol-2-yl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (19.6 mg, 0.024 mmol) in THF (3 mL) was added a solution of lithium hydroxide monohydrate (25.2 mg, 0.602 mmol) in water (1 mL). The reaction was heated to 75 °C for 6 h. The reaction mixture was concentrated, redissolved in MeOH (2 mL) and THF (1 mL) filtered and was injected onto reverse phase HPLC for purification using Prep HPLC method 3 to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(4-(pyridin-2-yl)thiazol-2-ylamino)-

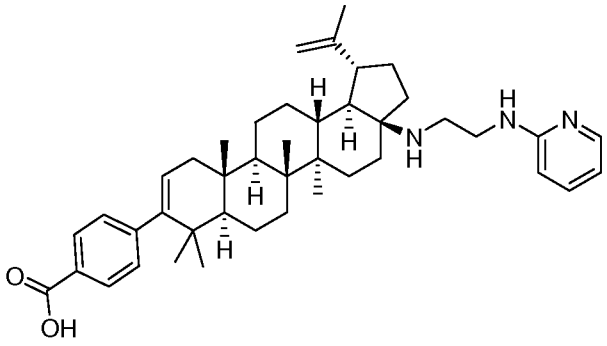
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, TFA (70.2 mg, 0.085 mmol, 50.7 % yield) and 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-oxo-2-(pyridin-2-yl)ethyl)(4-(pyridin-2-yl)thiazol-2-yl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, TFA (10.3 mg, 0.011 mmol, 6.86 % yield).

Example 187: LC/MS: m/e 690.3 $(M+H)^+$, 2.53 min (method 11). ^{1}H NMR (500MHz , *CHLOROFORM-d*) δ 9.67 (br. s., 1 H), 8.73 (td, *J* = 0.9, 5.0 Hz, 1 H), 8.14 (d, *J* = 7.9 Hz, 1 H), 8.02 (d, *J* = 8.2 Hz, 2 H), 7.96 (dt, *J* = 1.7, 7.9 Hz, 1 H), 7.42 (s, 1 H), 7.40 (ddd, *J* = 0.9, 4.9, 7.6 Hz, 1 H), 7.25 (d, *J* = 8.5 Hz, 2 H), 5.33 (d, *J* = 4.6 Hz, 1 H), 4.86 (s, 1 H), 4.71 (s, 1 H), 2.99 (dt, *J* = 4.9, 11.0 Hz, 1 H), 2.64 - 2.58 (m, 1 H), 2.41 (dd, *J* = 8.1, 12.7 Hz, 1 H), 2.23 (dt, *J* = 3.1, 12.1 Hz, 1 H), 2.16 (dd, *J* = 6.3, 17.2 Hz, 1 H), 2.06 - 2.00 (m, 1 H), 1.90 (t, *J* = 11.7 Hz, 1 H), 1.85 (d, *J* = 12.5 Hz, 1 H), 1.76 (s, 3 H), 1.70 (d, *J* = 17.1 Hz, 1 H), 1.64 - 1.55 (m, 1 H), 1.55 - 1.39 (m, 9 H), 1.30 - 1.21 (m, 1 H), 1.17 (d, *J* = 13.1 Hz, 1 H), 1.08 (s, 3 H), 1.06 (s, 3 H), 1.01 (s, 3 H), 0.95 (s, 3 H), 0.95 (s, 3 H). ^{13}C NMR (126MHz , *CHLOROFORM-d*) δ 170.8, 167.4, 149.3, 148.4, 146.3, 145.9, 141.1, 138.6, 129.9, 128.8, 126.8, 123.9, 123.9, 121.2, 110.4, 104.8, 77.3, 68.1, 52.6, 49.9, 49.3, 45.2, 41.6, 41.5, 40.4, 37.2, 36.5, 36.0, 33.3, 32.7, 29.2, 29.2, 26.9, 24.9, 20.8, 19.4, 19.2, 16.1, 15.4, 14.2.

Example 187A: LC/MS: m/e 809.5 $(M+H)^+$, 2.38 min (method 11).

Example 188

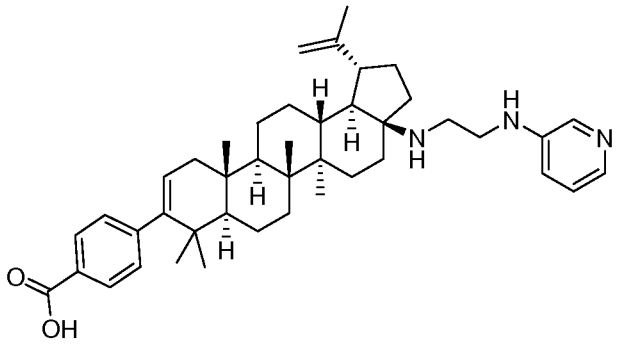
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridin-2-ylamino)ethylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



In a 1 dram vial under nitrogen were combined (2R)-1-[(1R)-1-[bis(1,1-dimethylethyl)phosphino]ethyl]-2-(dicyclohexylphosphino)ferrocene (CAS# 158923-11-6) (2.101 mg, 3.79 μmol), palladium(II) acetate (0.851 mg, 3.79 μmol) and dry DME (0.5 ml). The contents of the vial were stirred for 10 min, and were then added all at once to a separate mixture of 2-bromopyridine (0.012 g, 0.076 mmol) and sodium tert-butoxide (0.032 g, 0.333 mmol) in dry DME (0.5 mL) contained in a separate 1 dram vial. The resulting mixture was allowed to stir very briefly (1 min) before TBDMSCl (0.025 g, 0.167 mmol) was added. The vial was shaken briefly, and solid methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-aminoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate bis HCl salt (0.050 g, 0.076 mmol) was added in one portion. A mild exotherm resulted upon the final addition. The mixture was heated to 110 °C for 15 min. LCMS indicated essentially complete consumption of starting material. To the mixture was added water (0.5 mL) and methanol (1.5 mL) and the resulting mixture was stirred for 2 days. Purification of the crude mixture by reverse phase preparative HPLC using Prep HPLC Method 6 gave the title compound (0.0092 g, 13.1% yield) as a beige powder bis TFA salt. LCMS: m/e 650.4 $(M+H)^+$, 3.76 min (method 16). ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 8.01 (d, *J*=4.9 Hz, 1H), 7.95 - 7.88 (m, *J*=8.2 Hz, 2H), 7.72 (t, *J*=7.3 Hz, 1H), 7.23 - 7.16 (m, *J*=8.2 Hz, 2H), 6.92 (d, *J*=8.2 Hz, 1H), 6.85 (t, *J*=6.3 Hz, 1H), 5.29 (d, *J*=4.9 Hz, 1H), 4.86 (s, 1H), 4.74 (br. s., 1H), 3.90 - 3.72 (m, 2H), 3.23 - 3.14 (m, 1H), 2.78 - 2.67 (m, 1H), 2.17 - 2.04 (m, 2H), 2.03 - 1.82 (m, 5H), 1.73 (s, 3H), 1.71 - 1.66 (m, 1H), 1.65 - 1.46 (m, 6H), 1.45 - 1.22 (m, 9H), 1.21 - 1.09 (m, 1H), 1.06 (s, 3H), 0.99 (br. s., 3H), 0.98 (br. s., 3H), 0.94 (s, 3H), 0.93 (br. s., 3H), 0.91 - 0.84 (m, *J*=6.7, 3.4 Hz, 1H).

Example 189

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridin-3-ylamino)ethylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

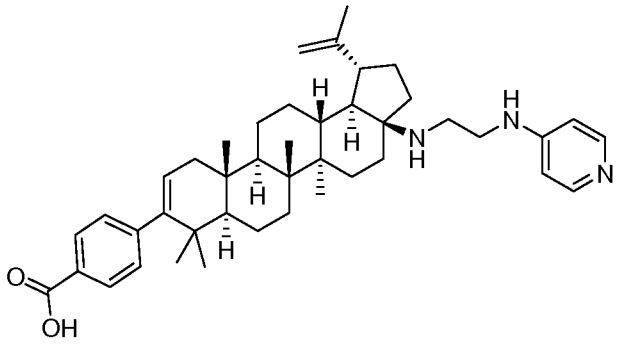


In a 1 dram vial under nitrogen were combined (2R)-1-[(1R)-1-[bis(1,1-dimethylethyl)phosphino]ethyl]-2-(dicyclohexylphosphino)ferrocene (CAS# 158923-11-6) (2.101 mg, 3.79 μmol), palladium(II) acetate (0.851 mg, 3.79 μmol) and dry DME (0.5 ml). The contents of the vial were stirred for 10 min, and were then added all at once to a separate mixture of 3-bromopyridine (0.014 g, 0.091 mmol) and sodium tert-butoxide, 2.0M solution in THF (0.167 mL, 0.333 mmol) in dry DME (0.333 mL) contained in a separate 1 dram vial. The resulting mixture was allowed to stir very briefly (1 min) before solid methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-aminoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate bis HCl salt (0.050 g, 0.076 mmol) was added in one portion. The mixture was heated to 110 °C overnight. To the mixture was added lithium hydroxide monohydrate (6.4 mg, 0.152 mmol) with water (0.2 mL) and methanol (0.5 mL) and the resulting mixture was stirred for 4 days. Purification of the crude mixture by reverse phase preparative HPLC using Prep HPLC Method 7 gave the title compound (0.0407 g, 57.5% yield) as a beige powder bis TFA salt. LCMS: m/e 650.4 $(M+H)^+$, 2.26 min (method 11). ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 8.26 (d, *J*=2.4 Hz, 1H), 8.02 (d, *J*=4.9 Hz,

1H), 7.94 - 7.87 (m, *J*=8.2 Hz, 2H), 7.77 (dd, *J*=8.9, 1.5 Hz, 1H), 7.67 (dd, *J*=8.9, 5.2 Hz, 1H), 7.22 - 7.14 (m, 2H), 5.28 (dd, *J*=6.3, 1.7 Hz, 1H), 4.82 (s, 1H), 4.74 (s, 1H), 3.89 - 3.78 (m, 1H), 3.70 (dt, *J*=14.6, 4.5 Hz, 1H), 3.30 - 3.23 (m, 2H), 2.85 (td, *J*=11.1, 5.5 Hz, 1H), 2.21 - 2.05 (m, 3H), 2.03 - 1.94 (m, 2H), 1.94 - 1.85 (m, 1H), 1.85 - 1.76 (m, 1H), 1.72 (s, 3H), 1.70 - 1.64 (m, 1H), 1.64 - 1.51 (m, 3H), 1.51 - 1.44 (m, 3H), 1.43 - 1.20 (m, 6H), 1.19 - 1.08 (m, 2H), 1.07 - 1.04 (m, 3H), 1.04 - 1.00 (m, 3H), 0.99 (s, 3H), 0.95 - 0.88 (m, 7H).

Example 190

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridin-4-ylamino)ethylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

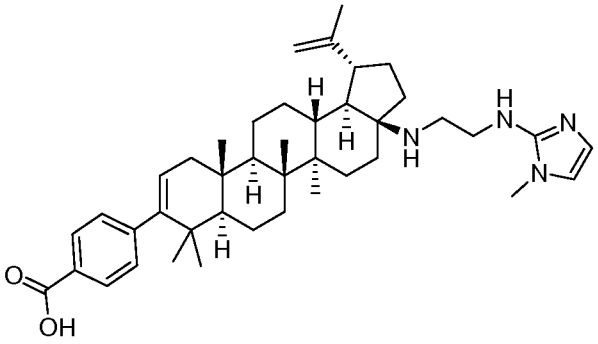


The title compound was prepared following a similar procedure as described for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridin-3-ylamino)ethylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 4-bromopyridine hydrochloride (0.018 g, 0.091 mmol) was used in place of 3-bromopyridine, and an additional 1.2 equivalents of sodium tert-butoxide, 2.0M solution in THF (for a total of 5.6 equivalents, 0.212 mL, 0.424 mmol) was employed. The product was isolated after reverse phase preparative HPLC purification using Prep HPLC Method 7 as a beige solid (74 mg, 54% yield) bis TFA salt. LCMS: m/e 650.4 $(M+H)^+$, 3.85 min (method 16). ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 8.19 - 7.97 (m, 2H), 7.91 (d, *J*=8.2 Hz, 2H), 7.19 (d, *J*=8.2 Hz, 2H), 7.06 (br. s., 2H), 5.28

(d, *J*=4.6 Hz, 1H), 4.83 (s, 1H), 4.73 (s, 1H), 3.96 - 3.81 (m, 2H), 3.31 - 3.19 (m, 2H), 2.88 - 2.76 (m, 1H), 2.18 - 2.03 (m, 3H), 1.97 (dd, *J*=10.4, 6.4 Hz, 3H), 1.83 (d, *J*=12.5 Hz, 1H), 1.72 (s, 3H), 1.68 (br. s., 1H), 1.66 - 1.45 (m, 7H), 1.44 - 1.28 (m, 5H), 1.24 (d, *J*=8.2 Hz, 1H), 1.18 - 1.11 (m, 1H), 1.09 (s, 3H), 1.06 (s, 3H), 1.01 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H).

Example 191

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(1-methyl-1H-imidazol-2-ylamino)ethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

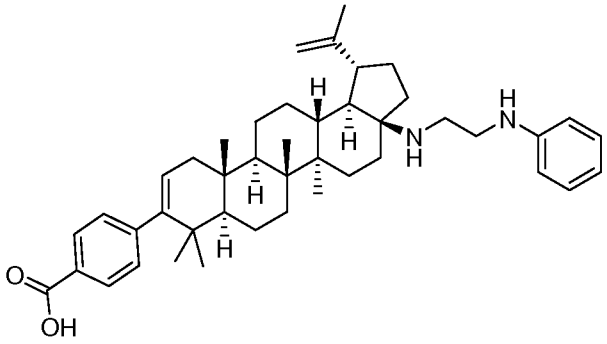


The title compound was prepared following a similar procedure as described for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridin-3-ylamino)ethylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-bromo-1-methyl-1H-imidazole (0.015 g, 8.88 µL, 0.091 mmol) was used in place of 3-bromopyridine. Also, addition of LiOH, water and methanol were unnecessary for this example, as the ester hydrolysis occurred spontaneously during the course of the amination reaction. The product was isolated after reverse phase preparative HPLC purification using Prep HPLC Method 8 as a beige solid (38.1 mg, 51.5% yield) bis TFA salt. LCMS: m/e 653.4 $(M+H)^+$, 3.88 min (method 16). ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 7.91 (d, *J*=8.2 Hz, 2H), 7.19 (d, *J*=7.9 Hz, 2H), 6.86 (s, 1H), 6.83 - 6.79 (m, 1H), 5.28 (d, *J*=5.5 Hz, 1H), 4.84 (s, 1H), 4.73 (s, 1H), 4.71

(br. s., 1H), 3.98 - 3.82 (m, 2H), 3.58 (s, 3H), 3.25 (br. s., 1H), 2.89 - 2.78 (m, 1H), 2.18 - 2.07 (m, 3H), 2.05 - 1.92 (m, 3H), 1.90 - 1.79 (m, 1H), 1.72 (s, 4H), 1.69 (br. s., 1H), 1.62 - 1.54 (m, 3H), 1.53 - 1.47 (m, 3H), 1.46 - 1.34 (m, 5H), 1.28 - 1.20 (m, 2H), 1.18 - 1.12 (m, 1H), 1.11 (s, 3H), 1.09 - 1.03 (m, 4H), 1.01 (s, 3H), 0.93 (br. s., 3H), 0.93 (br. s., 3H).

Example 192

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(phenylamino)ethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

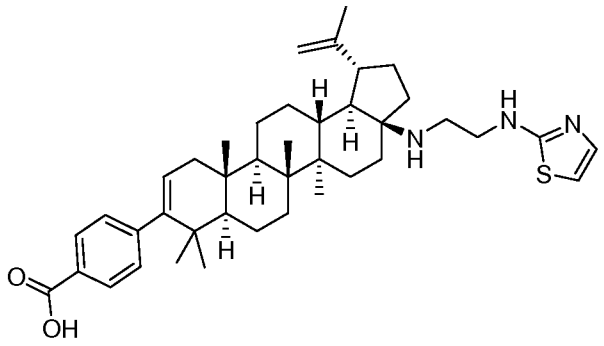


The title compound was prepared following a similar procedure as described for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridin-3-ylamino)ethylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except bromobenzene (0.014 g, 9.58 µL, 0.091 mmol) was used in place of 3-bromopyridine. The product was isolated after reverse phase preparative HPLC purification using Prep HPLC Method 7 as a beige solid (29.7 mg, 42% yield) bis TFA salt. LCMS: m/e 649.4 $(M+H)^+$, 2.42 min (method 11). ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 7.94 - 7.88 (m, *J*=7.9 Hz, 2H), 7.22 (t, *J*=7.8 Hz, 2H), 7.20 - 7.15 (m, *J*=8.2 Hz, 2H), 6.82 (t, *J*=7.3 Hz, 1H), 6.75 (d, *J*=7.9 Hz, 2H), 5.27 (d, *J*=5.5 Hz, 1H), 4.81 (s, 1H), 4.73 (s, 1H), 3.68 - 3.58 (m, 1H), 3.58 - 3.51 (m, 1H), 3.25 - 3.17 (m, 2H), 2.82 (td, *J*=11.0, 5.2 Hz, 1H), 2.18 - 2.05 (m, 2H), 2.01 - 1.92 (m, 2H), 1.90 (br. s., 1H), 1.83 - 1.72 (m, 2H), 1.71 (s, 3H), 1.68 (d, *J*=17.4 Hz, 1H), 1.64 - 1.46 (m, 6H), 1.45 -

1.30 (m, 5H), 1.27 - 1.11 (m, 4H), 1.10 - 1.02 (m, 2H), 1.02 - 0.99 (m, 6H), 0.98 (s, 3H), 0.93 (s, 3H), 0.91 (s, 3H).

Example 193

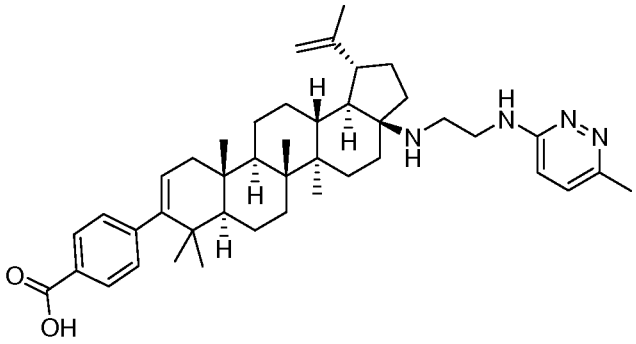
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(thiazol-2-ylamino)ethylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following a similar procedure as described for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridin-3-ylamino)ethylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-bromothiazole (0.015 g, 0.091 mmol) was used in place of 3-bromopyridine. The product was isolated after reverse phase preparative HPLC purification using Prep HPLC Method 7 as a beige solid (12.8 mg, 18% yield) bis TFA salt. LCMS: m/e 656.4 $(M+H)^+$, 2.38 min (method 11). ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 7.91 (d, *J*=8.2 Hz, 2H), 7.19 (d, *J*=8.2 Hz, 2H), 7.08 (d, *J*=3.7 Hz, 1H), 6.68 (d, *J*=4.0 Hz, 1H), 5.28 (d, *J*=4.6 Hz, 1H), 4.86 (s, 1H), 4.74 (br. s., 1H), 3.69 (dd, *J*=9.9, 5.3 Hz, 1H), 3.43 - 3.36 (m, 1H), 2.13 (dd, *J*=17.2, 6.3 Hz, 1H), 2.05 (d, *J*=15.0 Hz, 1H), 2.01 - 1.79 (m, 6H), 1.73 (s, 4H), 1.70 - 1.46 (m, 8H), 1.46 - 1.27 (m, 6H), 1.27 - 1.22 (m, 2H), 1.22 - 1.10 (m, 2H), 1.07 (s, 3H), 1.04 (s, 3H), 1.00 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H).

Example 194

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(6-methylpyridazin-3-ylamino)ethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

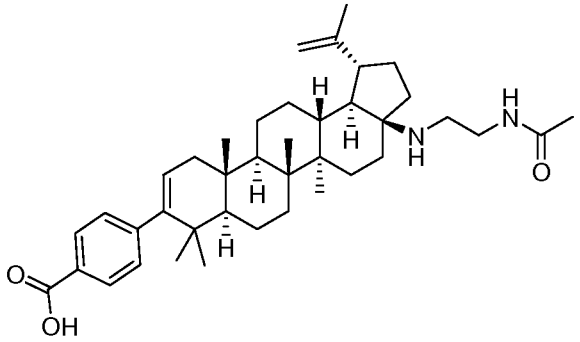


In a 1 dram vial under nitrogen were combined (2R)-1-[(1R)-1-[bis(1,1-dimethylethyl)phosphino]ethyl]-2-(dicyclohexylphosphino)ferrocene (CAS# 158923-11-6) (2.52 mg, 4.55 μmol), palladium(II) acetate (1.02 mg, 4.55 μmol) and dry DME (0.5 ml). The contents of the vial were stirred for 10 min, and were then added all at once to a separate mixture of 3-bromo-6-methylpyridazine (0.017 g, 0.100 mmol) and sodium tert-butoxide, 2.0M solution in THF (0.200 mL, 0.400 mmol) in dry DME (0.500 mL) contained in a separate 1 dram vial. The resulting mixture was allowed to stir very briefly (1 min) before solid methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-aminoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate bis HCl salt (0.060 g, 0.091 mmol) was added in one portion. The mixture was heated to 110 °C overnight. Iterative purification of the crude mixture by reverse phase preparative HPLC first using Prep HPLC Method 9 and then repurification by Prep HPLC Method 10 gave the title compound (0.0070 g, 8.3% yield) as a white glassy solid bis TFA salt. LCMS: m/e 665.5 $(M+H)^+$, 2.22 min (method 11). ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 7.90 (d, *J*=8.5 Hz, 2H), 7.49 - 7.42 (m, 1H), 7.32 - 7.23 (m, 1H), 7.18 (d, *J*=8.2 Hz, 2H), 5.27 (dd, *J*=6.0, 1.4 Hz, 1H), 4.88 (br. s., 1H), 4.72 (br. s., 1H), 3.94 - 3.84 (m, 1H), 3.84 - 3.73 (m, 1H), 3.26 - 3.13 (m, 1H), 2.84 (d, *J*=12.5 Hz, 1H), 2.57 (s, 3H), 2.12 (dd, *J*=16.9, 6.3 Hz, 1H), 2.05 (d, *J*=15.6 Hz, 1H), 2.01 - 1.91 (m, 2H), 1.91

- 1.74 (m, 2H), 1.70 (s, 3H), 1.69 - 1.59 (m, 2H), 1.59 - 1.43 (m, 4H), 1.43 - 1.28 (m, 4H), 1.28 - 1.18 (m, 4H), 1.18 - 1.06 (m, 2H), 1.05 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 0.92 (s, 3H), 0.92 - 0.89 (m, 3H).

Example 195

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-acetamidoethylamino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

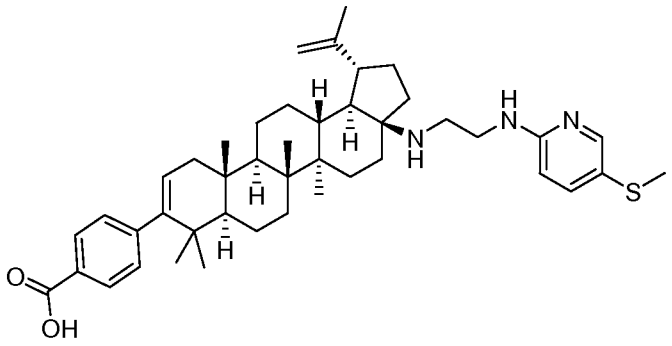


The title compound was prepared following a similar procedure as described for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(6-methylpyridazin-3-ylamino)ethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 4-bromopyrimidine (0.016 g, 0.100 mmol) was used in place of 3-bromo-6-methylpyridazine. The reaction did not produce the intended product but instead produced the byproduct title compound as the major isolate. Iterative purification of the crude mixture by reverse phase preparative HPLC first using Prep HPLC Method 9 and then repurification by Prep HPLC Method 10 gave the title compound as a white glassy solid (7.5 mg, 9.6% yield) mono TFA salt. LCMS: m/e 615.5 $(M+H)^+$, 2.42 min (method 11). ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 8.18 (s, 1H), 7.94 - 7.84 (m, *J*=8.2 Hz, 2H), 7.24 - 7.13 (m, *J*=8.2 Hz, 2H), 5.27 (d, *J*=4.6 Hz, 1H), 4.83 (s, 1H), 4.72 (br. s., 1H), 3.89 (s, 3H), 3.61 (br. s., 2H), 3.18 (br. s., 2H), 2.71 (td, *J*=11.1, 6.3 Hz, 2H), 2.12 - 1.92 (m, 6H), 1.90 - 1.76 (m, 3H), 1.76 - 1.66 (m, 5H),

1.66 - 1.43 (m, 9H), 1.42 - 1.33 (m, 3H), 1.24 (br. s., 2H), 1.17 (s, 3H), 1.07 (s, 3H), 1.01 (s, 3H), 0.93 (s, 3H), 0.92 (br. s., 3H).

Example 196

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(5-(methylthio)pyridin-2-ylamino)ethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

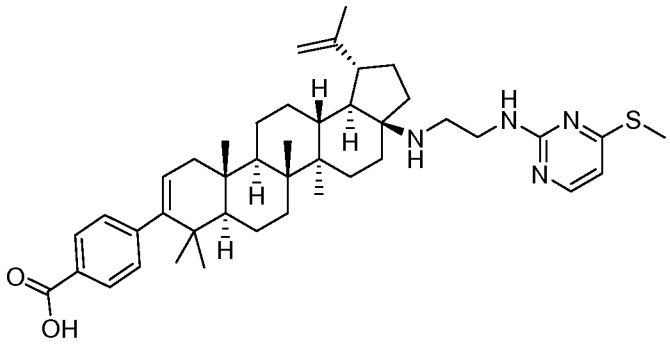


The title compound was prepared following a similar procedure as described for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(6-methylpyridazin-3-ylamino)ethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-bromo-5-(methylthio)pyridine (0.020 g, 0.100 mmol) was used in place of 3-bromo-6-methylpyridazine. Iterative purification of the crude mixture by reverse phase preparative HPLC first using Prep HPLC Method 9 and then repurification by Prep HPLC Method 10 gave the title compound as a white glassy solid (5.2 mg, 5.9% yield) bis TFA salt. LCMS: m/e 696.5 $(M+H)^+$, 2.34 min (method 11). ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 8.03 (d, *J*=1.8 Hz, 1H), 7.93 - 7.88 (m, *J*=8.2 Hz, 2H), 7.61 - 7.57 (m, 1H), 7.21 - 7.14 (m, *J*=8.2 Hz, 2H), 6.71 (d, *J*=8.9 Hz, 1H), 5.27 (dd, *J*=6.1, 1.5 Hz, 1H), 4.87 (s, 1H), 4.75 (br. s., 1H), 4.72 (br. s., 1H), 3.80 - 3.72 (m, 1H), 3.72 - 3.63 (m, 1H), 3.18 - 3.09 (m, 1H), 2.72 - 2.64 (m, 1H), 2.39 (s, 3H), 2.11 (dd, *J*=17.1, 6.4 Hz, 1H), 2.08 - 2.01 (m, 1H), 2.00 - 1.90 (m, 3H), 1.90 - 1.74 (m, 3H), 1.72 (s, 3H), 1.71 - 1.66 (m, 2H), 1.65 - 1.44 (m, 7H), 1.44 - 1.33 (m, 3H),

1.33 - 1.12 (m, 7H), 1.04 (s, 3H), 0.97 (s, 3H), 0.91 (br. s., 3H), 0.91 (br. s., 3H), 0.87 (s, 3H).

Example 197

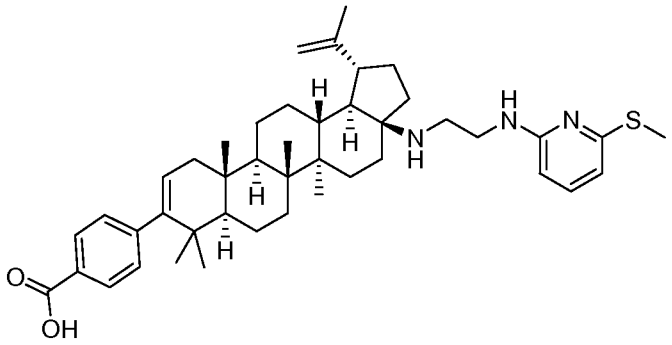
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(4-(methylthio)pyrimidin-2-ylamino)ethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following a similar procedure as described for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(6-methylpyridazin-3-ylamino)ethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-chloro-4-(methylthio)pyrimidine (0.016 g, 0.100 mmol) was used in place of 3-bromo-6-methylpyridazine. Iterative purification of the crude mixture by reverse phase preparative HPLC first using Prep HPLC Method 9 and then repurification by Prep HPLC Method 10 gave the title compound as a white glassy solid (12.0 mg, 14% yield) bis TFA salt. LCMS: m/e 697.5 $(M+H)^+$, 2.30 min (method 11). ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 7.99 - 7.85 (m, 3H), 7.17 (d, *J*=8.2 Hz, 2H), 6.75 - 6.63 (m, 1H), 5.26 (d, *J*=4.6 Hz, 1H), 4.82 (s, 1H), 4.70 (br. s., 1H), 3.96 (s, 1H), 3.85 (br. s., 2H), 3.43 - 3.34 (m, 1H), 3.25 (br. s., 1H), 2.72 (br. s., 1H), 2.55 (s, 3H), 2.10 (dd, *J*=17.1, 6.4 Hz, 1H), 2.04 (d, *J*=15.3 Hz, 1H), 2.01 - 1.89 (m, 3H), 1.89 - 1.77 (m, 2H), 1.70 (s, 4H), 1.68 - 1.49 (m, 5H), 1.46 (d, *J*=7.3 Hz, 3H), 1.42 - 1.18 (m, 7H), 1.18 - 1.06 (m, 2H), 1.03 (s, 3H), 0.97 (s, 3H), 0.95 (s, 3H), 0.92 (s, 3H), 0.91 (br. s., 3H).

Example 198

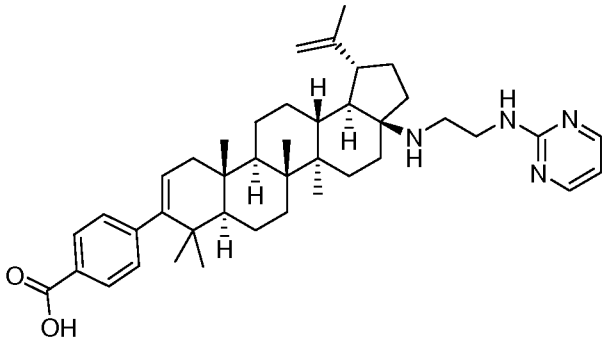
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(6-(methylthio)pyridin-2-ylamino)ethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following a similar procedure as described for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(6-methylpyridazin-3-ylamino)ethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-bromo-6-(methylthio)pyridine (0.020 g, 0.100 mmol) was used in place of 3-bromo-6-methylpyridazine. Iterative purification of the crude mixture by reverse phase preparative HPLC first using Prep HPLC Method 9 and then repurification by Prep HPLC Method 10 gave the title compound as a white glassy solid (10.3 mg, 12% yield) bis TFA salt. LCMS: m/e 696.5 $(M+H)^+$, 2.34 min (method 11). ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 7.95 - 7.85 (m, *J*=8.2 Hz, 2H), 7.39 (t, *J*=7.8 Hz, 1H), 7.20 - 7.12 (m, *J*=8.2 Hz, 2H), 6.53 (d, *J*=7.6 Hz, 1H), 6.37 (d, *J*=7.9 Hz, 1H), 5.25 (d, *J*=4.6 Hz, 1H), 4.85 (s, 1H), 4.72 (br. s., 1H), 3.96 (s, 1H), 3.78 - 3.59 (m, 2H), 3.28 - 3.13 (m, 2H), 2.95 - 2.83 (m, 1H), 2.49 (s, 3H), 2.08 - 1.86 (m, 6H), 1.78 - 1.69 (m, 4H), 1.69 - 1.52 (m, 5H), 1.52 - 1.31 (m, 6H), 1.31 - 1.07 (m, 7H), 1.01 (s, 3H), 0.95 - 0.83 (m, 9H), 0.57 (s, 3H).

Example 199

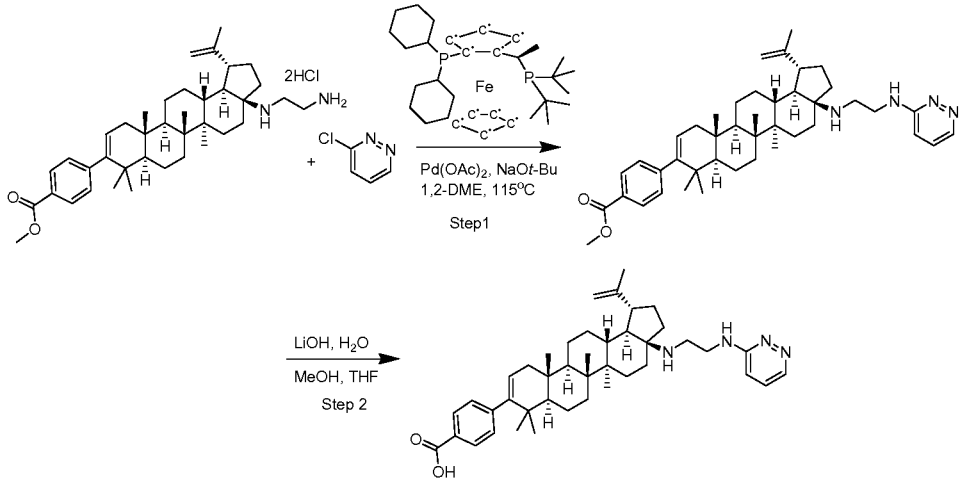
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyrimidin-2-ylamino)ethylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



The title compound was prepared following a similar procedure as described for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(6-methylpyridazin-3-ylamino)ethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-bromopyrimidine (0.016 g, 0.100 mmol) was used in place of 3-bromo-6-methylpyridazine. Iterative purification of the crude mixture by reverse phase preparative HPLC first using Prep HPLC Method 9 and then repurification by Prep HPLC Method 10 gave the title compound as a white glassy solid (8.0 mg, 8.2% yield) bis TFA salt. LCMS: m/e 651.5 $(M+H)^+$, 2.27 min (method 11).

Example 200

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridazin-3-ylamino)ethylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridazin-3-ylamino)ethylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

The title compound was prepared following a similar procedure as described for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(6-methylpyridazin-3-ylamino)ethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 3-chloropyridazine (0.011 g, 0.100 mmol) was used in place of 3-bromo-6-methylpyridazine. Purification of the crude mixture by reverse phase preparative HPLC using Prep HPLC Method 9 gave the title compound as a white glassy solid (4.9 mg, 6.0% yield) bis TFA salt. LCMS: m/e 665.5 $(M+H)^+$, 2.40 min (method 11).

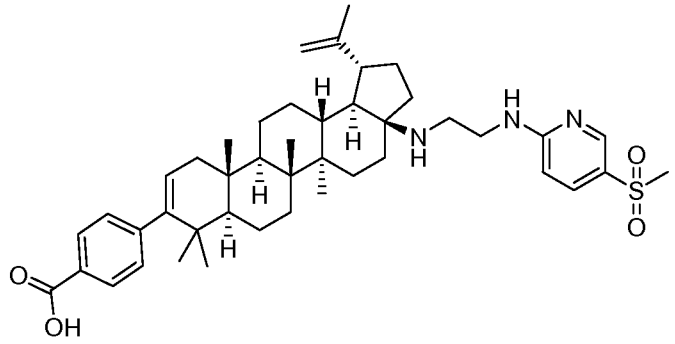
Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridazin-3-ylamino)ethylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

A solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridazin-3-ylamino)ethylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate and lithium hydroxide monohydrate (2.3 mg,

0.055 mmol) in a mixture of water (0.5 mL), THF (0.25 mL) and MeOH (0.25 mL) was stirred at rt for 2.5 days. Purification of the crude mixture by reverse phase preparative HPLC using Prep HPLC Method 10 gave the title compound as a white solid (5.0 mg, 100% yield) bis TFA salt. LCMS: m/e 651.5 $(M+H)^+$, 2.26 min (method 11).

Example 201

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(5-(methylsulfonyl)pyridin-2-ylamino)ethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



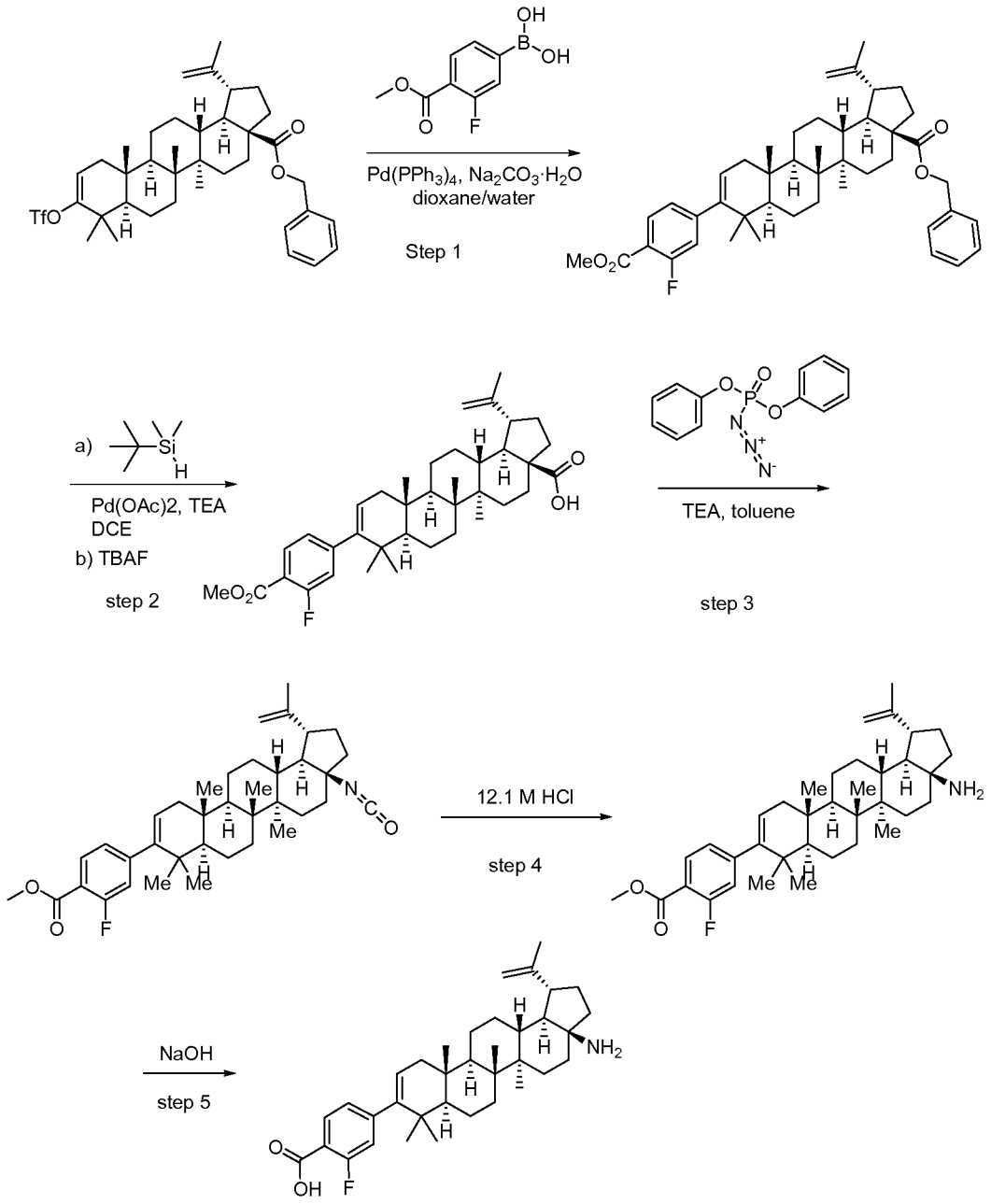
The title compound was prepared following a similar procedure as described for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-(2-(pyridazin-3-ylamino)ethylamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid, except 2-bromo-5-(methylsulfonyl)pyridine (0.024 g, 0.100 mmol) was used in place of 3-chloropyridazine. Purification of the crude Step 2 mixture by reverse phase preparative HPLC using Prep HPLC Method 10 gave the title compound as an off-white solid (10.6 mg, 11.9% yield over 2 steps) bis TFA salt. LCMS: m/e 728.5 $(M+H)^+$, 2.22 min (method 11). ^{1}H NMR (500 MHz, 1:1 mixture of *CDCl3* and *MeOD*, *MeOD* lock) δ ppm 8.61 (d, *J*=1.8 Hz, 1H), 7.95 - 7.87 (m, 3H), 7.19 (d, *J*=8.2 Hz, 2H), 6.80 (d, *J*=8.9 Hz, 1H), 5.29 (d, *J*=4.6 Hz, 1H), 4.90 (s, 1H), 4.82 (br. s., 1H), 3.96 - 3.85 (m, 1H), 3.85 - 3.71 (m, 1H), 3.42 (br. s., 1H), 3.37 (s, 3H), 3.27 - 3.18 (m, 1H), 3.10 (s, 3H), 2.70 (br. s., 1H), 2.14 (dd, *J*=17.2, 6.3 Hz, 1H), 2.10 - 1.95 (m, 5H), 1.91 - 1.77 (m, 3H), 1.74 (s, 3H), 1.71 (d, *J*=17.4

Hz, 2H), 1.65 - 1.47 (m, 6H), 1.47 - 1.34 (m, 3H), 1.34 - 1.11 (m, 6H), 1.06 (s, 3H), 1.00 (s, 3H), 0.94 (s, 6H), 0.93 (s, 3H).

Section 6. F-benzoic acid derivatives

Example A1

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-fluorobenzoic acid.



Step 1. Preparation of (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-benzyl 9-(3-fluoro-4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysene-3a-carboxylate.

A suspension of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-benzyl 5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-9-(trifluoromethylsulfonyloxy)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

cyclopenta[a]chrysene-3a-carboxylate (4.0 g, 5.91 mmol), 3-fluoro-4-(methoxycarbonyl)phenylboronic acid (1.287 g, 6.50 mmol), sodium carbonate monohydrate (2.198 g, 17.73 mmol), and $Pd(PPh_3)_4$ (0.205 g, 0.177 mmol) in 1,4-dioxane (24 mL) and water (6 mL) was flushed with N_2 and the mixture was heated to reflux. After 2 h of heating, the mixture was cooled to rt. The mixture was diluted with water (40 mL) and was extracted with dichloromethane (3 x 40 mL). The combined organic layers were dried with Na_2SO_4. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in DCM and was filtered through a pad of celite and silica gel, washing with a 25% EtOAc in hexanes solution. The filtrate was concentrated under reduced pressure to give the title compound (3.59 g, 5.27 mmol, 89% yield) as a dark grey foam. The crude product was used in the next step with no additional purification. ^{1}H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 7.80 (1 H, t, *J*=7.8 Hz), 7.29 - 7.42 (5 H, m), 6.96 (1 H, d, *J*=7.9 Hz), 6.91 (1 H, d, *J*=11.9 Hz), 5.28 - 5.33 (1 H, m), 5.16 (1 H, d, *J*=12.5 Hz), 5.09 (1 H, d, *J*=12.2 Hz), 4.73 (1 H, s), 4.59 (1 H, br. s.), 3.92 (3 H, s), 3.03 (1 H, td, *J*=10.8, 4.7 Hz), 2.20 - 2.33 (2 H, m), 2.09 (1 H, dd, *J*=17.1, 6.4 Hz), 1.81 - 1.97 (2 H, m), 1.68 (3 H, s), 0.96 (3 H, s), 0.92 (3 H, s), 0.92 (3 H, s), 0.91 (3 H, s), 0.81 (3 H, s), 0.79 - 1.75 (17 H, m).

Step 2. Preparation of (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(3-fluoro-4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysene-3a-carboxylic acid.

To a solution of (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-benzyl 9-(3-fluoro-4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysene-3a-carboxylate (3.59 g, 5.27 mmol) in DCE (25 mL) was added TEA (1.176 mL, 8.44 mmol), *t*-butyldimethylsilane (1.749 mL, 10.54 mmol), and palladium(II) acetate (0.118 g, 0.527 mmol). The mixture was flushed with N_2 and heated to 60 °C for 1 h. The mixture was cooled to rt and was filtered through a plug of celite and silica gel (washed with 25% EtOAc in hexanes). The filtrate was concentrated under reduced pressure. The residue was diluted with 25 mL of dioxane and TBAF (75% in water) (2.76 g, 7.91 mmol) was added. The mixture was stirred

for 30 minutes at rt then was diluted with 50 mL of 1N HCl. The solids that formed were collected by filtration and were washed with water to give the title compound (2.95 g, 4.99 mmol, 95% yield) as a white solid. ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.83 (1 H, t, *J*=7.9 Hz), 6.90 - 7.00 (2 H, m), 5.34 (1 H, dd, *J*=6.1, 1.6 Hz), 4.77 (1 H, d, *J*=2.0 Hz), 4.64 (1 H, s), 3.94 (3 H, s), 3.04 (1 H, td, *J*=10.7, 4.8 Hz), 2.24 - 2.34 (2 H, m), 2.13 (1 H, dd, *J*=17.3, 6.3 Hz), 1.96 - 2.06 (2 H, m), 1.72 (3 H, s), 1.03 (3 H, s), 1.02 (3 H, s), 0.98 (3 H, s), 0.93 - 0.96 (6 H, m), 0.91 - 1.80 (17 H, m).

Step 3. Preparation of methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

To a solution of (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(3-fluoro-4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysene-3a-carboxylic acid (2.95 g, 4.99 mmol) in toluene (50 mL) and TEA (1.39 mL, 9.99 mmol) was added diphenyl phosphorazidate (1.614 mL, 7.49 mmol) and the mixture was heated to reflux. After 3 h, the reaction mixture was concentrated under reduced pressure, was adsorbed to silica gel, and was purified by flash chromatography using a 0-10% EtOAc in hexanes gradient to give the title compound as a white solid. The material was used in the next step with no additional purification. ^{1}H NMR (500 MHz, *Chloroform-d*) δ ppm 7.81 (1 H, t, *J*=7.8 Hz), 6.96 (1 H, dd, *J*=7.9, 1.5 Hz), 6.92 (1 H, dd, *J*=11.9, 1.5 Hz), 5.31 (1 H, dd, *J*=6.3, 1.7 Hz), 4.75 (1 H, s), 4.64 (1 H, s), 3.92 (3 H, s), 2.55 (1 H, td, *J*=10.8, 5.8 Hz), 2.05 - 2.16 (2 H, m), 1.76 - 1.92 (4 H, m), 1.68 (3 H, s), 1.09 - 1.11 (3 H, m), 0.97 (3 H, s), 0.96 (3 H, s), 0.94 (3 H, s), 0.92 (3 H, s), 0.88 - 1.75 (16 H, m).

Step 4. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-fluorobenzoate dihydrochloride.

To a solution of crude methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (2.93 g, 4.99 mmol) in THF (35 mL) was added 12N HCl (10 mL, 121 mmol). After stirring the mixture for 24 h, the mixture was diluted with water (100 mL) until solids precipitated. The solids were collected by filtration and were washed with water to afford the title compound (2.75 g, 4.33 mmol, 87% yield), as an off-white solid that was used in the next step with no additional purification. LCMS: m/e 562 $(M+H)^+$, 1.96 min (method 2).

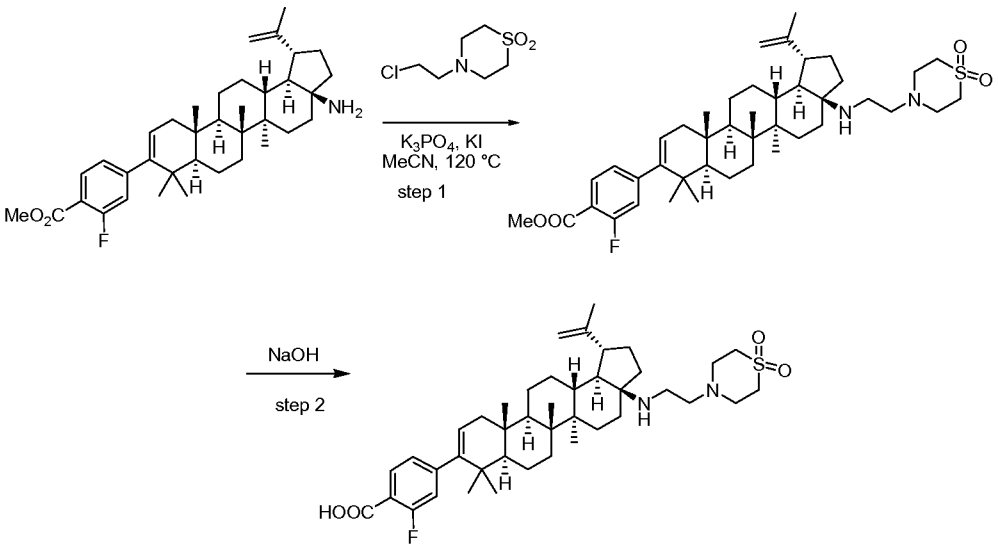
Step 5. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-fluorobenzoic acid.

To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-fluorobenzoate (100 mg, 0.178 mmol) in 1,4-dioxane (2 mL) was added 1N NaOH (0.890 mL, 0.890 mmol). Solids formed upon the addition of the NaOH. The mixture was heated to 60 °C. After 20 minutes of heating, the mixture still contained solids. The mixture was further diluted with 1 mL of MeOH and 2 mL of dioxane then was heated to 60 °C overnight (solids did not completely dissolve).

After 21 h of heating, the mixture was cooled to rt. The mixture was diluted with 3 mL of water and the solids that remained were collected by filtration and were washed with water then with ether to give 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-fluorobenzoic acid (67 mg, 0.113 mmol, 63.2% yield) as a white solid. . LCMS: m/e 548.4 $(M+H)^+$, 2.29 min (method 11).

Example A2

Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxido-4-thiomorpholinyl)ethyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl]-2-fluoro-, HCl



Step 1. Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxido-4-thiomorpholinyl)ethyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl]-2-fluoro-, methyl ester.

To a sealable flask containing methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-fluorobenzoate, HCl (319 mg, 0.533 mmol) was added thiomorpholine, 4-(2-chloroethyl)-, 1,1-dioxide, HCl (385 mg, 1.644 mmol), potassium iodide (240 mg, 1.446 mmol), and phosphoric acid, potassium salt (500 mg, 2.356 mmol). The mixture was diluted with acetonitrile (10 mL), was flushed with N_2, then the vial was sealed and heated to 120 °C for 115 h. The mixture was cooled to rt and was directly purified by flash chromatography using a 0-5% MeOH in DCM gradient. The fractions containing the expected product were

combined and were concentrated under reduced pressure to give the title compound (0.308 g, 0.426 mmol, 80% yield) as an off white foam. LCMS: m/e 723.5 $(M+H)^+$, 1.94 min (method 2).

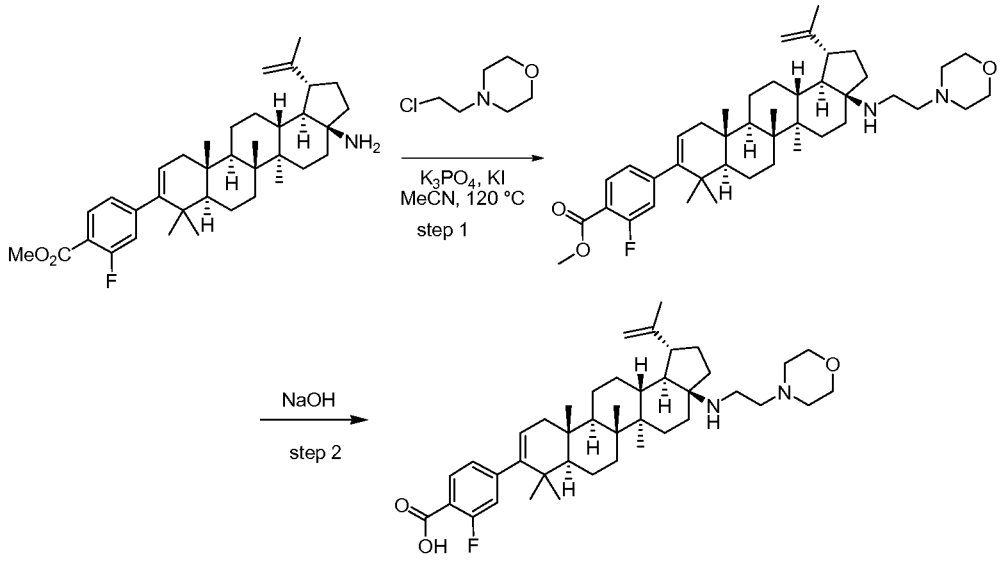
Step 2. Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxido-4-thiomorpholinyl)ethyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl]-2-fluoro-, HCl.

To a solution of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxido-4-thiomorpholinyl)ethyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl]-2-fluoro-, methyl ester (0.308g, 0.426 mmol) in 1,4-dioxane (5 mL) was added 1N sodium hydroxide (2.130 mL, 2.130 mmol). The mixture was heated to 70 °C for 18 h then was cooled to rt. To the mixture was added 1N HCl slowly until solids began to form. The solids were collected by filtration and were washed with water to give benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxido-4-thiomorpholinyl)ethyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl]-2-fluoro-, HCl as an off-white solid (0.295g, 0.396 mmol, 93% yield). LCMS: m/e 709.5 $(M+H)^+$, 1.66 min (method 2). ^{1}H NMR (500 MHz, *Acetic acid d4*) δ ppm 7.96 (1 H, t, *J*=7.8 Hz), 7.09 (1 H, dd, *J*=7.9, 1.5 Hz), 7.03 (1 H, d, *J*=11.9 Hz), 5.43 (1 H, d, *J*=4.6 Hz), 4.84 (1 H, s), 4.74 (1 H, s), 3.43 - 3.49 (1 H, m), 3.02 - 3.36 (11 H, m), 2.91 - 3.00 (1 H, m), 1.77 (3 H, s), 1.30 (3 H, s), 1.15 (3 H, s), 1.10 (3 H, s), 1.04 (3 H, s), 1.01 (3 H, s), 0.98 - 2.34 (22 H, m).

Example A3

Preparation of 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-morpholinoethylamino)-1-(prop-1-en-2-yl)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



Step 1. Preparation of methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-morpholinoethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

To a sealable flask containing methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-fluorobenzoate, HCl (0.1 g, 0.167 mmol) was added 4-(2-chloroethyl)morpholine, HCl (0.093 g, 0.501 mmol), phosphoric acid, potassium salt (0.156 g, 0.735 mmol) and potassium iodide (0.075 g, 0.451 mmol). The mixture was diluted with acetonitrile (3 mL), was flushed with N_2, and the vial was sealed and heated to 120 °C. After heating the mixture for 16 h, the it was cooled to rt. The crude product was adsorbed to silica gel then was purified by flash chromatography using a Thomson 12 g silica gel column and a 0-5% MeOH in DCM gradient. The fractions containing the expected product were combined and concentrated under reduced pressure to give methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-morpholinoethylamino)-1-(prop-1-en-2-yl)-

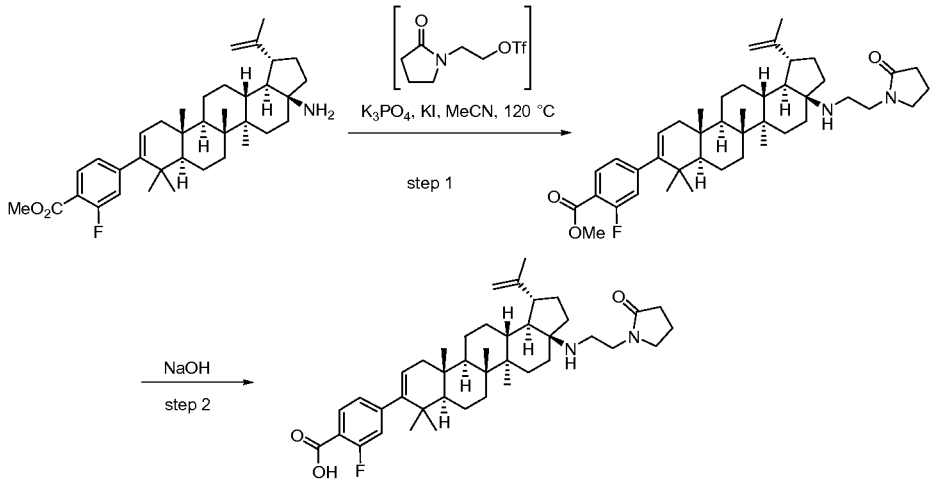
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (77 mg, 0.114 mmol, 68.3% yield) as an off-white foam. LCMS: m/e 675.5 $(M+H)^+$, 1.91 min (method 2).

Step 2. Preparation of 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-morpholinoethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

To a solution of methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-morpholinoethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.075 g, 0.111 mmol) in 1,4-dioxane (1 mL) was added NaOH (1M) (0.5 mL, 0.500 mmol). The mixture was heated to 75 °C for 15 h then was cooled to rt. The mixture was purified by prep HPLC. The fractions containing the expected product were combined and concentrated under reduced pressure to give 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-morpholinoethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (30 mg, 0.043 mmol, 38.8% yield) as a white solid. LCMS: m/e 661.5 $(M+H)^+$, 1.66 min (method 2). ^{1}H NMR (500 MHz, *Acetic Acid* d_4) δ ppm 7.96 (1 H, t, *J*=7.9 Hz), 7.09 (1 H, dd, *J*=8.2, 1.2 Hz), 7.03 (1 H, d, *J*=11.6 Hz), 5.42 (1 H, d, *J*=4.6 Hz), 4.86 (1 H, s), 4.74 (1 H, s), 3.89 - 3.99 (4 H, m), 3.53 - 3.69 (4 H, m), 3.29 (4 H, br. s.), 2.81 - 2.90 (1 H, m), 1.77 (3 H, s), 1.23 (3 H, s), 1.13 (3 H, s), 1.08 (3 H, s), 1.04 (3 H, s), 1.01 (3 H, s), 0.85 - 2.26 (22 H, m).

Example A4

Preparation of 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(2-oxopyrrolidin-1-yl)ethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



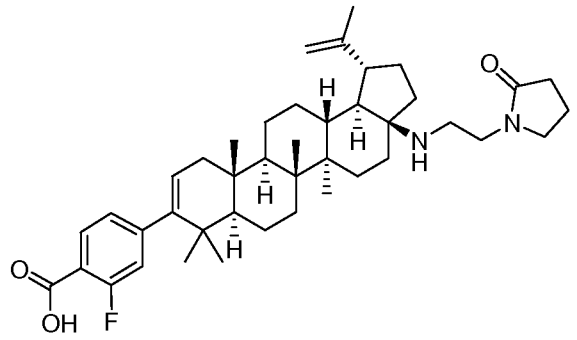
Step 1. Preparation of methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(2-oxopyrrolidin-1-yl)ethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

To a vial containing *N*-(2-hydroxyethyl)-2-pyrrolidone (0.5 mL, 4.42 mmol) was added DMAP (0.054 g, 0.442 mmol) and TEA (0.925 mL, 6.64 mmol). The mixture was diluted with d-chloroform (10 mL) and was cooled to 0 °C then triflic anhydride (0.822 mL, 4.87 mmol) was added slowly. The mixture turned a dark red color as the anhydride was added. The mixture was warmed to rt and stirred for 45 minutes. The 0.442 M solution was used directly as the alkylating agent for the following reaction.

To a sealable flask containing methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-fluorobenzoate (50 mg, 0.089 mmol) was added potassium iodide (39.9 mg, 0.240 mmol) and phosphoric acid, potassium salt (83 mg, 0.392 mmol). The mixture was diluted with acetonitrile (1 mL) and the crude alkylating solution described above (1.007 mL, 0.445 mmol) was added. The mixture was flushed with N_2 and the vial was sealed and heated to 120 °C. After 15.5 h of heating, the mixture was cooled to rt. An additional 0.5 mL of the crude alkylating solution was added and the mixture was again heated to 120 °C. After

70.25 h, the mixture was cooled to rt. The mixture was adsorbed to silica gel and was purified by flash chromatography using a 0-5% MeOH in DCM gradient and a Thomson 12 g silica gel column. The fractions containing the expected product were combined and were concentrated under reduced pressure to give methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(2-oxopyrrolidin-1-yl)ethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (25 mg, 0.037 mmol, 41.7% yield) as a yellow film. LCMS: m/e 673.5 $(M+H)^+$, 2.03 min (method 2).

Step 2. Preparation of 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(2-oxopyrrolidin-1-yl)ethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

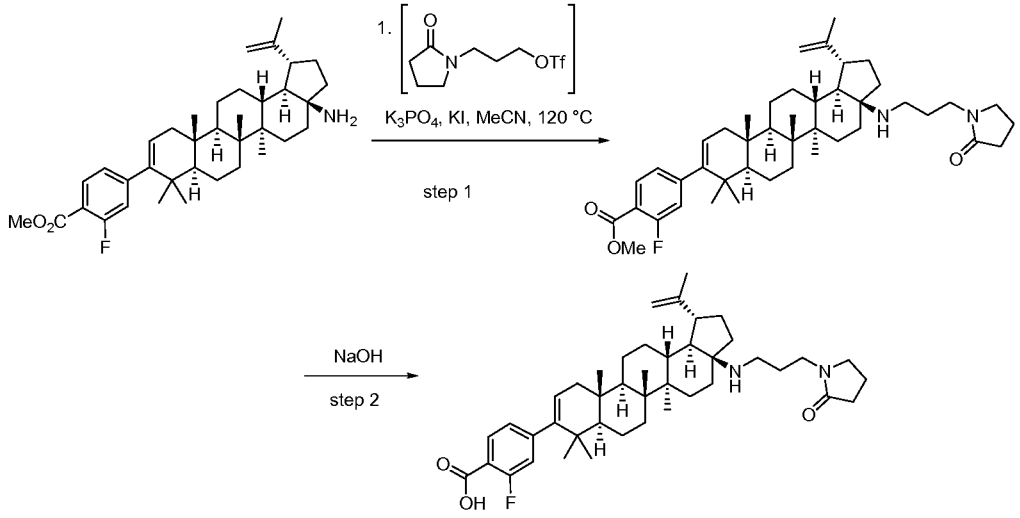


To a solution of methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(2-oxopyrrolidin-1-yl)ethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.025 g, 0.037 mmol) in 1,4-dioxane (1 mL) was added NaOH (1N) (0.5 mL, 0.500 mmol). The mixture was warmed to 60 °C for 15. 5h then was cooled to rt and purified by prep HPLC. The fractions containing the expected product were combined and concentrated under reduced pressure to give 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-(2-oxopyrrolidin-1-yl)ethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

cyclopenta[a]chrysen-9-yl)benzoic acid (11 mg, 0.016 mmol, 42.2% yield) as a white solid. LCMS: m/e 659.5 $(M+H)^+$, 1.77 min (method 2). ^{1}H NMR (500MHz, CHLOROFORM-d) δ 7.82 (t, *J*=6.9 Hz, 1H), 6.91 (d, *J*=6.1 Hz, 1H), 6.86 (d, *J*=11.9 Hz, 1H), 5.27 (d, *J*=4.6 Hz, 1H), 4.71 (s, 1H), 4.58 (s, 1H), 3.54 - 3.43 (m, 3H), 3.39 - 3.31 (m, 1H), 1.68 (s, 3H), 1.06 (s, 3H), 0.96 (s, 3H), 0.93 (s, 3H), 0.90 (s, 3H), 0.90 (s, 3H), 2.75 - 0.66 (m, 29H).

Example A5

Preparation of 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(2-oxopyrrolidin-1-yl)propylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.



Step 1. Preparation of methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(2-oxopyrrolidin-1-yl)propylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

To a vial containing 1-(3-hydroxypropyl)-2-pyrrolidone (0.5 mL, 3.84 mmol) was added DMAP (0.047 g, 0.384 mmol) and TEA (0.803 mL, 5.76 mmol). The mixture was diluted with d-chloroform (10 mL) and was cooled to 0 °C. To the

cooled solution was added trifluoromethanesulfonic anhydride (0.714 mL, 4.23 mmol) slowly. The mixture turned dark red as the anhydride was added. The mixture was slowly warmed to rt as the ice bath melted. After 1h of stirring at rt, ^{1}HNMR showed no starting material remained. The crude reaction mixture was used directly in the following reaction with no purification.

To a sealable flask containing methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-fluorobenzoate (50 mg, 0.089 mmol) was added potassium iodide (39.9 mg, 0.240 mmol) and phosphoric acid, potassium salt (83 mg, 0.392 mmol). The mixture was diluted with acetonitrile (1 mL) and 3-(2-oxopyrrolidin-1-yl)propyl trifluoromethanesulfonate (the crude solution prepared above) (1.0 mL, 0.384 mmol) was added. The mixture was flushed with N_2, then the vial was sealed and heated to 120 °C. After 15.5 h of heating, the mixture was cooled to rt. An additional 0.5 mL of the above crude solution containing the triflate was added and the mixture was again heated to 120 °C. After heating the mixture for an additional 70.25 h, the mixture was cooled to rt. The mixture was adsorbed to silica gel and was purified by flash chromatography using a 0-5% MeOH in DCM gradient and a Thomson 12 g silica gel column. The fractions containing the expected product were combined and concentrated under reduced pressure to give methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(2-oxopyrrolidin-1-yl)propylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (16 mg, 0.023 mmol, 26.2% yield) as a yellow film. LCMS: m/e 687.5 $(M+H)^+$, 2.04 min (method 2).

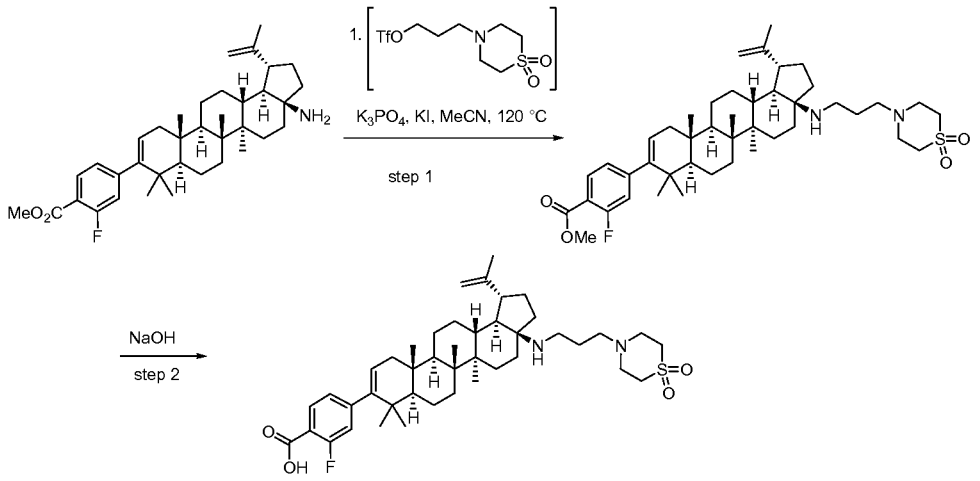
Step 2. Preparation of 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(2-oxopyrrolidin-1-yl)propylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

To a solution of methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(2-oxopyrrolidin-1-yl)propylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

cyclopenta[a]chrysen-9-yl)benzoate (16 mg, 0.023 mmol) in 1,4-dioxane (1 mL) was added NaOH (1N) (0.25 mL, 0.250 mmol). The mixture was heated to 60 °C overnight for 15.25h then was cooled to rt. The mixture was directly loaded onto the prep HPLC for purification. The fractions containing the expected product were combined and concentrated under reduced pressure to give 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(3-(2-oxopyrrolidin-1-yl)propylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (6 mg, 8.02 µmol, 34.5% yield) as a clear, colorless film. LCMS: m/e 673.5 $(M+H)^+$, 1.75 min (method 2). ^{1}H NMR (500MHz, *Acetic acid d4*) δ 7.96 (t, *J*=7.9 Hz, 1H), 7.09 (dd, *J*=7.9, 1.2 Hz, 1H), 7.03 (d, *J*=11.9 Hz, 1H), 5.42 (d, *J*=4.6 Hz, 1H), 4.86 (s, 1H), 4.74 (s, 1H), 3.58 - 3.40 (m, 4H), 3.26 - 3.16 (m, 2H), 2.94 - 2.85 (m, 1H), 2.56 - 2.48 (m, 2H), 1.76 (s, 3H), 1.22 (s, 3H), 1.13 (s, 3H), 1.08 (s, 3H), 1.04 (s, 3H), 1.01 (s, 3H), 2.29 - 0.85 (m, 26H).

Example A6

Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-thiomorpholinyl)propyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl]-2-fluoro-



Step 1. Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-thiomorpholinyl)propyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl]-2-fluoro-, methyl ester.

To a vial containing *N*-(3-hydroxypropyl)thiomorpholine-1,1-dioxide (0.15 g, 0.776 mmol) was added DMAP (9.48 mg, 0.078 mmol) and TEA (0.162 mL, 1.164 mmol). The mixture was diluted with d-chloroform (2 mL) and was cooled to 0 °C. To the cooled solution was added trifluoromethanesulfonic anhydride (0.144 mL, 0.854 mmol) slowly. The mixture turned orange as the anhydride was added and became a thick gel which did not stir well. After 2 h the mixture was diluted with an additional 1 mL of d-chloroform and was used directly in the following reaction as the crude reaction mixture.

To a sealable flask containing methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-fluorobenzoate (50 mg, 0.089 mmol) was added potassium iodide (39.9 mg, 0.240 mmol) and phosphoric acid, potassium salt (83 mg, 0.392 mmol). The mixture was diluted with acetonitrile (1 mL) and a solution of the crude mixture from the reaction above (1.718 mL, 0.445 mmol) was added. The mixture was flushed with N_2 and the vial was sealed and heated to 120 °C. After stirring the mixture for 66 h it was cooled to rt. The mixture was adsorbed to silica gel and was purified by flash chromatography using a 12 g Thomson silica gel column and a 0-5% MeOH in DCM gradient. The fractions containing the expected product were combined and concentrated under reduced pressure to give benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-thiomorpholinyl)propyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl]-2-fluoro-, methyl ester (43 mg, 0.058 mmol, 65.6% yield) as a yellow film. LCMS: m/e 737.5 $(M+H)^+$, 1.88 min (method 2).

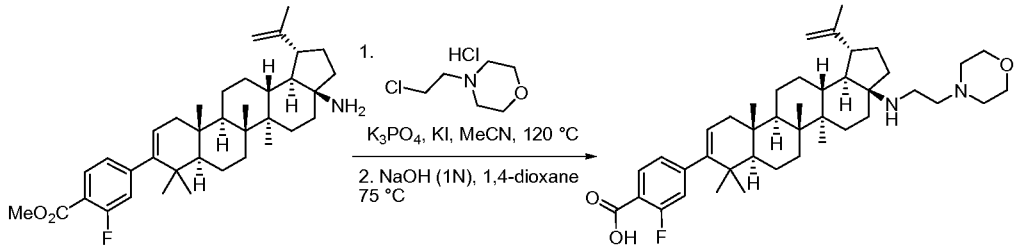
Step 2. Preparation of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-thiomorpholinyl)propyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl]-2-fluoro-.

To a solution of benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-thiomorpholinyl)propyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl]-2-fluoro-, methyl ester (0.043 g, 0.058 mmol) in 1,4-dioxane (1 mL) was added NaOH (1M) (0.5 ml, 0.500 mmol). The mixture was heated to 60 °C for 15.25h and was cooled to rt. The mixture was directly loaded onto the prep HPLC for purification. The fractions containing the expected product were combined and concentrated under reduced pressure to give benzoic acid, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-thiomorpholinyl)propyl]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-5a,5b,8,8,11a-pentamethyl-1-(1-methylethenyl)-1H-cyclopenta[a]chrysen-9-yl]-2-fluoro- (13.2 mg, 0.017 mmol, 29.4% yield) as a white solid. LCMS: m/e 723.5 $(M+H)^+$, 1.62 min (method 2). ^{1}H NMR (400MHz, *Acetic acid d4*) δ 7.92 (t, *J*=7.9 Hz, 1H), 7.04 (d, *J*=8.0 Hz, 1H), 6.98 (d, *J*=11.8 Hz, 1H), 5.38 (d, *J*=4.8 Hz, 1H), 4.82 (s, 1H), 4.70 (s, 1H), 3.71 (br. s., 4H), 3.48 (br. s., 4H), 3.25 (t, *J*=7.5 Hz, 4H), 2.82 (br. s., 1H), 2.46 - 2.30 (m, 2H), 1.72 (s, 3H), 1.16 (s, 3H), 1.08 (s, 3H), 1.03 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 2.24 - 0.82 (m, 22H).

Example A7

Preparation of 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-morpholinoethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



Step 1. Preparation of methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-morpholinoethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

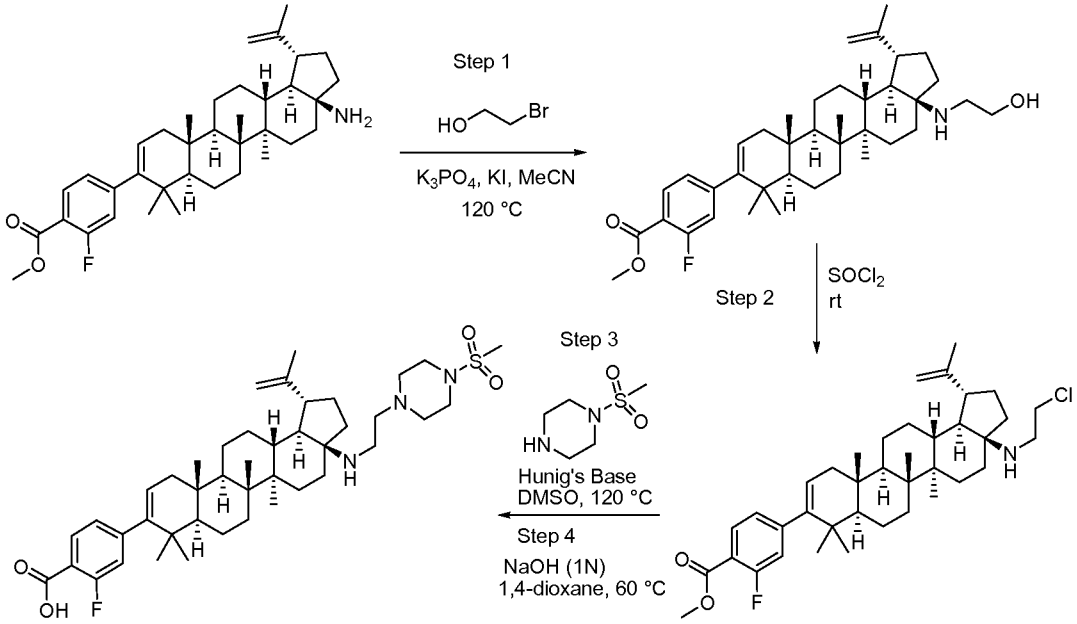
To a sealable flask containing methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-fluorobenzoate hydrochloride (0.1 g, 0.167 mmol) was added 4-(2-chloroethyl)morpholine hydrochloride (0.093 g, 0.501 mmol), phosphoric acid, potassium salt (0.156 g, 0.735 mmol) and potassium iodide (0.075 g, 0.451 mmol). The mixture was diluted with acetonitrile (3mL), was flushed with nitrogen, then the vial was sealed and heated to 120 °C. After heating the mixture for 16h, the mixture was cooled to rt. The crude product was adsorbed to silica gel then was purified by flash chromatography using a Thomson 12g silica gel column and a 0-5% methanol in dichloromethane gradient. The fractions containing the expected product were combined and concentrated under reduced pressure to give methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-morpholinoethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (77 mg, 0.114 mmol, 68.3 % yield) as an off-white foam. LCMS: m/e 675.5 $(M+H)^+$, 1.91 min (method 2).

Step 2. To a solution of methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-morpholinoethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

cyclopenta[a]chrysen-9-yl)benzoate (0.075 g, 0.111 mmol) in 1,4-Dioxane (1 mL) was added NaOH (1M) (0.5 mL, 0.500 mmol). The mixture was heated to 75 °C for 15h then was cooled to rt. The mixture was acidified with 1N HCl (3 mL) and was concentrated under reduced pressure. The residue was diluted with 15 mL of water and the solids that remained were collected by filtration and were washed with water then with ether. The compound was dissolved in DMF and methanol and was purified by prep HPLC. Fractions containing the expected product were combined and concentrated under reduced pressure to give 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-(2-morpholinoethylamino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (30 mg, 0.043 mmol, 38.8 % yield) as a white solid. LCMS: m/e 661.5 $(M+H)^+$, 1.67 min (method 2). ^{1}H NMR (500 MHz, *Acetic acid* d_4) ppm 7.96 (1 H, t, *J*=7.9 Hz), 7.09 (1 H, dd, *J*=8.2, 1.2 Hz), 7.03 (1 H, d, *J*=11.6 Hz), 5.42 (1 H, d, *J*=4.6 Hz), 4.86 (1 H, s), 4.74 (1 H, s), 3.89 - 3.99 (4 H, m), 3.53 - 3.69 (4 H, m), 3.29 (4 H, br. s.), 2.81 - 2.90 (1 H, m), 1.77 (3 H, s), 1.23 (3 H, s), 1.13 (3 H, s), 1.08 (3 H, s), 1.04 (3 H, s), 1.01 (3 H, s), 0.85 - 2.26 (22 H, m).

Example A8

Preparation of 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



Step 1. Preparation of methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-hydroxyethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

To a sealable flask containing methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-fluorobenzoate, HCl (1.0 g, 1.671 mmol) was added potassium iodide (0.694 g, 4.18 mmol), phosphoric acid, potassium salt (1.774 g, 8.36 mmol) and 2-bromoethanol (0.475 mL, 6.69 mmol). The mixture was diluted with acetonitrile (15 mL) and the vial was sealed and heated to 120 °C for 21h then was cooled to rt and was diluted with water (50 mL). The solids were collected by filtration then were washed with water. The solids were purified by flash chromatography in silica gel using a 0-5% methanol in dichloromethane gradient with 0.1% ammonium hydroxide added to the mixture The fractions containing the expected product were combined and were concentrated under reduced pressure. The product was repurified a second time using a 0-20% EtOAc in hexanes gradient with 0.1% TEA added to the mixture. The fractions containing the product combined and were concentrated under reduced pressure to give methyl 2-fluoro-4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-hydroxyethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.135g, 0.223 mmol, 13% yield) as an off-white solid. LCMS: m/e 606.7 $(M+H)^+$, 2.02 min (method 2).

Step 2. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-chloroethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-fluorobenzoate, HCl.

To a flask containing methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-hydroxyethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.135 g, 0.223 mmol) was added thionyl chloride (2.5 ml, 34.3 mmol). The clear, colorless solution was stirred at rt for 2.5h the reaction was carefully quenched with water (20 mL) and the solids that formed were collected by filtration and were washed with water. The expected product, methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-chloroethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-fluorobenzoate, HCl (0.173 g, 0.262 mmol, 117 % yield), was isolated as an off-white solid which was directly used in the next step with no additional purification. LCMS: m/e 624.6 $(M+H)^+$, 2.42 min (method 11).

Step 3. Preparation of methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

To a suspension of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-chloroethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

cyclopenta[a]chrysen-9-yl)-2-fluorobenzoate, HCl (0.147 g, 0.223 mmol) in DMSO (2 mL) was added 1-methanesulfonyl-piperazine (0.073 g, 0.446 mmol) and Hunig's Base (0.195 mL, 1.115 mmol). Upon addition of the base, the solids dissolved. The solution was heated to 120 °C for 2h then was cooled to rt, was diluted with water (20 mL) and was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with water (2 x 30 mL) then with brine (20 mL), then were dried over magnesium sulfate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography in silica gel using a 0-50% ethyl acetate in hexanes gradient with 0.1% triethyl amine added to the mixture. The fractions containing the expected product were combined and were concentrated under reduced pressure to give methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.056 g, 0.074 mmol, 33.4 % yield) as an off-white solid. LCMS: m/e 752.7 $(M+H)^+$, 1.95 min (method 2).

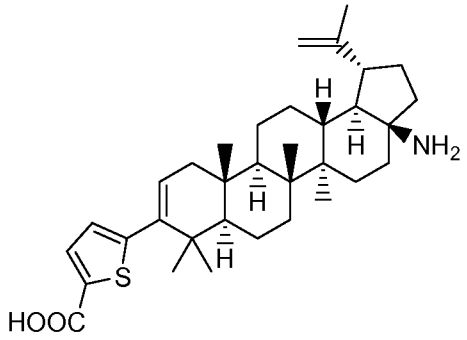
Step 4. To a solution of methyl 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (0.056 g, 0.074 mmol) in 1,4-dioxane (2 mL) was added NaOH (1N) (0.372 mL, 0.372 mmol). The mixture was heated to 60 °C for 6.5 h then was cooled to rt. The mixture was diluted with methanol and 1,4-dioxane, was filtered through a plug of glass wool and was purified by prep HPLC. The fractions containing the expected product were combined and were concentrated under reduced pressure to give 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (30.1 mg, 0.039 mmol, 52.0 % yield) as a white solid. LCMS: m/e 738.6 $(M+H)^+$, 1.66 min (method 2). ^{1}H NMR (400MHz, *Acetic acid* d_4) δ7.92 (t, *J*=7.9 Hz, 1H), 7.04 (dd, *J*=8.0, 1.5 Hz, 1H), 7.01 - 6.96 (m,

1H), 5.38 (d, *J*=5.0 Hz, 1H), 4.81 (s, 1H), 4.70 (s, 1H), 3.59 - 3.25 (m, 8H), 3.15 (br. s., 4H), 2.90 (s, 3H), 2.94 - 2.81 (m, 1H), 1.72 (s, 3H), 1.21 (s, 3H), 1.09 (s, 3H), 1.04 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 2.23 - 0.83 (m, 22H).

Section B. Amines (Continued)

Example B1

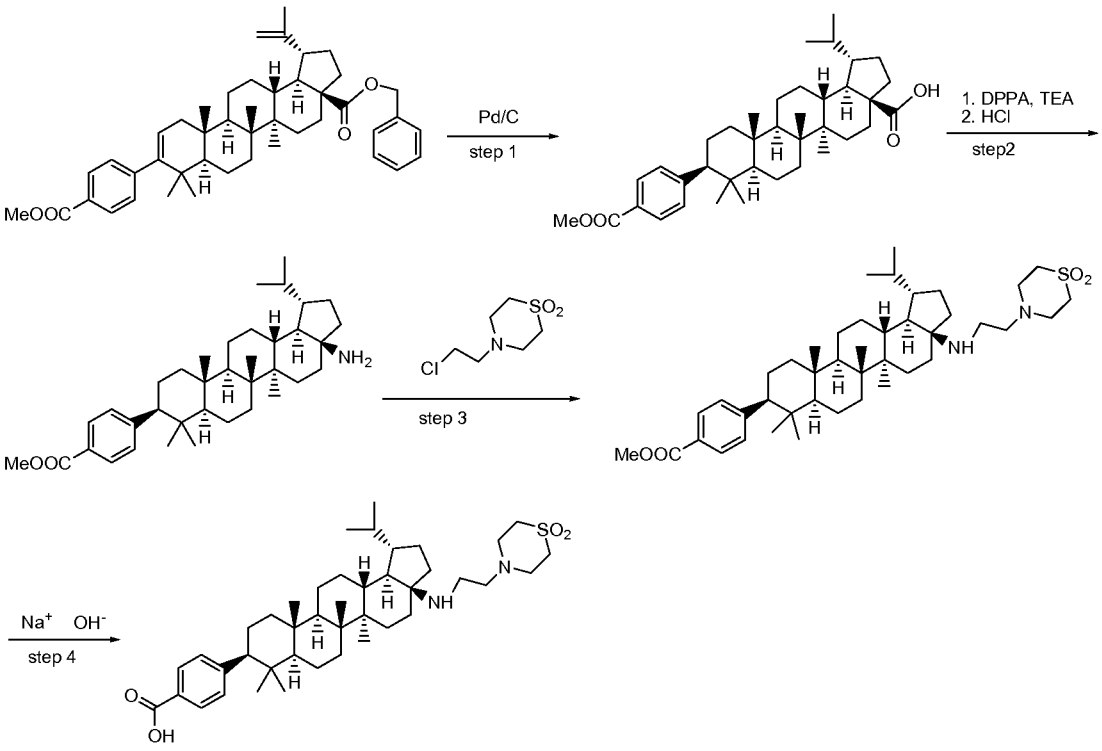
Preparation of 5-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)thiophene-2-carboxylic acid



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-fluorobenzoic acid using 5-(methoxycarbonyl)thiophen-2-ylboronic acid as the coupling reagent in Step 1. The product was isolated as a white solid (2.7 mg, 44%). LCMS: m/e 536.30 $(M+H)^+$, 2.25 min (method 10). ^1H NMR (500MHz, Acetic) δ 7.77 (d, *J*=4.0 Hz, 1H), 6.98 (d, *J*=3.7 Hz, 1H), 5.87 (d, *J*=4.3 Hz, 1H), 4.88 (s, 1H), 4.75 (s, 1H), 2.79 (td, *J*=10.5, 6.7 Hz, 1H), 2.35 - 2.13 (m, 4H), 1.98 - 1.85 (m, 4H), 1.83 - 1.07 (m, 14H), 1.77 (s, 3H), 1.19 (s, 3H), 1.14 (s, 3H), 1.14 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H).

Example B2

Preparation of 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



Step 1. Preparation of (1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-1-isopropyl-9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysene-3a-carboxylic acid

A mixture of palladium on carbon (67.4 mg, 0.063 mmol) and (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-benzyl 9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysene-3a-carboxylate (140 mg, 0.211 mmol) in methanol (2mL) was stirred at 20 °C under hydrogen at 1 atmosphere of pressure for 20 hours. The reaction mixture was filtered through a celite pad to remove Pd/C. The filtrates were concentrated under reduced pressure to provide the title compound as a white solid (100 mg, 82%). LCMS: m/e 577.33 $(M+H)^+$, 3.22 min (method 10).

Step 2. Preparation of methyl 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-amino-1-isopropyl-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate

A mixture of (1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-1-isopropyl-9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysene-3a-carboxylic acid (100 mg, 0.173 mmol), diphenyl phosphorazidate (0.056 mL, 0.260 mmol) and triethylamine (0.072 mL, 0.520 mmol) in toluene (4 mL) was refluxed for 18 hours. TLC indicated the consumption of starting material and the formation of desired product. The mixture was cooled to room temperature, filtered through a silica gel pad and the filtrates were concentrated under reduced pressure to produce the desired intermediate as colorless oil. To this intermediate (70 mg, 0.122 mmol) in THF (4 mL) was added HCl (0.037 mL, 1.220 mmol). The reaction mixture was stirred for 18 hours at room temperature. The reaction mixture was purified by chromatography in silica gel with 20-70% ethyl acetate/hexanes to provide the title compound as white solid (50mg, 50%). LCMS: m/e 548.49 $(M+H)^+$, 2.58 min (method 11).

Step 3. Preparation of methyl 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate

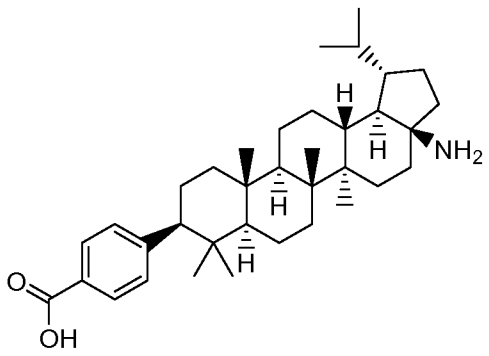
A mixture of methyl 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-amino-1-isopropyl-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (50 mg, 0.091 mmol), 4-(2-chloroethyl)thiomorpholine 1,1-dioxide (54.1 mg, 0.274 mmol), potassium phosphate (77 mg, 0.365 mmol) and potassium iodide (36.4 mg, 0.219 mmol) in acetonitrile (2 mL) was heated up at 120 °C for 20 hours. The reaction mixture was quenched with distilled water (5 mL), extracted with dichloromethane (3x 5 mL), the organic phases were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to provide the crude product as a yellow solid (40 mg, 62%). LCMS: m/e 709.53 $(M+H)^+$, 2.46 min (method 11).

Step 4. Preparation of 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

A mixture of methyl 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (40 mg, 0.056 mmol) and sodium hydroxide (0.564 mL, 0.564 mmol) in dioxane (1 mL) was heated up at 80 °C for 3 hours. The reaction mixture was filtered and purified by HPLC to provide the title compound as white solid (30 mg, 73%). LCMS: m/e 695.46 $(M+H)^+$, 2.55 min (method 10). ^{1}H NMR (500MHz, Acetic) δ 8.02 (d, *J*=8.5 Hz, 2H), 7.36 (d, *J*=8.5 Hz, 2H), 3.44 - 3.36 (m, 1H), 3.35 - 3.21 (m, 6H), 3.19 - 2.99 (m, 5H), 2.50 (dd, *J*=13.0, 2.9 Hz, 1H), 2.34 - 1.01 (m, 26H), 1.28 (s, 3H), 1.13 (s, 3H), 1.10 (s, 3H), 0.93 (d, *J*=6.7 Hz, 3H), 0.85 (d, *J*=6.7 Hz, 3H), 0.84 (s, 3H), 0.80 (s, 3H).

Example B3

Preparation of 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-amino-1-isopropyl-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

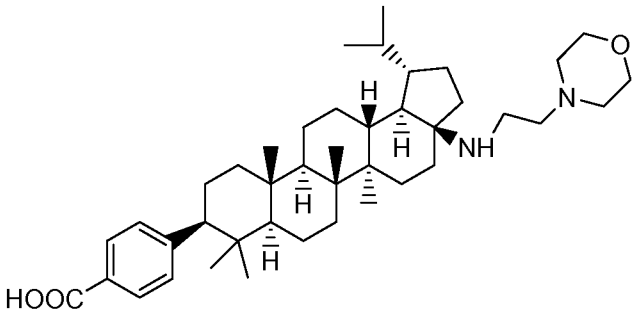


The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)-2-fluorobenzoic acid using methyl 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-amino-1-isopropyl-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate as the starting material in Step 5. The product was isolated as a white solid (12 mg, 47%).

LCMS: m/e 532.43 $(M-H)^-$, 2.37 min (method 10). ^{1}H NMR (500MHz, METHANOL-d_4) δ 7.84 (d, *J*=8.2 Hz, 2H), 7.19 (d, *J*=8.2 Hz, 2H), 2.42 (dd, *J*=13.0, 2.9 Hz, 1H), 2.18 (qd, *J*=13.3, 3.1 Hz, 1H), 2.07 - 1.24 (m, 25H), 1.16 (s, 3H), 1.07 (s, 3H), 1.03 (s, 3H), 0.93 (d, *J*=6.7 Hz, 3H), 0.83 (d, *J*=6.7 Hz, 3H), 0.79 (s, 3H), 0.74 (s, 3H).

Example B4

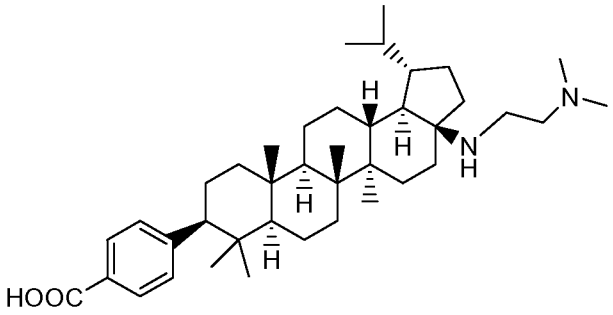
Preparation of 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-((2-morpholinoethyl)amino)icosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared following the method described above for the synthesis of 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 4-(2-chloroethyl)morpholine as the alkylating reagent in Step 3. The product was isolated as a colorless oil (4 mg, 39%). LCMS: m/e 647.58 $(M+H)^+$, 2.35 min (method 11). ^{1}H NMR (500MHz, Acetic) δ 8.02 (d, *J*=8.2 Hz, 2H), 7.36 (d, *J*=8.2 Hz, 2H), 3.94 (d, *J*=3.7 Hz, 4H), 3.73 - 3.44 (m, 4H), 3.27 (br. s., 4H), 2.50 (d, *J*=10.4 Hz, 1H), 2.32 - 1.01 (m, 26H), 1.21 (s, 3H), 1.12 (s, 3H), 1.08 (s, 3H), 0.93 (d, *J*=6.7 Hz, 3H), 0.86 (d, *J*=6.7 Hz, 3H), 0.83 (s, 3H), 0.79 (s, 3H).

Example B5

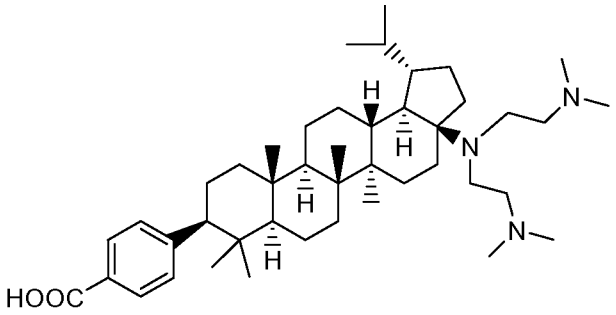
Preparation of 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-(dimethylamino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared following the method described above for the synthesis of 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 2-chloro-N,N-dimethylethanamine as the alkylating reagent in Step 3. The product was isolated as a colorless oil (0.9 mg, 37%). LCMS: m/e 605.56 $(M+H)^+$, 2.35 min (method 11). ^{1}H NMR (500MHz, Acetic) δ 8.02 (d, *J*=8.2 Hz, 2H), 7.36 (d, *J*=8.2 Hz, 2H), 3.89 - 3.72 (m, 2H), 3.70 - 3.55 (m, 1H), 3.07 - 2.91 (m, 1H), 3.00 (s, 6H), 2.60 - 2.40 (m, 1H), 2.34 - 1.04 (m, 26H), 1.18 (s, 3H), 1.12 (s, 3H), 1.07 (s, 3H), 0.93 (d, *J*=6.7 Hz, 3H), 0.86 (d, *J*=6.7 Hz, 3H), 0.83 (s, 3H), 0.79 (s, 3H).

Example B6

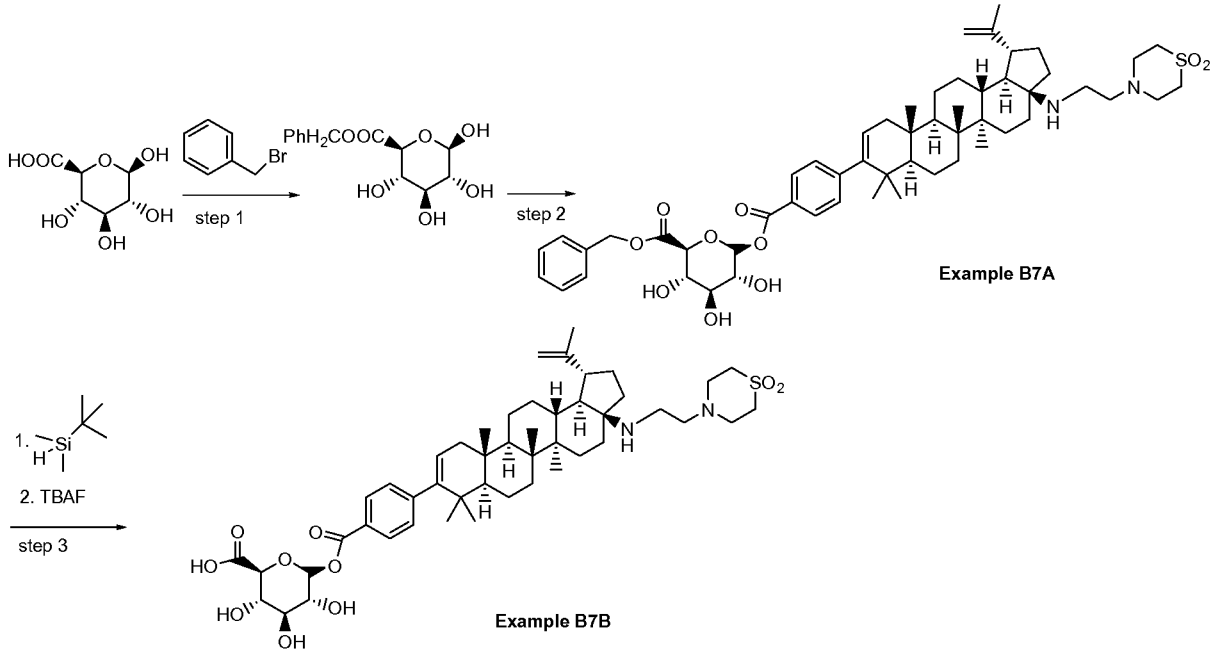
Preparation of 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-(bis(2-(dimethylamino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



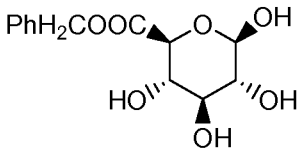
The title compound was obtained as a side product in the preparation 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-(dimethylamino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid. The product was isolated as a colorless oil (0.7 mg, 26%). LCMS: m/e 676.63 $(M+H)^+$, 2.33 min (method 11). ^{1}H NMR (500MHz, Acetic) δ 8.02 (d, *J*=8.2 Hz, 2H), 7.35 (d, *J*=8.2 Hz, 2H), 4.33 - 4.09 (m, 4H), 3.85 (br. s., 3H), 3.73 (br. s., 1H), 3.40 (s, 6H), 3.01 (s, 6H), 2.50 (d, *J*=14.0 Hz, 1H), 2.37 - 1.04 (m, 26H), 1.17 (s, 3H), 1.12 (s, 3H), 1.07 (s, 3H), 0.93 (d, *J*=6.7 Hz, 3H), 0.87 (d, *J*=6.7 Hz, 3H), 0.8s (s, 3H), 0.79 (s, 3H).

Example B7A and B7B

Preparation of (2S,3S,4S,5R,6R)-6-((4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoyl)oxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid



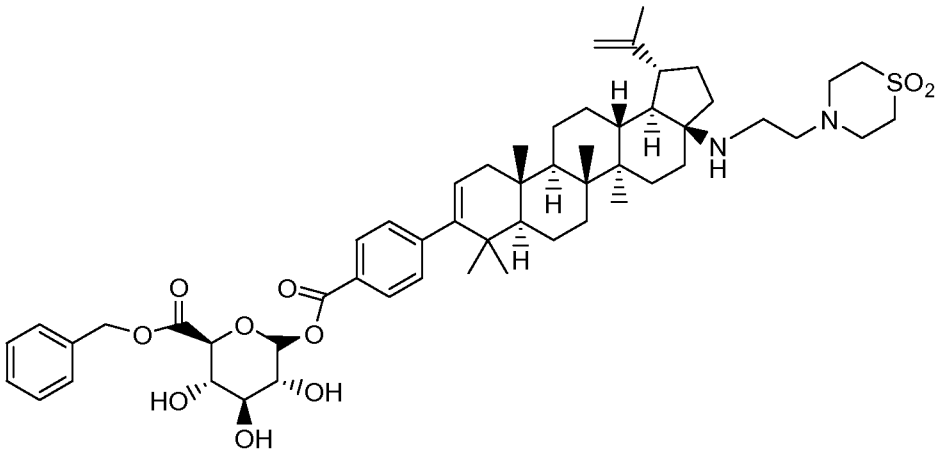
Step 1. Preparation of (2S,3S,4S,5R,6R)-benzyl 3,4,5,6-tetrahydroxytetrahydro-2H-pyran-2-carboxylate



To a solution of (2S,3S,4S,5R,6R)-3,4,5,6-tetrahydroxytetrahydro-2H-pyran-2-carboxylic acid (1 g, 5.15 mmol) and TBAF in THF (6.18 mL, 6.18 mmol) in DMF (7 mL) was slowly added (bromomethyl)benzene (0.925 g, 5.41 mmol) at 0°C. The clear solution was warmed up to room temperature slowly and let it stir for 17 hours. TLC indicated the reaction was completed (20% iPrOH/CH_2Cl_2). The solvent was removed and the reaction residue was purified by silica gel chromatography with 10-20% iPrOH/ CH_2Cl_2 to provide the desired product as a colorless oil (950 mg, 65%). LCMS: m/e 283.31 $(M-H)^-$, 2.55 min (method 10).

Step 2. Preparation of (2S,3S,4S,5R,6R)-benzyl 6-((4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

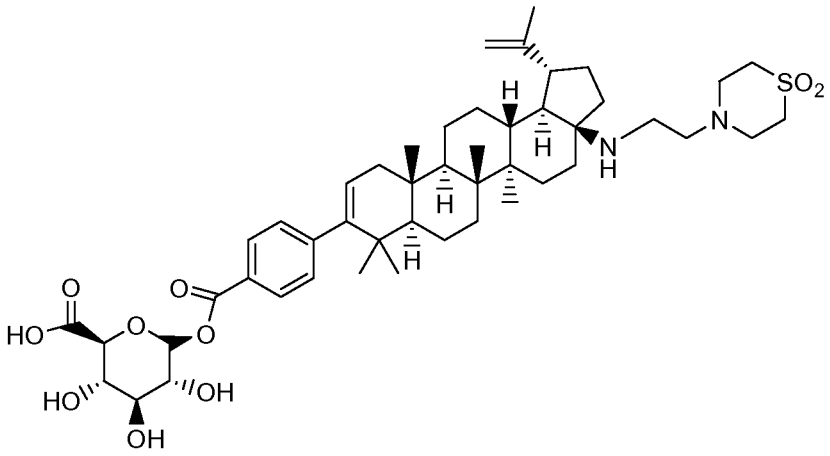
cyclopenta[a]chrysen-9-yl)benzoyl)oxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylate



A mixture of (2S,3S,4S,5R)-benzyl 3,4,5,6-tetrahydroxytetrahydro-2H-pyran-2-carboxylate (61.7 mg, 0.217 mmol), 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (100 mg, 0.145 mmol), HATU (88 mg, 0.232 mmol) and N-methylmorpholine (0.048 mL, 0.434 mmol) in dioxane (3 mL) was stirred overnight at room temperature. The reaction mixture was filtered, the clear solution was purified by prep HPLC with acetonitrile/water/ammonium acetate to provide the desired product as white solid (20 mg, 14%). LCMS: m/e 957.7 $(M+H)^+$, 2.36 min (method 6). ^{1}H NMR (500MHz, Acetic) δ 8.05 (d, *J*=8.2 Hz, 2H), 7.58 - 7.14 (m, 7H), 5.95 (d, *J*=7.6 Hz, 1H), 5.38 (d, *J*=4.6 Hz, 1H), 5.26 (s, 2H), 4.84 (s, 1H), 4.74 (s, 1H), 4.30 (d, *J*=9.5 Hz, 1H), 4.05 - 3.78 (m, 3H), 3.46 (d, *J*=11.9 Hz, 1H), 3.38 - 3.22 (m, 6H), 3.20 - 3.11 (m, 3H), 3.07 (br. s., 2H), 2.95 (dt, *J*=10.8, 5.5 Hz, 1H), 2.42 - 1.01 (m, 22H), 1.77 (s, 3H), 1.30 (s, 3H), 1.15 (s, 3H), 1.12 (s, 3H), 1.03 (s, 3H), 1.00 (s, 3H).

Step 3. Preparation of (2S,3S,4S,5R,6R)-6-((4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

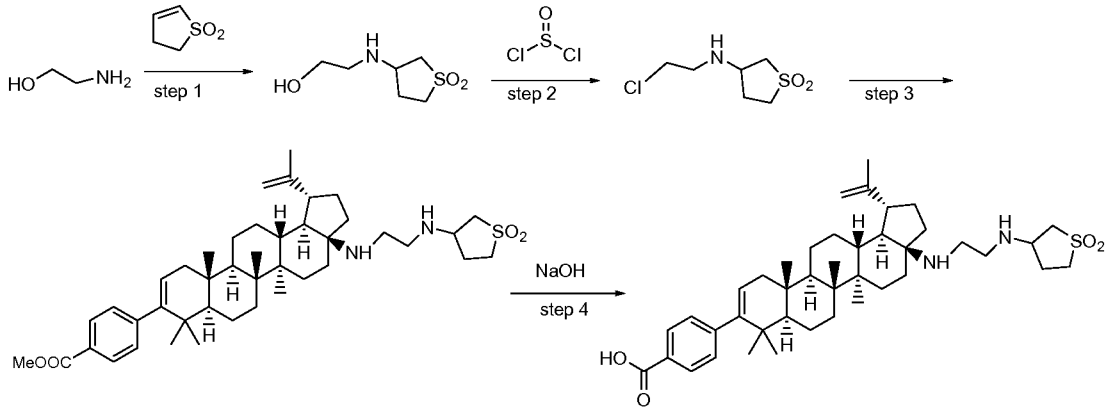
cyclopenta[a]chrysen-9-yl)benzoyl)oxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylic acid



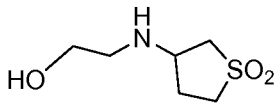
A mixture of (2S,3S,4S,5R,6R)-benzyl 6-((4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoyl)oxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-carboxylate (8 mg, 8.36 μmol), tert-butyldimethylsilane (1.943 mg, 0.017 mmol), palladium acetate (3.75 mg, 0.017 mmol) and triethylamine (5.82 μl, 0.042 mmol) in dichloroethane (1 mL) was heated up at 60 °C for 2 hours. The reaction mixture was cooled to room temperature, filtered and the filtrates were concentrated to provide the residue. To this residue in THF (1.0 mL) was added TBAF (10.93 mg, 0.042 mmol), the reaction mixture was stirred for 1 hours. The reaction mixture was then purified by prep. HPLC to provide the desired product as a colorless oil (4 mg, 52%). LCMS: m/e 867.69 $(M+H)^+$, 2.42 min (method 10). ^{1}H NMR (500MHz, Acetic) δ 8.06 (d, *J*=8.2 Hz, 2H), 7.31 (d, *J*=8.2 Hz, 2H), 5.96 (d, *J*=7.9 Hz, 1H), 5.37 (d, *J*=4.4 Hz, 1H), 4.84 (s, 1H), 4.74 (s, 1H), 4.40 - 4.16 (m, 1H), 4.02 - 3.76 (m, 3H), 3.46 (d, *J*=12.3 Hz, 1H), 3.37 - 3.22 (m, 6H), 3.20 - 3.11 (m, 3H), 3.07 (br. s., 2H), 3.00 - 2.82 (m, 1H), 2.37 - 1.03 (m, 22H), 1.76 (s, 3H), 1.29 (s, 3H), 1.14 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 0.99 (s, 3H).

Example B8

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-((1,1-dioxidotetrahydrothiophen-3-yl)amino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

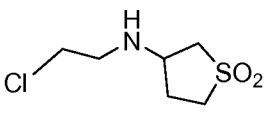


Step 1. Preparation of 3-((2-hydroxyethyl)amino)tetrahydrothiophene 1,1-dioxide



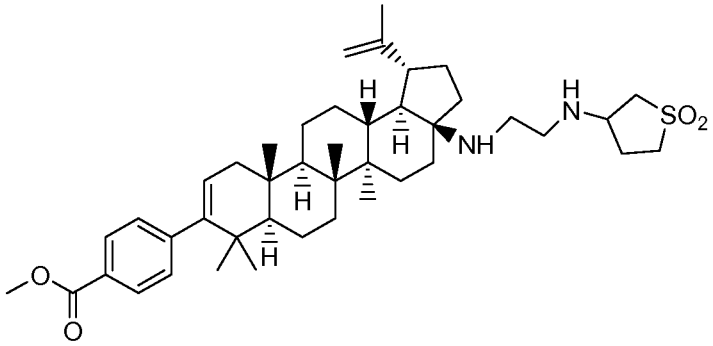
A mixture of 2-aminoethanol (310 mg, 5.08 mmol), triethylamine (514 mg, 5.08 mmol) and 2,3-dihydrothiophene 1,1-dioxide (200 mg, 1.693 mmol) in ethanol (3 mL) was heated up at 78 °C for 16 hours. TLC indicated the starting material was consumed and desired product was formed (30% methanol/ethyl acetate). The reaction mixture was concentrated under reduced pressure, the residue was purified by silica gel chromatography with 0-35% methanol/ethyl acetate to provide the title compound as a colorless oil (260 mg, 86%). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 3.78 - 3.56 (m, 3H), 3.38 - 3.21 (m, 2H), 3.14 - 3.00 (m, 1H), 2.94 (dd, *J*=13.3, 6.0 Hz, 1H), 2.85 - 2.68 (m, 2H), 2.53 - 2.34 (m, 1H), 2.22 - 2.03 (m, 1H).

Step 2. Preparation of 3-((2-chloroethyl)amino)tetrahydrothiophene 1,1-dioxide



A mixture of 3-((2-hydroxyethyl)amino)tetrahydrothiophene 1,1-dioxide (260 mg, 1.451 mmol) and sulfurous dichloride (863 mg, 7.25 mmol) in dichloroethane (3 mL) was heated up at 78 °C for 3 hours. The mixture was cooled to room temperature and concentrated under reduced pressure to provide the black oil. To this black oil was added THF(5 mL) and dichloromethane (5 mL), grey-white solid was observed. The solid was filtered and collected to provide the desired product as a grey solid (230 mg, 80%). LCMS: m/e 198.1 $(M+H)^+$, 0.60 min (method 6).

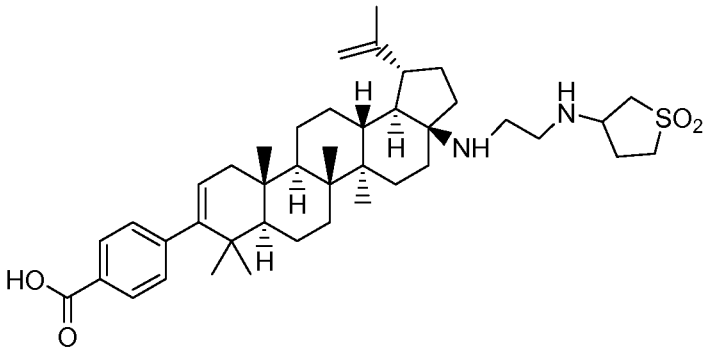
Step 3. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-((1,1-dioxidotetrahydrothiophen-3-yl)amino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (50 mg, 0.092 mmol), 3-((2-chloroethyl)amino)tetrahydrothiophene 1,1-dioxide (45.4 mg, 0.230 mmol), potassium phosphate (58.5 mg, 0.276 mmol) and potassium iodide (30.5 mg, 0.184 mmol) in acetonitrile (1 mL) was heated up at 120 °C for 18 hours. The reaction mixture was quenched with distilled water (3 mL), extracted with dichloromethane (3x 3 mL), the organic phases were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to provide the crude product as a white solid (40mg, 62%). LCMS: m/e 705.48 $(M+H)^+$, 2.44 min (method 11).

Step 4. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-((1,1-dioxidotetrahydrothiophen-3-yl)amino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-

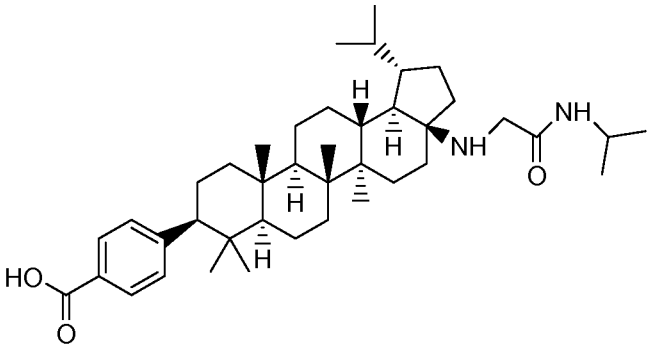
(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-((1,1-dioxidotetrahydrothiophen-3-yl)amino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (40 mg, 0.057 mmol) and sodium hydroxide (0.567 mL, 0.567 mmol) in dioxane (1 mL) was heated up at 78 °C for 3 hours. The reaction mixture was cooled to room temperature, filtered and the clear solution was purified by HPLC to provide the title compound as a white solid (26 mg, 63%). LCMS: m/e 691.46 $(M+H)^+$, 2.24 min (method 11). ^{1}H NMR (500MHz, Acetic) δ 8.04 (d, *J*=8.2 Hz, 2H), 7.30 (d, *J*=8.2 Hz, 2H), 5.37 (d, *J*=4.9 Hz, 1H), 4.87 (s, 1H), 4.75 (s, 1H), 4.06 (quin, *J*=7.7 Hz, 1H), 3.67 - 3.45 (m, 4H), 3.44 - 3.34 (m, 1H), 3.33 - 3.11 (m, 2H), 2.92 - 2.80 (m, 1H), 2.77 - 2.59 (m, 1H), 2.42 - 2.29 (m, 1H), 2.26 - 1.02 (m, 23H), 1.77 (s, 3H), 1.22 (s, 3H), 1.13 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H).

Example B9

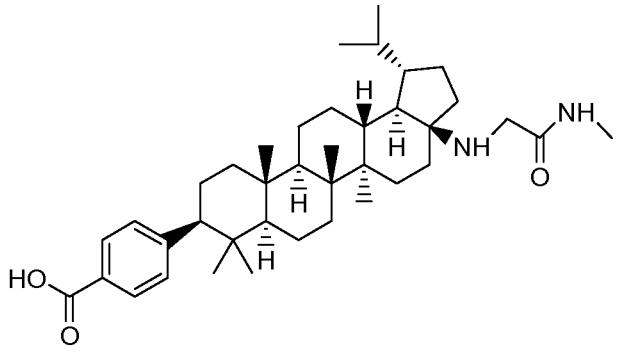
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-((1,1-dioxidotetrahydrothiophen-3-yl)amino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



A mixture of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(isopropylamino)-2-oxoethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid (15 mg, 0.024 mmol) and Pd/C (7.61 mg, 7.16 μmol) in methanol (1 mL) and ethyl acetate (1.000 mL) was stirred for 12 hours at room temperature under hydrogen at 1 atmosphere of pressure. The reaction mixture was filtered and the solution was purified by HPLC to provide the title compound as a white solid (6 mg, 38%). LCMS: m/e 633.48 $(M+H)^+$, 2.62 min (method 10). ^{1}H NMR (500MHz, Acetic) δ 8.02 (d, *J*=8.2 Hz, 2H), 7.36 (d, *J*=8.5 Hz, 2H), 4.17 (d, *J*=15.6 Hz, 1H), 4.09 (quin, *J*=6.6 Hz, 1H), 3.82 (d, *J*=15.3 Hz, 1H), 2.50 (dd, *J*=13.1, 2.7 Hz, 1H), 2.34 - 1.05 (m, 26H), 1.27 (s, 3H), 1.19 (s, 3H), 1.18 (s, 3H), 1.13 (s, 3H), 1.08 (s, 3H), 0.94 (d, *J*=6.7 Hz, 3H), 0.86 (d, *J*=6.7 Hz, 3H), 0.84 (s, 3H), 0.80 (s, 3H).

Example B10

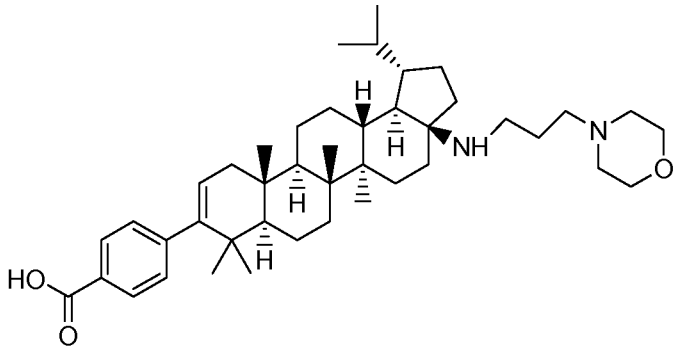
Preparation of 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-((2-(methylamino)-2-oxoethyl)amino)icosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared following the method described above for the synthesis 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-((1,1-dioxidotetrahydrothiophen-3-yl)amino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(methylamino)-2-oxoethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid as the starting material. The product was isolated as a white solid (3 mg, 28%). LCMS: m/e 605.45 $(M+H)^+$, 2.58 min (method 10). ^{1}H NMR (500MHz, Acetic) δ 8.02 (d, *J*=8.2 Hz, 2H), 7.36 (d, *J*=8.2 Hz, 2H), 4.22 (d, *J*=15.6 Hz, 1H), 3.85 (d, *J*=15.6 Hz, 1H), 2.87 (s, 3H), 2.50 (dd, *J*=13.1, 2.4 Hz, 1H), 2.35 - 1.02 (m, 26H), 1.28 (s, 3H), 1.13 (s, 3H), 1.08 (s, 3H), 0.95 (d, *J*=6.7 Hz, 3H), 0.87 (d, *J*=6.7 Hz, 3H), 0.84 (s, 3H), 0.80 (s, 3H).

Example B11

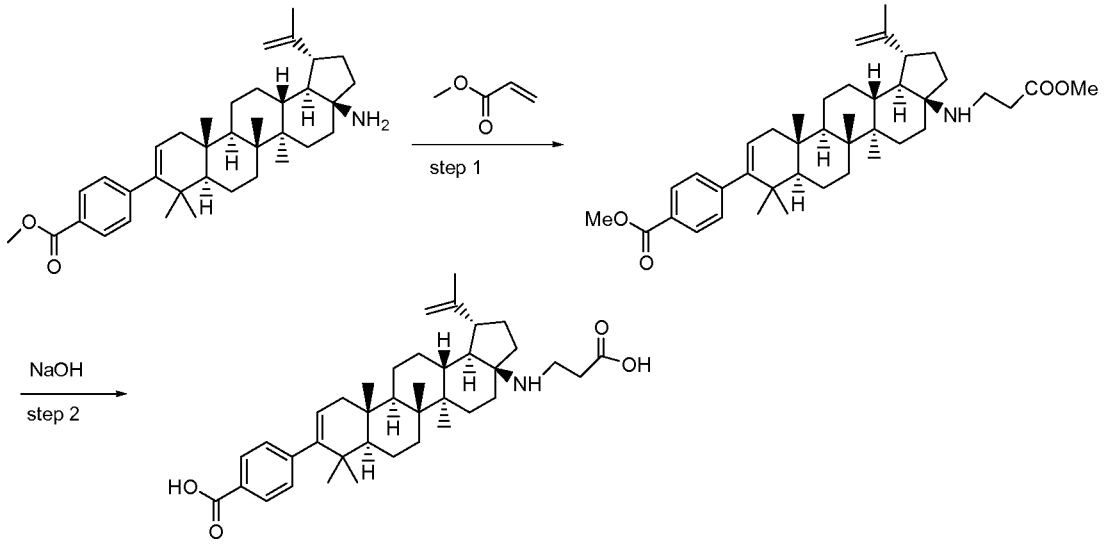
Preparation of 4-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-((3-morpholinopropyl)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared following the method described above for the synthesis 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-((1,1-dioxidotetrahydrothiophen-3-yl)amino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((3-morpholinopropyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid as the starting material. The product was isolated as a white solid (5 mg, 40%). LCMS: m/e 659.55 $(M+H)^+$, 2.86 min (method 10). ^{1}H NMR (500MHz, Acetic) δ 8.04 (d, *J*=8.5 Hz, 2H), 7.30 (d, *J*=8.2 Hz, 2H), 5.38 (d, *J*=4.6 Hz, 1H), 3.98 (br. s., 4H), 3.47 - 3.14 (m, 6H), 2.58 - 2.34 (m, 1H), 2.30 - 1.04 (m, 27H), 1.21 (s, 3H), 1.11 (s, 3H), 1.11 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H), 0.93 (d, *J*=6.7 Hz, 4H), 0.86 (d, *J*=6.7 Hz, 3H).

Example B12

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-carboxyethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((3-methoxy-3-oxopropyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate

A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (20 mg, 0.037 mmol), methyl acrylate (0.013 mL, 0.147 mmol) and triethylamine (0.026 mL, 0.184 mmol) in ethanol (1 mL) was refluxed for 5 hours. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure to provide the desired product as a yellow oil (15 mg 65%). LCMS: m/e 630.43 $(M+H)^+$, 3.81 min (method 10).

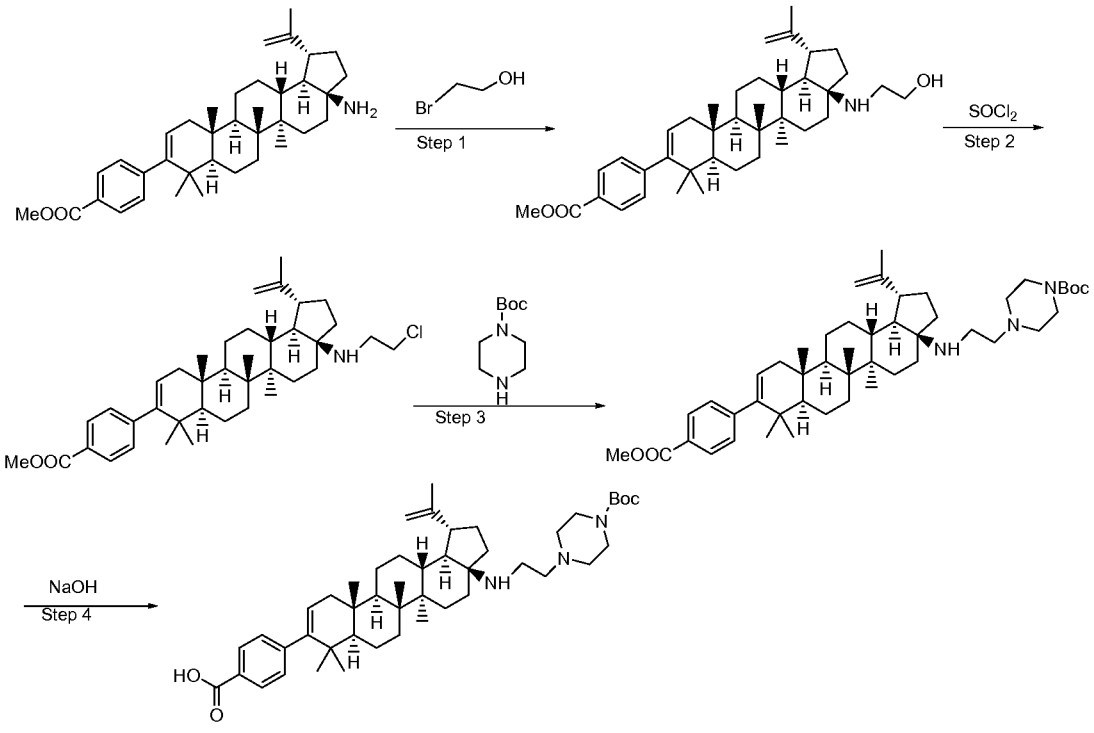
Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-carboxyethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((3-methoxy-3-oxopropyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (15 mg, 0.024 mmol) and sodium hydroxide (0.238 mL, 0.238 mmol) in dioxane (1 mL) was heated up at 80 °C for 3 hours. The

reaction mixture was cooled to room temperature and then filtered, the clear solution was purified by HPLC to provide the title compound as a white solid (5 mg, 33%). LCMS: m/e 602.43 $(M+H)^+$, 2.25 min (method 10). ^{1}H NMR (500MHz, Acetic) δ 8.04 (d, *J*=8.2 Hz, 2H), 7.30 (d, *J*=8.2 Hz, 2H), 5.37 (d, *J*=4.9 Hz, 1H), 4.86 (s, 1H), 4.74 (s, 1H), 3.39 (t, *J*=4.4 Hz, 2H), 3.17 - 3.02 (m, 1H), 2.98 - 2.80 (m, 2H), 2.31 - 1.02 (m, 22H), 1.77 (s, 3H), 1.24 (s, 3H), 1.14 (s, 3H), 1.09 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H).

Example B13

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(tert-butoxycarbonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-hydroxyethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate

A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (1500 mg, 2.76 mmol), 2-bromoethanol (1034 mg, 8.27 mmol), potassium phosphate (1756 mg, 8.27 mmol) and potassium iodide (916 mg, 5.52 mmol) in acetonitrile (10 mL) was heated up at 120 °C for 15 hours. The reaction mixture was poured into distilled water (40 mL). The white precipitate was filtered and washed with distilled water (100 mL). The white solid was dried under vacuum to provide the desired product (1.4g, 86%). LCMS: m/e 588.5 $(M+H)^+$, 2.40 min (method 11).

Step 2. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-chloroethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate

A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-hydroxyethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (1400 mg, 2.381 mmol) and thionyl chloride (1.738 mL, 23.81 mmol) in dichloroethane (15 mL) was heated up at 60 °C for 2 hours. The reaction mixture was concentrated under reduced pressure to provide the desired product as brown solid (1.3g, 90%). LCMS: m/e 606.48 $(M+H)^+$, 2.46 min (method 11).

Step 3. Preparation of tert-butyl 4-(2-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-yl)amino)ethyl)piperazine-1-carboxylate

A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-chloroethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (230 mg, 0.379 mmol), Hunig's Base (0.331 mL,

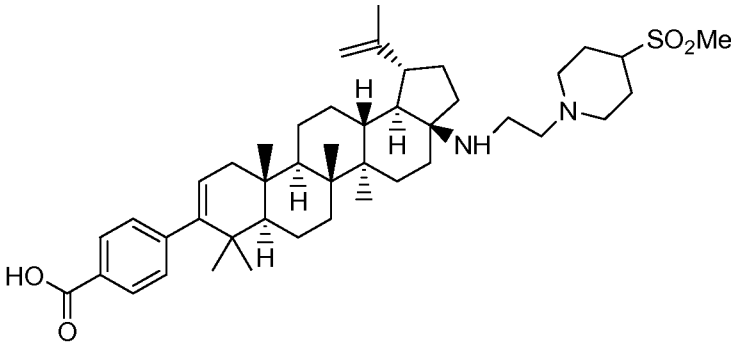
1.895 mmol)and tert-butyl piperazine-1-carboxylate (141 mg, 0.759 mmol) in DMSO (3 mL) was heated up at 120 °C for 1 hour. The reaction mixture was quenched with water (10 mL), extracted with ethyl acetate (3x8 mL), the extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to provide the crude, the crude was purified by silica gel chromatography with 0-30% ethyl acetate/hexanes to provide the desired product as a white solid (150 mg, 52%). LCMS: m/e 756.66 $(M+H)^+$, 2.50 min (method 11).

Step 4. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(tert-butoxycarbonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

A mixture of tert-butyl 4-(2-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-yl)amino)ethyl)piperazine-1-carboxylate (4 mg, 5.29 μmol) and sodium hydroxide (0.053 mL, 0.053 mmol) in dioxane (1 mL) was heated up at 80 °C for 3 hours. The reaction mixture was filtered and the clear solution was purified by HPLC to provide the desired product as white solid (1.6 mg, 39%). LCMS: m/e 742.65 $(M-H)^-$, 2.68 min (method 10). ^{1}H NMR (500MHz, Acetic) δ 8.03 (d, *J*=8.2 Hz, 2H), 7.30 (d, *J*=8.2 Hz, 2H), 5.37 (d, *J*=4.6 Hz, 1H), 4.86 (s, 1H), 4.75 (s, 1H), 3.73 (br. s., 4H), 3.66 - 3.45 (m, 4H), 3.21 (br. s., 4H), 2.98 - 2.75 (m, 1H), 2.31 - 1.00 (m, 22H), 1.77 (s, 3H), 1.50 (s, 9H), 1.23 (s, 3H), 1.13 (s, 3H), 1.09 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H).

Example B14

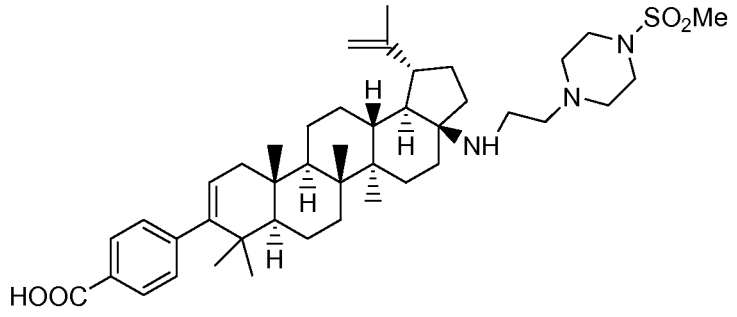
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(tert-butoxycarbonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 4-(methylsulfonyl)piperidine as the alkylating reagent in Step 3. The product was isolated as a white solid (200 mg, 84%). LCMS: m/e 719.58 $(M+H)^+$, 2.31 min (method 11). ^{1}H NMR (500MHz, Acetic) δ 8.04 (d, *J*=8.5 Hz, 2H), 7.30 (d, *J*=8.2 Hz, 2H), 5.37 (d, *J*=4.6 Hz, 1H), 4.87 (s, 1H), 4.75 (s, 1H), 3.76-3.70 (m, 2H), 3.68 - 3.54 (m, 4H), 3.48 - 3.29 (m, 1H), 3.18 - 3.03 (m, 2H), 3.02 (s, 3H), 2.84 (td, *J*=11.8, 4.7 Hz, 1H), 2.46 - 1.03 (m, 26H), 1.77 (s, 3H), 1.22 (s, 3H), 1.14 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H).

Example B15

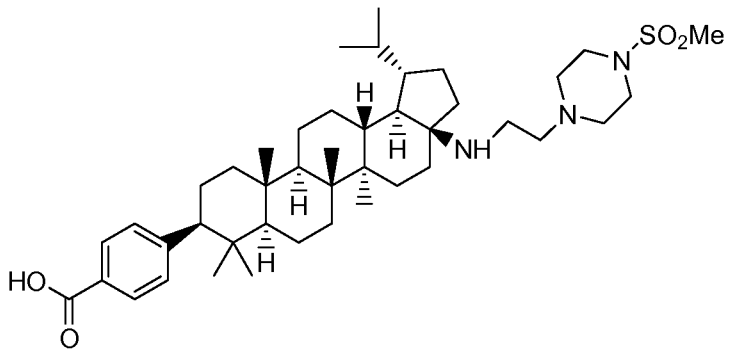
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(tert-butoxycarbonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 1-(methylsulfonyl)piperazine as the alkylating reagent in Step 3. The product was isolated as a white solid (220 mg, 89%). LCMS: m/e 720.58 $(M+H)^+$, 2.25 min (method 11). ^{1}H NMR (500MHz, Acetic) δ 8.04 (d, *J*=8.2 Hz, 2H), 7.30 (d, *J*=8.2 Hz, 2H), 5.37 (d, *J*=4.6 Hz, 1H), 4.86 (s, 1H), 4.74 (s, 1H), 3.74 - 3.38 (m, 7H), 3.37 - 3.25 (m, 1H), 3.17 (br. s., 4H), 2.94 (s, 3H), 2.91 - 2.80 (m, 1H), 2.35 - 1.01 (m, 22H), 1.77 (s, 3H), 1.26 (s, 3H), 1.14 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H).

Example B16

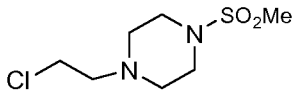
Preparation of 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperazin-1-yl)ethyl)amino)icosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared following the method described in Example B2 for the synthesis of 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 1-(2-chloroethyl)-4-(methylsulfonyl)piperazine (prepared as described below) as the alkylating reagent in Step 3. The product was isolated as a white solid (11 mg, 56%).

LCMS: m/e 724.6 $(M+H)^+$, 2.44 min (method 10). ^1H NMR (500MHz, Acetic) δ 8.02 (d, *J*=8.2 Hz, 2H), 7.36 (d, *J*=8.2 Hz, 2H), 3.63 - 3.29 (m, 7H), 3.25 - 3.14 (m, 1H), 3.13 - 2.99 (m, 4H), 2.93 (s, 3H), 2.50 (dd, *J*=13.0, 2.6 Hz, 1H), 2.32 - 0.98 (m, 26H),1.25 (s, 3H), 1.12 (s, 3H), 1.08 (s, 3H), 0.93 (d, *J*=6.7 Hz, 3H), 0.86 (d, *J*=6.7 Hz, 3H), 0.83 (s, 3H), 0.79 (s, 3H).

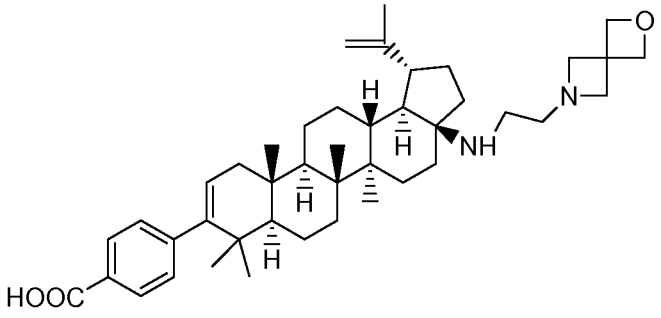
Preparation of 1-(2-chloroethyl)-4-(methylsulfonyl)piperazine



A mixture of 1-(methylsulfonyl)piperazine (250 mg, 1.522 mmol), potassium carbonate (1262 mg, 9.13 mmol) and 1-bromo-2-chloroethane (1092 mg, 7.61 mmol) in acetonitrile (5 mL) was stirred for 6 hours at room temperature. LCMS indicated the formation of desired product. The reaction mixture was filtered to remove the white precipitate, then quenched with distilled water (10 mL), extracted with ethyl acetate (3x8 mL), the extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to provide the clean desired product as white solid (100 mg, 29%). LCMS: m/e 227.15 $(M+H)^+$, 1.21 min (method 10).

Example B17

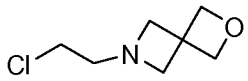
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-((1,1-

dioxidotetrahydrothiophen-3-yl)amino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 6-(2-chloroethyl)-2-oxa-6-azaspiro[3.3]heptane (prepared as described below) as the alkylating reagent in Step 3. The product was isolated as a white solid (1.1 mg, 18%). LCMS: m/e 655.53 $(M+H)^+$, 2.29 min (method 11). ^{1}H NMR (500MHz, Acetic) δ 8.04 (d, *J*=8.2 Hz, 2H), 7.30 (d, *J*=8.5 Hz, 2H), 5.37 (d, *J*=4.9 Hz, 1H), 4.93 (s., 4H), 4.86 (s, 1H), 4.75 (br. s., 1H), 4.71 - 4.32 (m, 4H), 4.05 - 3.86 (m, 2H), 3.70 - 3.40 (m, 2H), 3.00 - 2.66 (m, 1H), 2.25 - 1.05 (m, 22H), 1.76 (s, 3H), 1.18 (s, 3H), 1.13 (s, 3H), 1.08 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H).

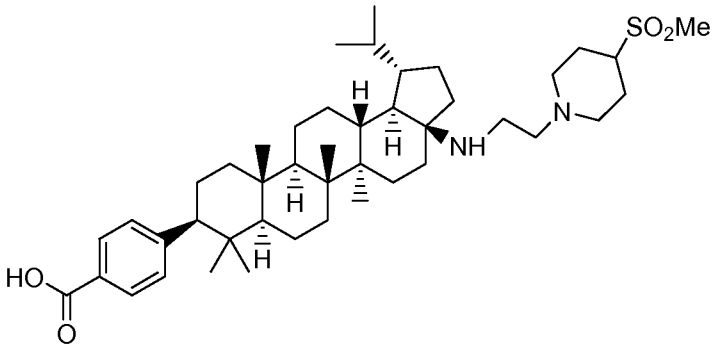
Preparation of 6-(2-chloroethyl)-2-oxa-6-azaspiro[3.3]heptane



The title compound was prepared following the method described above for the synthesis of 1-(2-chloroethyl)-4-(methylsulfonyl)piperazine using 2-oxa-6-azaspiro[3.3]heptane as the starting reagent. The product was isolated as colorless oil (10 mg, 12%). LCMS: m/e 162.15 $(M+H)^+$, 0.87 min (method 10).

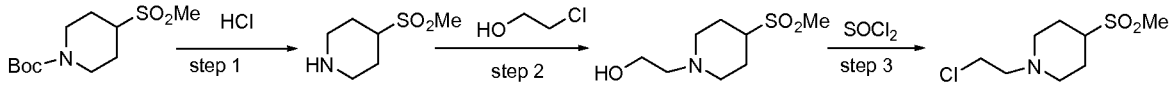
Example B18

Preparation of 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-1-isopropyl-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(methylsulfonyl)piperidin-1-yl)ethyl)amino)icosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

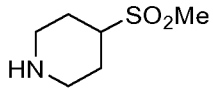


The title compound was prepared following the method described in above for the synthesis of 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidothiomorpholino)ethyl)amino)-1-isopropyl-5a,5b,8,8,11a-pentamethylicosahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 1-(2-chloroethyl)-4-(methylsulfonyl)piperidine (prepared as described below) as the alkylating reagent in Step 3. The product was isolated as a white solid (24 mg, 36%). LCMS: m/e 723.56 $(M+H)^+$, 2.28 min (method 11). ^{1}H NMR (500MHz, Acetic) δ 8.02 (d, *J*=8.2 Hz, 2H), 7.36 (d, *J*=8.2 Hz, 2H), 3.77 - 3.63 (m, 2H), 3.62 - 3.54 (m, 3H), 3.50 (d, *J*=5.5 Hz, 1H), 3.35 (td, *J*=11.4, 3.7 Hz, 1H), 3.08 - 2.89 (m, 2H), 3.02 (s, 3H), 2.50 (d, *J*=13.1 Hz, 1H), 2.42 - 2.29 (m, 2H), 2.28 - 1.03 (m, 28H), 1.21 (s, 3H), 1.12 (s, 3H), 1.08 (s, 3H), 1.01 (d, *J*=11.3 Hz, 1H), 0.93 (d, *J*=6.7 Hz, 4H), 0.86 (d, *J*=6.7 Hz, 4H), 0.83 (s, 3H), 0.79 (s, 3H).

Preparation of 1-(2-chloroethyl)-4-(methylsulfonyl)piperidine

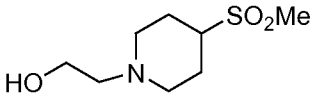


Step 1. Preparation of 4-(methylsulfonyl)piperidine



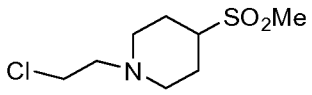
A mixture of tert-butyl 4-(methylsulfonyl)piperidine-1-carboxylate (1.5 g, 5.70 mmol) and hydrogen chloride (7.12 mL, 28.5 mmol) in THF (20 mL) was stirred at 20 °C for 15 hours. TLC indicated the formation of desired product, the reaction mixture was filtered and the pale yellow solid was collected to provide desired product (1 g, 88%). LCMS: m/e 163.96 $(M+H)^+$, 0.25 min (method 10).

Step 2. Preparation of 2-(4-(methylsulfonyl)piperidin-1-yl)ethanol



A mixture of 4-(methylsulfonyl)piperidine hydrochloride (900 mg, 4.51 mmol), 2-bromoethanol (1126 mg, 9.01 mmol) and potassium carbonate (1869 mg, 13.52 mmol) in acetonitrile (4 mL) was heated up at 60 °C for 13 hours. The reaction mixture was cooled to room temperature and concentrated under reduced pressure to provide the crude, the crude was purified by 0-35% ethyl acetate/methanol to provide the desired product as colorless oil (620 mg, 66%). LCMS: m/e 208.1 $(M+H)^+$, 0.27 min (method 6).

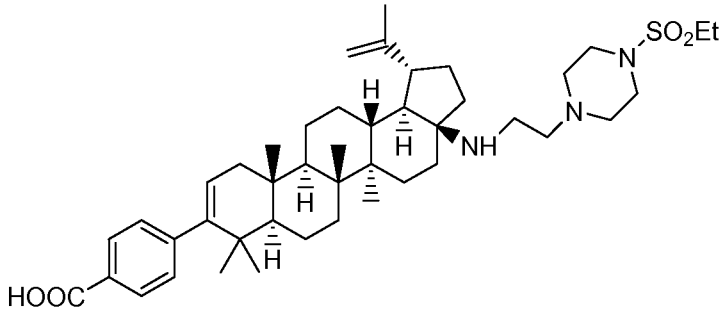
Step 3. Preparation of 1-(2-chloroethyl)-4-(methylsulfonyl)piperidine



A mixture of 2-(4-(methylsulfonyl)piperidin-1-yl)ethanol (620 mg, 2.99 mmol) and thionyl chloride (1.092 mL, 14.95 mmol) in dichloroethane (5 mL) was heated up at 74 °C for 4 hours. The reaction mixture was concentrated under reduced pressure to provide the crude, to the crude was added THF (10 mL), the grey precipitate was observed and collected. The solid was dried under vacuum for 20 hour to provide the desired product as grey solid (400mg, 59%). LCMS: m/e 226.1 $(M+H)^+$, 1.00 min (method 6).

Example B19

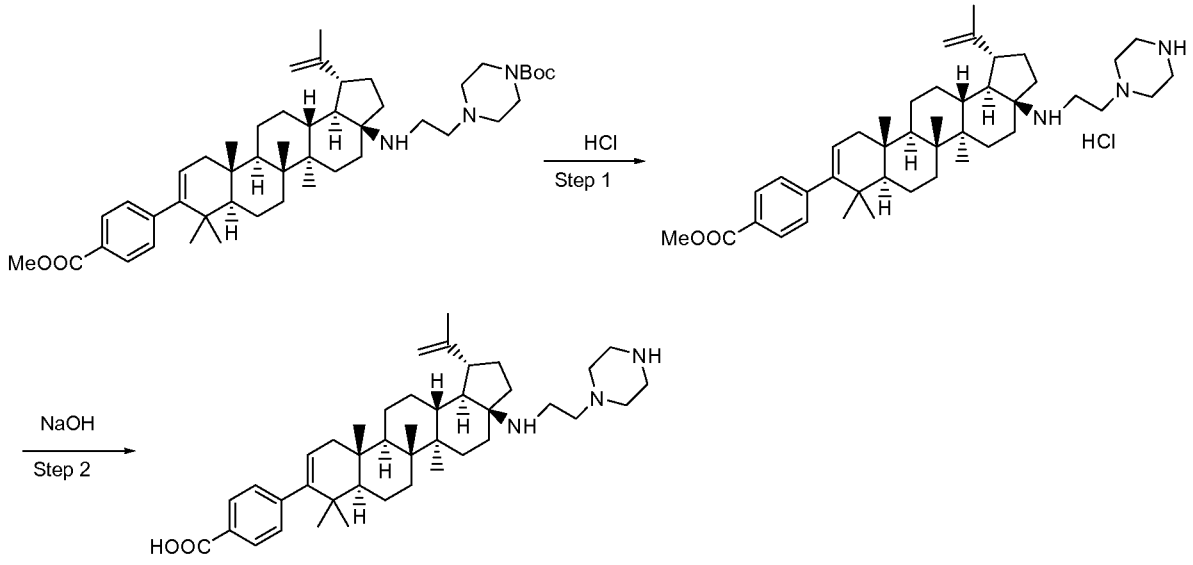
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(ethylsulfonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared following the method described in above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(tert-butoxycarbonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 1-(ethylsulfonyl)piperazine as the alkylating reagent in Step 3. The product was isolated as a white solid (11 mg, 53%). LCMS: m/e 734.56 $(M+H)^+$, 2.28 min (method 11). ^{1}H NMR (400MHz, Acetic) δ 7.99 (d, *J*=8.5 Hz, 2H), 7.26 (d, *J*=8.3 Hz, 2H), 5.34 (d, *J*=4.5 Hz, 1H), 4.81 (s, 1H), 4.70 (s, 1H), 3.63 - 3.28 (m, 7H), 3.26 - 3.16 (m, 1H), 3.14 - 2.98 (m, 6H), 2.95 - 2.75 (m, 1H), 2.33 - 1.06 (m, 22H), 1.73 (s, 3H), 1.32 (t, *J*=7.4 Hz, 3H), 1.23 (s, 3H), 1.10 (s, 3H), 1.06 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H).

Example B20

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate hydrochloride

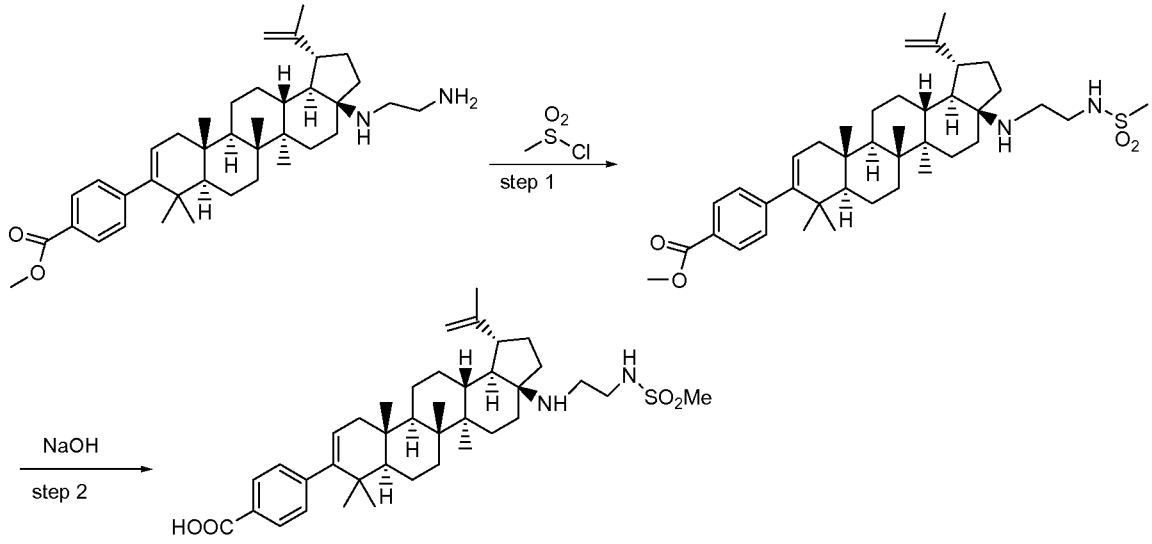
A mixture of tert-butyl 4-(2-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(methoxycarbonyl)phenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-yl)amino)ethyl)piperazine-1-carboxylate (150 mg, 0.198 mmol) and HCl (0.248 mL, 0.992 mmol) in THF (4 mL) was stirred at 20 °C for 18 hours. The reaction mixture was concentrated under reduced pressure to provide the desired product as brown solid (120 mg, 87%). LCMS: m/e 656.7 $(M+H)^+$, 1.62 min (method 11).

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (7.5 mg, 0.011 mmol) and sodium hydroxide (0.057 mL, 0.057 mmol) in dioxane (1 mL) was heated up at 80 °C for 3 hours. The reaction mixture was filtered and the clear solution was purified by HPLC to provide the desired product as white solid (2.3 mg, 31%). LCMS: m/e 642.62 $(M+H)^+$, 2.29 min (method 11). ^{1}H NMR (400MHz, Acetic) δ 8.00 (d, *J*=8.5 Hz, 2H), 7.26 (d, *J*=8.5 Hz, 2H), 5.34 (d, *J*=4.8 Hz, 1H), 4.80 (s, 1H), 4.70 (s, 1H), 3.59 - 3.28 (m, 6H), 3.25 - 3.11 (m, 1H), 3.09 - 2.73 (m, 6H), 2.31 - 1.15 (m, 22H), 1.73 (s, 3H), 1.26 (s, 3H), 1.11 (s, 3H), 1.08 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H).

Example B21

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(methylsulfonamido)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(methylsulfonamido)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

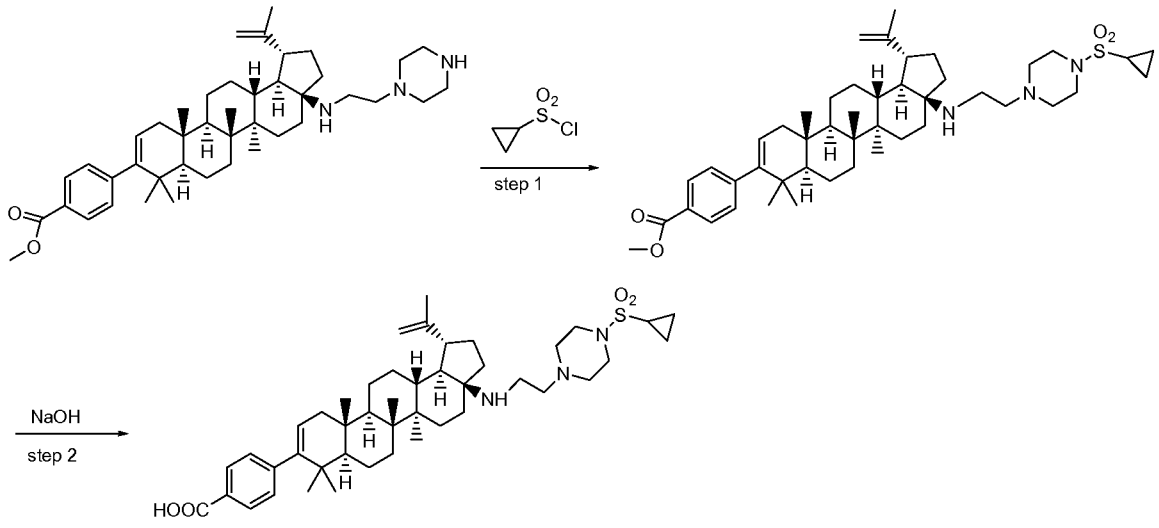
To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-aminoethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (15 mg, 0.026 mmol) and Hunig's Base (0.013 mL, 0.077 mmol) in dichloromethane (1 mL) was added methanesulfonyl chloride (3.81 mg, 0.033 mmol) in dichloromethane (1 mL). The reaction mixture was stirred at 20 °C for 2 hours. The reaction mixture was diluted with distilled water (3 mL), extracted with dichloromethane (3x3 mL), the extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to provide the desired product as a yellow solid (15 mg, 88%). LCMS: m/e 665.55 $(M+H)^+$, 2.44 min (method 11).

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(methylsulfonamido)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid.

A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(methylsulfonamido)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (15 mg, 0.023 mmol) and sodium hydroxide (0.113 mL, 0.113 mmol) in dioxane (1 mL) was heated up at 80 °C for 3 hours. The reaction mixture was filtered and the clear solution was purified by HPLC to provide the title compound as a white solid (7 mg, 45%). LCMS: m/e 651.52 $(M+H)^+$, 2.28 min (method 11). ^{1}H NMR (400MHz, Acetic) δ 7.99 (d, *J*=8.3 Hz, 2H), 7.26 (d, *J*=8.3 Hz, 2H), 5.33 (d, *J*=4.5 Hz, 1H), 4.81 (s, 1H), 4.71 (s, 1H), 3.53 (br. s., 2H), 3.36 - 3.26 (m, 2H), 3.07 (s, 3H), 2.96 - 2.75 (m, 1H), 2.30 - 2.11 (m, 3H), 1.84 - 1.06 (m, 19H), 1.74 (s, 3H), 1.22 (s, 3H), 1.10 (s, 3H), 1.06 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H).

Example B22

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(cyclopropylsulfonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(cyclopropylsulfonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-

1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate.

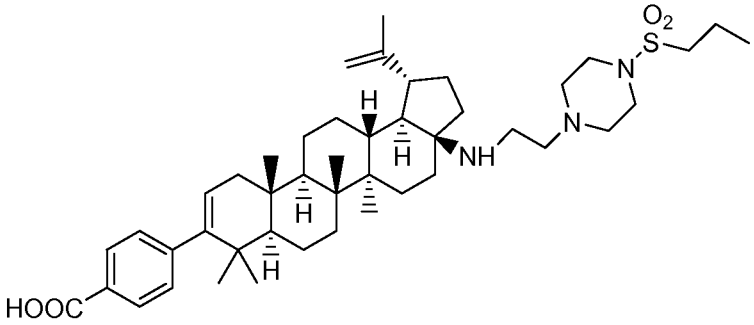
To a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (26 mg, 0.040 mmol) and Hunig's Base (0.035 mL, 0.198 mmol) in dichloromethane (1 mL) was added a solution of cyclopropanesulfonyl chloride (11.14 mg, 0.079 mmol) in dichloromethane (1 mL) at room temperature. The reaction mixture was stirred for 2 hours at 20 °C or LCMS indicated the formation of desired product and consumption of starting material. The reaction mixture was diluted with distilled water (4 mL), extracted with dichloromethane (3x4 mL), the extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to provide the desired product as a yellow solid (30 mg, 100%). LCMS: m/e 760.61 $(M+H)^+$, 2.40 min (method 11).

Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(cyclopropylsulfonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(cyclopropylsulfonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (30 mg, 0.039 mmol) and sodium hydroxide (0.395 mL, 0.395 mmol) in dioxane (0.5 mL) was heated up at 80 °C for 3 hours. The reaction mixture was filtered and the clear solution was purified by HPLC to provide the title compound as a white solid (13 mg, 42%). LCMS: m/e 746.58 $(M+H)^+$, 2.27 min (method 11). ^{1}H NMR (400MHz, Acetic) δ 7.99 (d, *J*=8.3 Hz, 2H), 7.26 (d, *J*=8.3 Hz, 2H), 5.34 (d, *J*=4.8 Hz, 1H), 4.81 (s, 1H), 4.70 (s, 1H), 3.63 - 3.44 (m, 5H), 3.43 - 3.26 (m, 2H), 3.24 - 3.13 (m, 1H), 3.05 (d, *J*=4.3 Hz, 4H), 2.86 (br. s., 1H), 2.58 - 2.40 (m, 1H), 2.27 - 1.02 (m, 22H), 1.73 (s, 3H)
1.24 (s, 3H), 1.13 (d, *J*=4.5 Hz, 2H), 1.10 (s, 3H), 1.06 (s, 3H), 1.02 (d, *J*=4.5 Hz, 2H), 0.97 (s, 3H), 0.96 (s, 3H).

Example B23

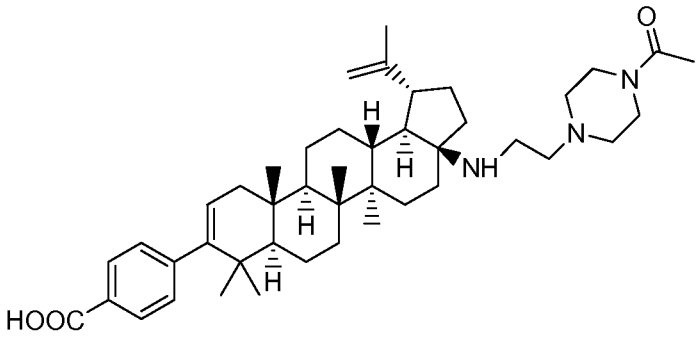
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((2-(4-(propylsulfonyl)piperazin-1-yl)ethyl)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared following the method described in above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(cyclopropylsulfonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using propane-1-sulfonyl chloride as the reagent in Step 1. The product was isolated as a white solid (8 mg, 48%). LCMS: m/e 748.6 $(M+H)^+$, 2.30 min (method 11). ^{1}H NMR (400MHz, Acetic) δ 7.99 (d, *J*=8.3 Hz, 2H), 7.26 (d, *J*=8.5 Hz, 2H), 5.34 (d, *J*=4.5 Hz, 1H), 4.81 (s, 1H), 4.70 (s, 1H), 3.59 - 3.26 (m, 7H), 3.23 - 3.11 (m, 1H), 3.09 - 2.95 (m, 6H), 2.93 - 2.80 (m, 1H), 2.27 - 1.02 (m, 24H), 1.73 (s, 3H), 1.24 (s, 3H), 1.10 (s, 3H), 1.07 (s, 3H), 1.05 (t, *J*=8.3 Hz, 3H), 0.98 (s, 3H), 0.97 (s, 3H).

Example B24

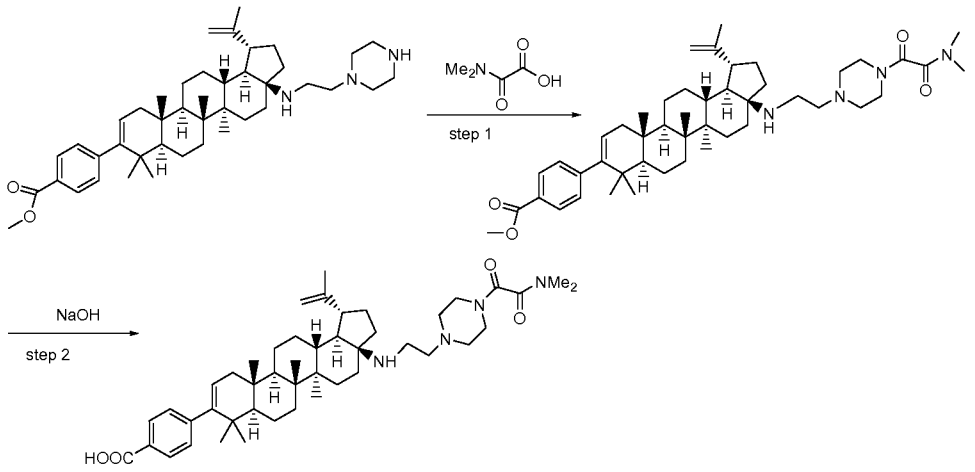
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-acetylpiperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(cyclopropylsulfonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using acetyl chloride as the reagent in Step 1. The product was isolated as a white solid (5.4 mg, 35%). LCMS: m/e 684.67 $(M+H)^+$, 2.27 min (method 11). ^{1}H NMR (400MHz, Acetic) δ 7.99 (d, *J*=8.3 Hz, 2H), 7.26 (d, *J*=8.5 Hz, 2H), 5.33 (d, *J*=4.8 Hz, 1H), 4.82 (s, 1H), 4.72 (s, 1H), 4.09 - 3.89 (m, 1H), 3.85 (br. s., 3H), 3.68 (br. s., 4H), 3.53 - 3.14 (m, 4H), 2.92 - 2.66 (m, 1H), 2.28 - 1.01 (m, 22H), 2.17 (s, 3H), 1.73 (s, 3H), 1.18 (s, 3H), 1.10 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H).

Example B25

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(2-(dimethylamino)-2-oxoacetyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



Step 1. Preparation of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(2-(dimethylamino)-2-oxoacetyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate

A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (50 mg, 0.076 mmol), 2-(1H-benzo[d][1,2,3]triazol-1-yl)-1,1,3,3-tetramethylisouronium tetrafluoroborate (29.4 mg, 0.091 mmol), N-ethyl-N-isopropylpropan-2-amine (11.82 mg, 0.091 mmol) and 2-(dimethylamino)-2-oxoacetic acid (26.8 mg, 0.229 mmol) in dichloromethane (2 mL) was stirred at 20 °C for 2 hours. The reaction mixture was diluted with distilled water (5 mL), extracted with ethyl acetate (3x4 mL), the extracts were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to provide the desired product as a yellow oil (40 mg, 70%). LCMS: m/e 755.68 $(M+H)^+$, 2.42 min (method 11).

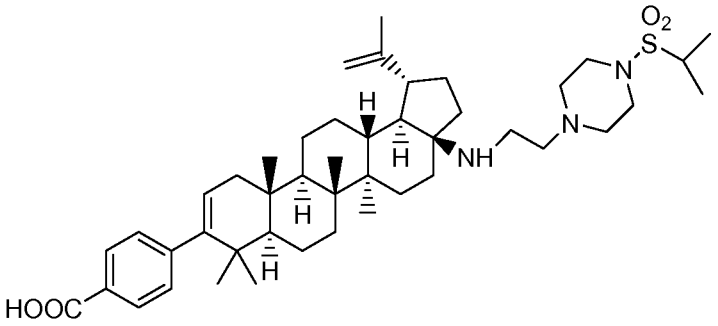
Step 2. Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(2-(dimethylamino)-2-oxoacetyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

A mixture of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(2-(dimethylamino)-2-oxoacetyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-

pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (40 mg, 0.053 mmol) and sodium hydroxide (0.530 mL, 0.530 mmol) in dioxane (1 mL) was heated up at 82 °C for 3 hours. The reaction mixture was cooled to room temperature, filtered and the clear solution was purified by HPLC to provide the title compound as a white solid (17 mg, 41%). LCMS: m/e 741.65 $(M+H)^+$, 2.29 min (method 11). ^{1}H NMR (400MHz, Acetic) δ 7.99 (d, *J*=8.3 Hz, 2H), 7.26 (d, *J*=8.3 Hz, 2H), 5.33 (d, *J*=4.5 Hz, 1H), 4.82 (s, 1H), 4.71 (s, 1H), 4.14 - 3.78 (m, 2H), 3.75 - 3.36 (m, 6H), 3.22 (br. s., 4H), 3.03 (s, 3H), 3.00 (s, 3H), 2.92 - 2.75 (m, 1H), 2.29 - 1.05 (m, 22H), 1.73 (s, 3H), 1.20 (s, 3H), 1.10 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H).

Example B26

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(isopropylsulfonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

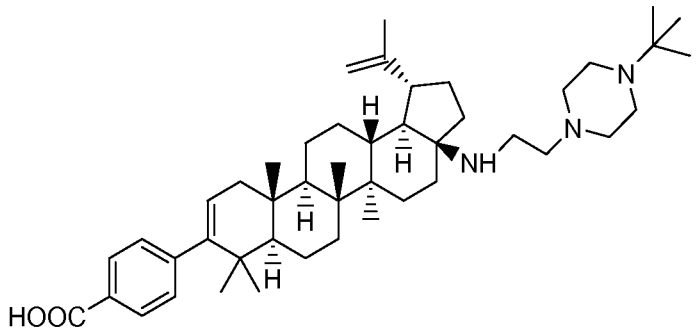


The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(cyclopropylsulfonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using propane-2-sulfonyl chloride as the reagent in Step 1. The product was isolated as a colorless oil (6 mg, 36%). LCMS: m/e 748.63 $(M+H)^+$, 2.31 min (method 11). ^{1}H NMR (400MHz, Acetic) δ 7.99 (d, *J*=8.0 Hz, 2H), 7.26 (d, *J*=8.0 Hz, 2H), 5.33 (d, *J*=5.3 Hz, 1H), 4.82 (s, 1H), 4.71 (s, 1H), 3.80 - 3.55 (m, 8H), 3.49 - 3.25 (m, 5H), 2.92 - 2.68 (m, 1H), 2.32 - 1.04 (m,

22H), 1.73 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H), 1.17 (s, 3H), 1.10 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H).

Example B27

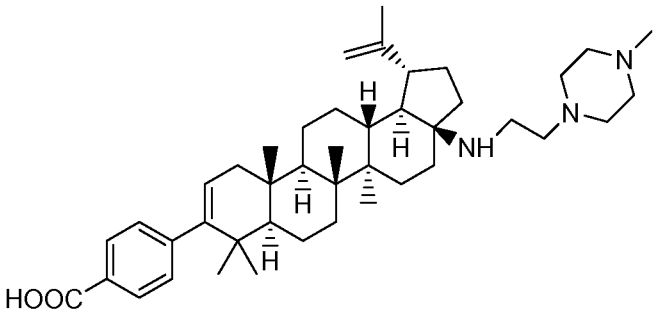
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(tert-butyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(tert-butoxycarbonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 1-(tert-butyl)piperazine as the alkylating reagent in Step 3. The product was isolated as a white solid (9 mg, 40%). LCMS: m/e 698.67 $(M+H)^+$, 2.27 min (method 11). ^{1}H NMR (500MHz, Acetic) δ 8.04 (d, *J*=8.0 Hz, 2H), 7.30 (d, *J*=8.0 Hz, 2H), 5.38 (d, *J*=5.2 Hz, 1H), 4.84 (s, 1H), 4.74 (s, 1H), 3.77 (br. s., 2H), 3.51 - 2.82 (m, 11H), 2.41 - 1.16 (m, 22H), 1.77 (s, 3H), 1.49 (s, 9H), 1.30 (s, 3H), 1.15 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 1.01 (s, 3H).

Example B28

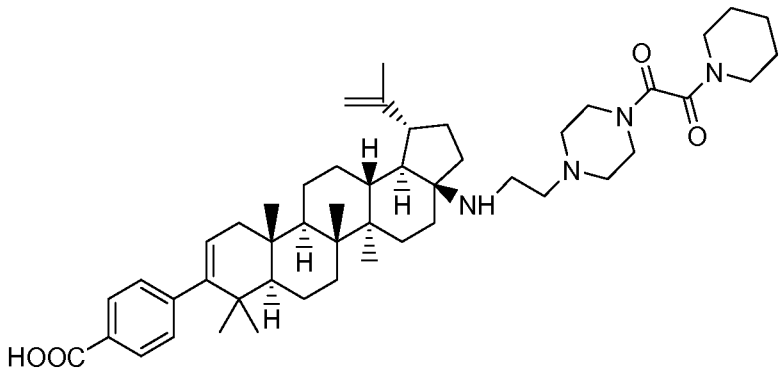
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-methylpiperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared following the method described in above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(tert-butoxycarbonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 1-methylpiperazine as the alkylating reagent in Step 3. The product was isolated as a white solid (3 mg, 19%). LCMS: m/e 656.62 $(M+H)^+$, 2.19 min (method 11). ^{1}H NMR (500MHz, Acetic) δ 8.04 (d, *J*=8.0 Hz, 2H), 7.30 (d, *J*=8.0 Hz, 2H), 5.38 (d, *J*=5.7 Hz, 1H), 4.84 (s, 1H), 4.74 (s, 1H), 3.73 (br. s., 1H), 3.62 - 2.85 (m, 12H), 2.94 (s, 3H), 2.34 - 1.15 (m, 22H), 1.77 (s, 3H), 1.29 (s, 3H), 1.15 (s, 3H), 1.11 (s, 3H), 1.03 (s, 3H), 1.01 (s, 3H).

Example B29

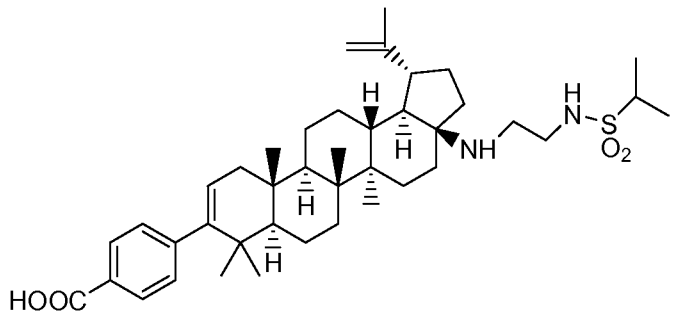
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(2-oxo-2-(piperidin-1-yl)acetyl)piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(2-(dimethylamino)-2-oxoacetyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 2-oxo-2-(piperidin-1-yl)acetic acid as the acid in Step 1. The product was isolated as a white solid (1.1 mg, 18%). LCMS: m/e 781.7 $(M+H)^+$, 1.72 min (method 11). ^{1}H NMR (500MHz, CHLOROFORM-d) δ 7.99 (d, *J*=8.4 Hz, 2H), 7.24 (d, *J*=8.4 Hz, 2H), 5.31 (d, *J*=4.6 Hz, 1H), 4.77 (s, 1H), 4.65 (s, 1H), 3.84 (dd, *J*=7.6, 2.7 Hz, 1H), 3.68 - 3.56 (m, 3H), 3.49 (t, *J*=4.9 Hz, 2H), 3.43 - 3.30 (m, 2H), 2.93 - 2.63 (m, 9H), 2.60 - 1.05 (m, 28H), 1.72 (s, 3H), 1.17 (s, 3H), 1.04 (s, 3H), 1.00 (s, 3H), 0.97 (s, 3H), 0.97 (s, 3H).

Example B30

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(1-methylethylsulfonamido)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

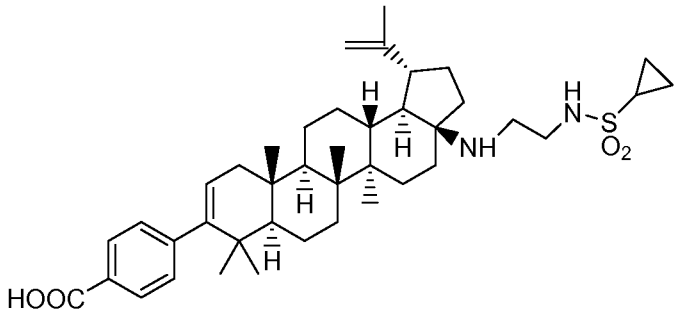


The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(methylsulfonamido)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using propane-2-sulfonyl chloride as the reagent in Step 1. The product was isolated as a colorless oil (3.5 mg, 34%). LCMS: m/e 679.55 $(M+H)^+$, 2.36 min (method 11). ^{1}H NMR (400MHz, CHLOROFORM-d)

δ 9.56 (br. s., 1H), 7.98 (d, *J*=8.5 Hz, 2H), 7.23 (d, *J*=8.3 Hz, 2H), 6.91 (t, *J*=6.3 Hz, 1H), 5.94 (br. s., 1H), 5.18 (d, *J*=4.5 Hz, 1H), 4.87 (s, 1H), 4.71 (s, 1H), 3.88 - 3.69 (m, 1H), 3.63 - 3.49 (m, 1H), 3.37 - 3.16 (m, 3H), 2.90 - 2.68 (m, 1H), 2.26 - 1.07 (m, 22H), 1.70 (s, 3H), 1.44 (dd, *J*=8.8, 6.8 Hz, 6H), 1.20 (s, 3H), 1.02 (s, 3H), 0.96 (s, 3H), 0.96 (s, 3H), 0.92 (s, 3H).

Example B31

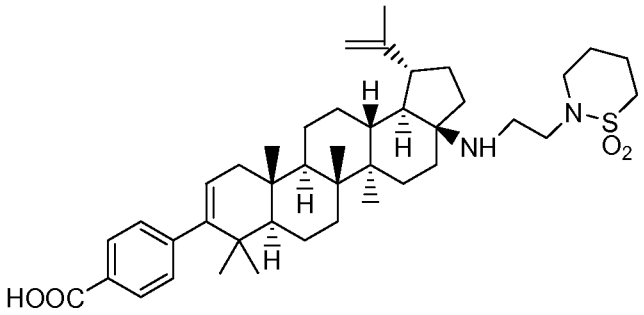
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(cyclopropanesulfonamido)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(methylsulfonamido)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using cyclopropanesulfonyl chloride as the reagent in Step 1. The product was isolated as a colorless oil (3.5 mg, 34%). LCMS: m/e 677.52 $(M+H)^+$, 2.32 min (method 11). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 9.55 (br. s., 1H), 7.98 (d, *J*=8.3 Hz, 2H), 7.23 (d, *J*=8.3 Hz, 2H), 6.76 (br. s., 1H), 5.99 (br. s., 1H), 5.21 (d, *J*=5.0 Hz, 1H), 4.85 (s, 1H), 4.71 (s, 1H), 3.92 - 3.71 (m, 1H), 3.69 - 3.55 (m, 1H), 3.23 (br. s., 2H), 2.91 - 2.70 (m, 1H), 2.63 - 2.44 (m, 1H), 2.25 - 1.02 (m, 26H), 1.70 (s, 3H), 1.18 (s, 3H), 1.02 (s, 3H), 0.97 (s, 3H), 0.92 (s, 3H), 0.92 (s, 3H).

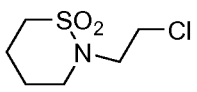
Example B32

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-1,2-thiazinan-2-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-((1,1-dioxidotetrahydrothiophen-3-yl)amino)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using 1-(2-chloroethyl)-4-(methylsulfonyl)piperazine (prepared as described below) as the alkylating reagent in Step 3. The product was isolated as a white solid (5.2 mg, 36%). LCMS: m/e 691.55 $(M+H)^+$, 2.35 min (method 11). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.99 (d, *J*=8.3 Hz, 2H), 7.23 (d, *J*=8.5 Hz, 2H), 5.27 (d, *J*=4.5 Hz, 1H), 4.82 (s, 1H), 4.70 (s, 1H), 3.87 - 3.74 (m, 1H), 3.72 - 3.48 (m, 3H), 3.39 (br. s., 2H), 3.18 - 3.08 (m, 2H), 2.96 - 2.78 (m, 1H), 2.34 - 1.10 (m, 26H), 1.71 (s, 3H), 1.23 (s, 3H), 1.05 (s, 3H), 0.99 (s, 3H), 0.96 (s, 3H), 0.96 (s, 3H).

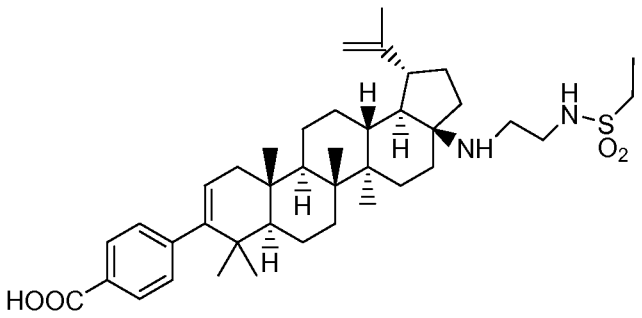
Preparation of 1-(2-chloroethyl)-4-(methylsulfonyl)piperazine



The title compound was prepared following the method described in previously for the synthesis of 1-(2-chloroethyl)-4-(methylsulfonyl)piperazine using 1,2-thiazinane 1,1-dioxide as the starting reagent and sodium hydride as the base. The product was isolated as colorless oil (120 mg, 41%). LCMS: m/e 198.08 $(M+H)^+$, 1.24 min (method 11).

Example B33

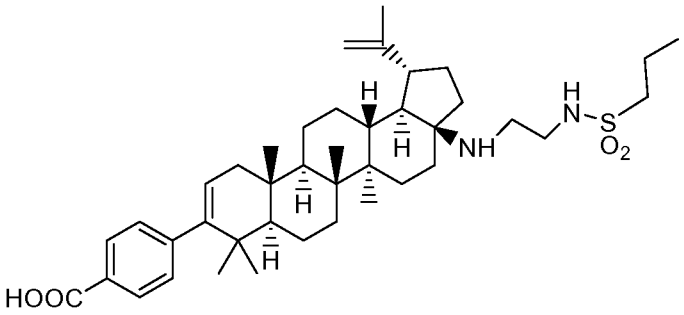
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(ethylsulfonamido)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(methylsulfonamido)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using ethanesulfonyl chloride as the reagent in Step 1. The product was isolated as a white solid (8.7 mg, 56%). LCMS: m/e 665.46 $(M+H)^+$, 2.29 min (method 11). ^1H NMR (500MHz, CHLOROFORM-d) δ 9.27 (br. s., 1H), 8.00 (d, *J*=7.1 Hz, 2H), 7.25 (d, *J*=7.1 Hz, 2H), 6.84 (br. s., 1H), 6.07 (br. s., 1H), 5.24 (d, *J*=6.3 Hz, 1H), 4.85 (s, 1H), 4.73 (s, 1H), 3.84 - 3.68 (m, 1H), 3.54 (d, *J*=14.8 Hz, 1H), 3.37 - 3.21 (m, 2H), 3.17 (q, *J*=7.4 Hz, 2H), 2.83-2.76 (m, 1H), 2.36 – 0.95 (m, 22H), 1.72 (s, 3H), 1.46 (t, *J*=7.4 Hz, 3H), 1.20 (s, 3H), 1.05 (s, 3H), 0.97 (s, 3H), 0.95 (s, 3H), 0.95 (s, 3H).

Example B34

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((2-(propylsulfonamido)ethyl)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared following the method described above for the synthesis of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(methylsulfonamido)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid using propane-1-sulfonyl chloride as the reagent in Step 1. The product was isolated as a white solid (9 mg, 49%). LCMS: m/e 679.48 $(M+H)^+$, 2.34 min (method 11). ^{1}H NMR (500MHz, CHLOROFORM-d) δ 9.36 (br. s., 1H), 8.00 (d, *J*=8.4 Hz, 2H), 7.25 (d, *J*=8.2 Hz, 2H), 6.81 (br. s., 1H), 6.04 (br. s., 1H), 5.31 - 5.19 (m, 1H), 4.86 (s, 1H), 4.73 (s, 1H), 3.85 - 3.67 (m, 1H), 3.54 (d, *J*=14.7 Hz, 1H), 3.38 - 3.18 (m, 2H), 3.15 - 3.07 (m, 2H), 2.80 (td, *J*=11.2, 5.9 Hz, 1H), 2.26 – 0.95 (m, 24H), 1.71 (s, 3H), 1.20 (s, 3H), 1.12 (t, *J*=7.4 Hz, 3H), 1.05 (s, 3H), 0.97 (s, 3H), 0.96 (s, 3H), 0.94 (s, 3H).

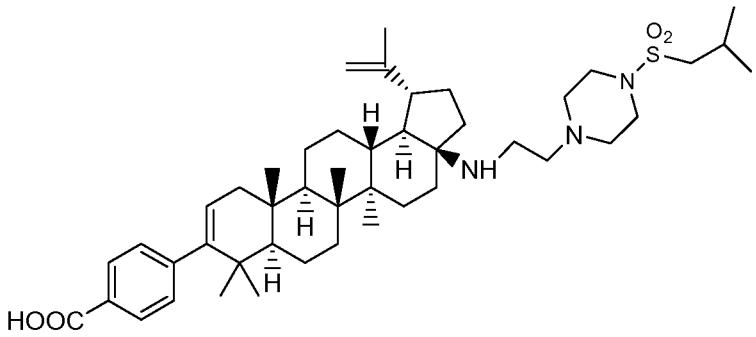
General procedure for the preparation of examples B35-B-52.

To the corresponding substituted sulfonyl chloride reagent (sulfonylating agent) (0.075 mmol) was added a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (29 mg, 0.044 mmol) and DIPEA (0.039 mL, 0.221 mmols) in DCE (1 mL) at room temperature. The reaction mixture was stirred overnight at room temperature. The solvent was evaporated to provide the dry residue. To the residue in dioxane (0.8 mL) was added a solution of lithium hydroxide monohydrate (14.7 mg, 0.35 mmol) in water (0.2 mL). The reaction mixture was agitated at 350 rpm on an Innova platform shaker at 70° C overnight. The solvent was removed and DMF (1.5 mL) was added. The mixture was filtered and the clear solution was purified by HPLC to provide the desired products with yield ranged from 6-50% over two steps.

Example B35

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(isobutylsulfonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

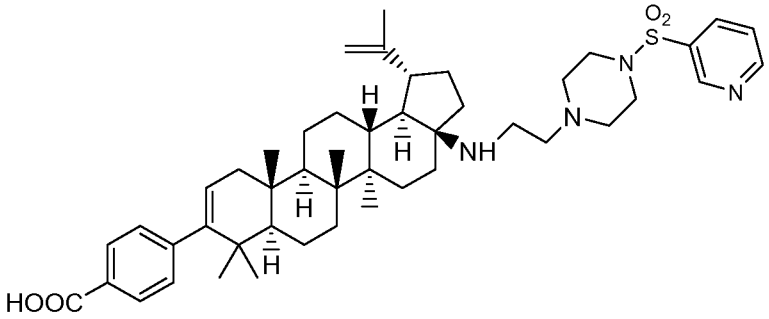


The title compound was prepared to provide 11.9 mg from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using isobutanesulfonyl chloride as the sulfonylating agent. LCMS: m/e 762.8 $(M+H)^+$, 3.65 min (method 14). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.87 (d, *J*=8.2 Hz, 2H), 7.22 (d, *J*=8.2 Hz, 2H), 5.25 (d, *J*=4.9 Hz, 1H), 4.70 (s, 1H), 4.57 (s, 1H), 3.17

(br. s., 4H), 3.00 - 2.82 (m, 2H), 2.70 - 2.53 (m, 5H), 2.48 - 2.30 (m, 4H), 2.24 - 2.03 (m, 2H), 2.00 - 1.83 (m, 2H), 1.80-1.01 (m, 19H), 1.67 (s, 3H), 1.11 (s, 3H), 1.06 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H).

Example B36

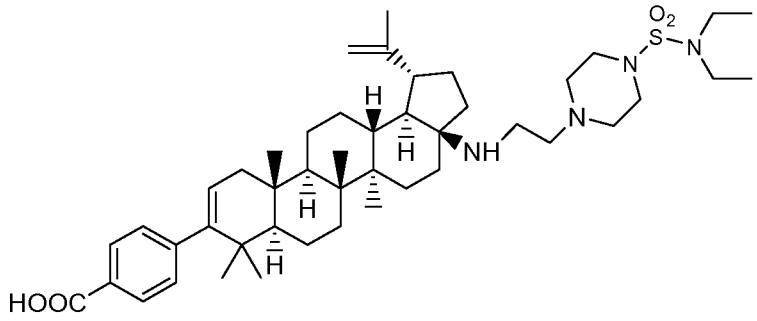
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((2-(4-(pyridin-3-ylsulfonyl)piperazin-1-yl)ethyl)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared to provide 12.7 mg from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using pyridine-3-sulfonyl chloride as the sulfonylating agent. LCMS: m/e 783.8 $(M+H)^+$, 3.42 min (method 14). ^{1}H NMR (500MHz, DMSO-d_6) δ 8.95 (d, *J*=2.1 Hz, 1H), 8.89 (dd, *J*=4.7, 1.4 Hz, 1H), 8.32 - 8.16 (m, 1H), 7.88 (d, *J*=8.2 Hz, 2H), 7.73 (dd, *J*=7.9, 4.9 Hz, 1H), 7.25 (d, *J*=7.9 Hz, 2H), 5.25 (d, *J*=4.9 Hz, 1H), 4.64 (d, *J*=1.8 Hz, 1H), 4.53 (s, 1H), 3.11 - 2.92 (m, 4H), 2.65 - 2.46 (m, 5H), 2.45 - 2.20 (m, 4H), 2.05 (dd, *J*=17.4, 6.4 Hz, 1H), 1.91 - 1.76 (m, 2H), 1.73 – 0.99 (m, 19H), 1.63 (s, 3H), 1.03 (s, 3H), 0.94 (s, 3H), 0.91 (s, 3H), 0.87 (s, 3H), 0.61 (s, 3H).

Example B37

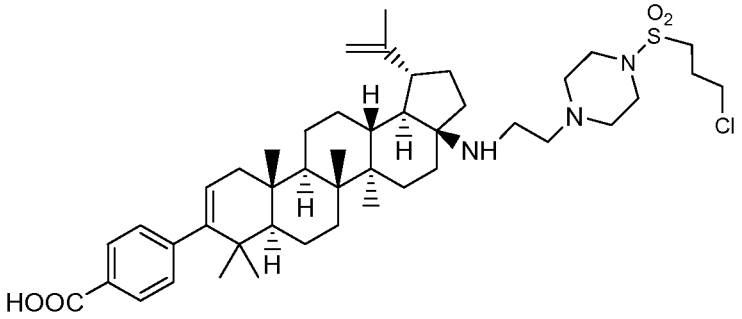
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(N,N-diethylsulfamoyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared to provide 10.6 mg from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using dimethylsulfamoyl chloride as the sulfonylating agent. LCMS: m/e 777.8 $(M+H)^+$, 3.82 min (method 14). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.87 (d, *J*=7.9 Hz, 2H), 7.22 (d, *J*=8.2 Hz, 2H), 5.25 (d, *J*=4.6 Hz, 1H), 4.70 (d, *J*=2.1 Hz, 1H), 4.56 (s, 1H), 3.22 (q, *J*=7.1 Hz, 4H), 3.08 (br. s., 4H), 2.69 - 2.57 (m, 1H), 2.56 - 2.47 (m, 4H), 2.44 - 2.31 (m, 4H), 2.08 (dd, *J*=17.5, 6.3 Hz, 1H), 1.95 - 1.00 (m, 21H), 1.67 (s, 3H), 1.12 (t, *J*=7.0 Hz, 6H), 1.09 (s, 3H), 0.97 (s, 3H), 0.96 (s, 3H), 0.91 (s, 3H), 0.90 (s, 3H).

Example B38

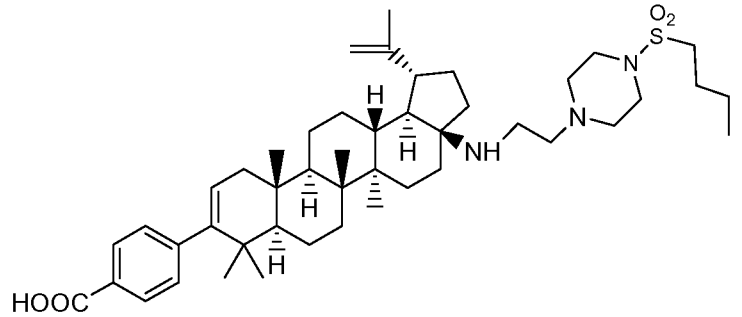
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-((3-chloropropyl)sulfonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared to provide 10.9 mg from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using 3-chloropropanesulfonyl chloride as the sulfonylating agent. LCMS: m/e 782.7 $(M+H)^+$, 3.59 min (method 14). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.87 (d, *J*=7.9 Hz, 2H), 7.22 (d, *J*=8.2 Hz, 2H), 5.25 (d, *J*=4.9 Hz, 1H), 4.70 (d, *J*=2.1 Hz, 1H), 4.57 (s, 1H), 3.76 (t, *J*=6.4 Hz, 2H), 3.26 - 3.13 (m, 6H), 2.63 (td, *J*=10.5, 4.9 Hz, 1H), 2.56 (d, *J*=7.6 Hz, 4H), 2.48 - 2.33 (m, 4H), 2.21 - 2.04 (m, 3H), 1.98 - 1.83 (m, 2H), 1.83 - 1.02 (m, 19H), 1.67 (s, 3H), 1.10 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H), 0.90 (s, 3H), 0.90 (s, 3H).

Example B39

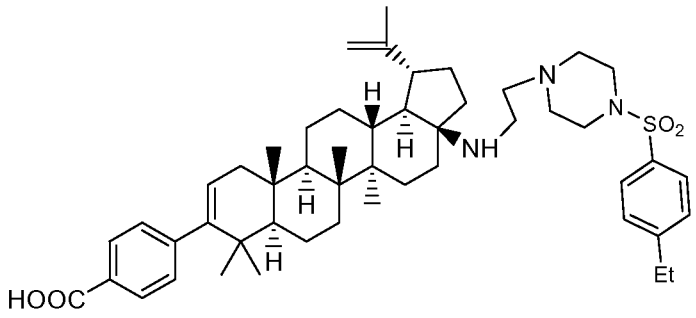
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(butylsulfonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared to provide 13.6 mg from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using butane-1-sulfonyl chloride as the sulfonylating agent. LCMS: m/e 762.8 $(M+H)^+$, 3.66 min (method 14). ^1H NMR (500MHz, DMSO-d_6) δ 7.87 (d, *J*=8.2 Hz, 2H), 7.22 (d, *J*=8.2 Hz, 2H), 5.25 (d, *J*=4.6 Hz, 1H), 4.70 (d, *J*=2.1 Hz, 1H), 4.56 (s, 1H), 3.19 (br. s., 4H), 3.12 - 2.96 (m, 2H), 2.63 (td, *J*=10.8, 5.3 Hz, 1H), 2.55 (br. s., 4H), 2.47 - 2.30 (m, 4H), 2.08 (dd, *J*=17.2, 6.3 Hz, 1H), 1.98 - 1.83 (m, 2H), 1.82 - 1.02 (m, 23H), 1.67 (s, 3H), 1.10 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.91 (t, *J*=4.7 Hz, 3H), 0.90 (s, 3H), 0.89 (s, 3H).

Example B40

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-((4-ethylphenyl)sulfonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

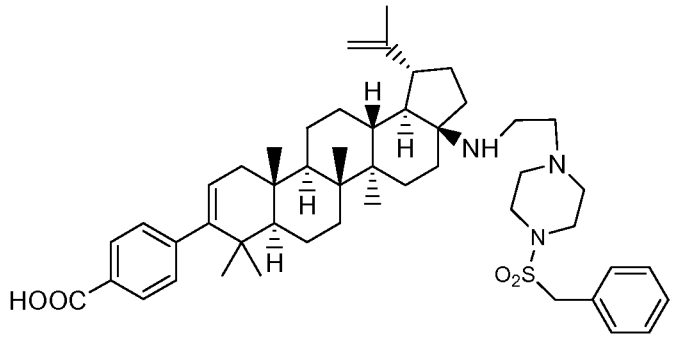


The title compound was prepared to provide 3.7 mg from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described

above using 4-ethyl-benzene-1-sulfonyl chloride as the sulfonylating agent. LCMS: m/e 810.9 $(M+H)^+$, 4.12 min (method 14). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.89 (d, *J*=8.2 Hz, 2H), 7.68 (d, *J*=8.2 Hz, 2H), 7.49 (d, *J*=8.2 Hz, 2H), 7.24 (d, *J*=8.2 Hz, 2H), 5.26 (d, *J*=4.9 Hz, 1H), 4.63 (br. s., 1H), 4.55 (br. s., 1H), 3.03 - 2.90 (m, 4H), 2.71 (q, *J*=7.7 Hz, 2H), 2.52 (d, *J*=1.5 Hz, 5H), 2.49 - 2.34 (m, 4H), 2.06 (dd, *J*=17.7, 6.4 Hz, 1H), 1.80 (d, *J*=9.8 Hz, 2H), 1.75 - 1.01 (m, 19H), 1.63 (s, 3H), 1.21 (t, *J*=7.5 Hz, 3H), 0.96 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H), 0.92 (s, 3H), 0.85 (s, 3H).

Example B41

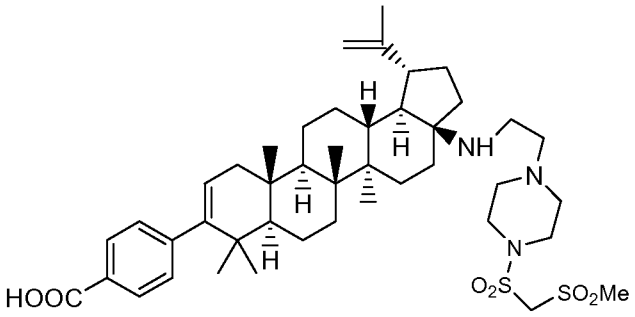
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(benzylsulfonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared to provide 16.4 mg from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using phenyl-methanesulfonyl chloride as the sulfonylating agent. LCMS: m/e 796.8 $(M+H)^+$, 3.73 min (method 14). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.87 (d, *J*=8.2 Hz, 2H), 7.46 - 7.41 (m, 2H), 7.41 - 7.31 (m, 3H), 7.22 (d, *J*=8.2 Hz, 2H), 5.25 (d, *J*=4.6 Hz, 1H), 4.72 (d, *J*=1.5 Hz, 1H), 4.58 (s, 1H), 4.53 - 4.39 (m, 2H), 3.11 (br. s., 4H), 2.64 - 2.54 (m, 1H), 2.53 - 2.45 (m, 2H), 2.46 - 2.29 (m, 6H), 2.09 (dd, *J*=17.2, 6.3 Hz, 1H), 1.96 - 1.80 (m, 3H), 1.78 - 1.02 (m, 18H), 1.68 (s, 3H), 1.10 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H), 0.89 (s, 3H), 0.87 (s, 3H).

Example B42

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(((methylsulfonyl)methyl)sulfonyl)piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

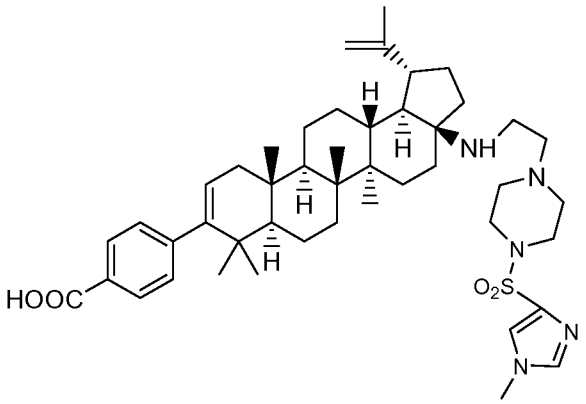


The title compound was prepared to provide 5.5 mg from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using methanesulfonyl-methanesulfonyl chloride as the sulfonylating agent. LCMS: m/e 798.8 $(M+H)^+$, 3.28 min (method 14). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.87 (d, *J*=7.9 Hz, 2H), 7.22 (d, *J*=7.9 Hz, 2H), 5.29 (s, 2H), 5.25 (d, *J*=4.6 Hz, 1H), 4.70 (s, 1H), 4.57 (s, 1H), 3.29 (br. s., 8H), 3.19 (s, 3H), 2.64 - 2.55 (m, 1H), 2.48 - 2.34 (m, 4H), 2.08 (dd, *J*=17.2, 6.3 Hz, 1H), 1.97 - 1.80 (m, 3H), 1.79 – 0.99 (m, 18H), 1.67 (s, 3H), 1.09 (s, 3H), 0.97 (s, 3H), 0.97 (s, 3H), 0.90 (s, 3H), 0.90 (s, 3H).

Example B43

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-((1-methyl-1H-imidazol-4-yl)sulfonyl)piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-

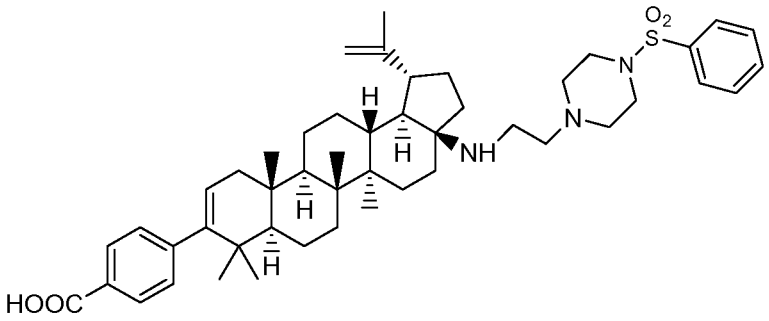
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared to provide 17 mg from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using 1-methyl-1H-imidazole-4-sulfonyl chloride as the sulfonylating agent. LCMS: m/e 786.8 $(M+H)^+$, 3.08 min (method 14). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.92 - 7.84 (m, 3H), 7.77 (s, 1H), 7.23 (d, *J*=7.9 Hz, 2H), 5.26 (d, *J*=4.9 Hz, 1H), 4.66 (d, *J*=1.8 Hz, 1H), 4.55 (s, 1H), 3.73 (s, 3H), 3.04 (br. s., 4H), 2.63 - 2.47 (m, 5H), 2.45 - 2.26 (m, 4H), 2.08 (dd, *J*=17.4, 6.4 Hz, 1H), 1.91 - 1.77 (m, 2H), 1.77 - 1.00 (m, 19H), 1.65 (s, 3H), 0.96 (s, 3H), 0.94 (s, 3H), 0.94 (s, 3H), 0.93 (s, 3H), 0.89 (s, 3H).

Example B44

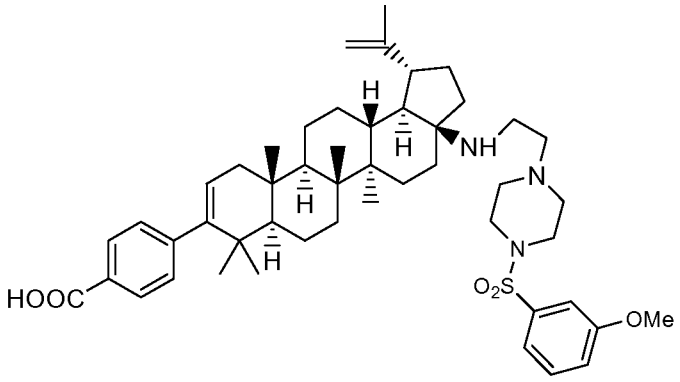
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(phenylsulfonyl)piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared to provide 3.9 mg from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using benzenesulfonyl chloride as the sulfonylating agent. LCMS: m/e 782.8 $(M+H)^+$, 4.98 min (method 15). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.89 (d, *J*=8.2 Hz, 2H), 7.78 (d, *J*=7.0 Hz, 2H), 7.75 - 7.62 (m, 3H), 7.26 (d, *J*=7.9 Hz, 2H), 5.25 (d, *J*=4.9 Hz, 1H), 4.64 (br. s., 1H), 4.54 (br. s., 1H), 2.92 (br. s., 4H), 2.57 (br. s., 5H), 2.47 - 2.27 (m, 4H), 2.05 (dd, *J*=17.4, 6.4 Hz, 1H), 1.93 - 1.77 (m, 2H), 1.76 – 0.98 (m, 19H), 1.63 (s, 3H), 1.03 (s, 3H), 0.95 (s, 3H), 0.91 (s, 3H), 0.86 (s, 3H), 0.58 (s, 3H).

Example B45

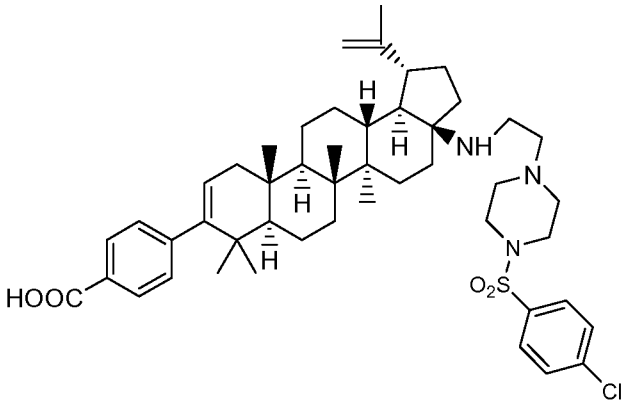
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-((3-methoxyphenyl)sulfonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared to provide 3.2 mg from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using 3-methoxybenzenesulfonyl chloride as the sulfonylating agent. LCMS: m/e 812.8 $(M+H)^+$, 4.98 min (method 15). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.89 (d, *J*=8.2 Hz, 2H), 7.64 - 7.51 (m, 1H), 7.34 (d, *J*=7.9 Hz, 1H), 7.28 - 7.13 (m, 4H), 5.25 (d, *J*=4.6 Hz, 1H), 4.64 (s, 1H), 4.53 (s, 1H), 3.85 (s, 3H), 3.03 - 2.87 (m, 4H), 2.64 - 2.51 (m, 5H), 2.46 - 2.22 (m, 4H), 2.05 (dd, *J*=17.2, 6.3 Hz, 1H), 1.93 - 1.76 (m, 2H), 1.75 – 0.98 (m, 19H), 1.63 (s, 3H), 1.02 (s, 3H), 0.94 (s, 3H), 0.91 (s, 3H), 0.87 (s, 3H), 0.63 (s, 3H).

Example B46

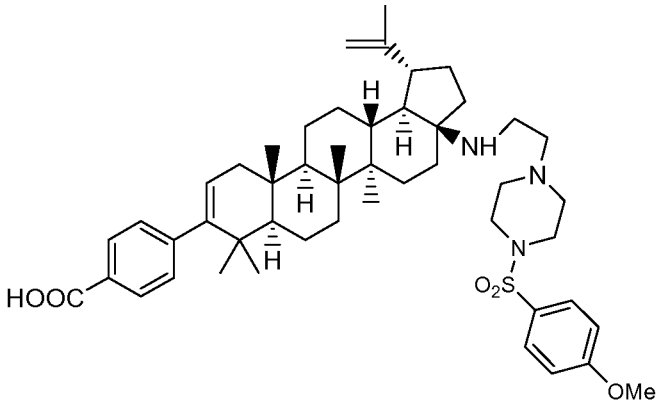
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-((4-chlorophenyl)sulfonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared to provide 2.1 mg from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using 4-chlorobenzene-1-sulfonyl chloride as the sulfonylating agent. LCMS: m/e 816.8 $(M+H)^+$, 3.94 min (method 14). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.89 (d, *J*=8.2 Hz, 2H), 7.81 (d, *J*=8.5 Hz, 2H), 7.73 (d, *J*=8.9 Hz, 2H), 7.24 (d, *J*=7.9 Hz, 2H), 5.25 (d, *J*=4.6 Hz, 1H), 4.66 (br. s., 1H), 4.57 (br. s., 1H), 2.96 (br. s., 4H), 2.71 - 2.55 (m, 4H), 2.51 - 2.30 (m, 5H), 2.06 (dd, *J*=17.4, 6.4 Hz, 1H), 1.98 - 1.79 (m, 2H), 1.78 – 0.89 (m, 19H), 1.65 (s, 3H), 1.00 (s, 3H), 0.93 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H), 0.80 (s, 3H).

Example B47

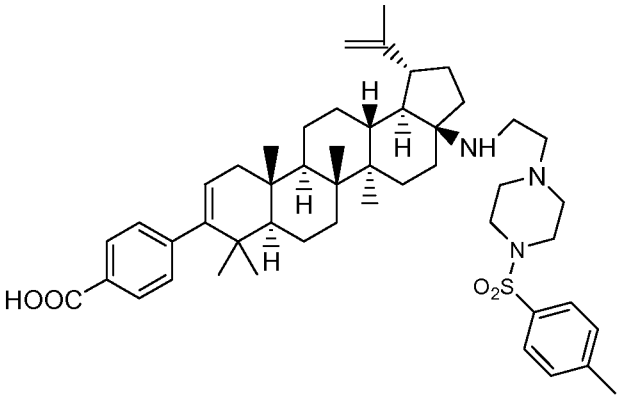
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-((4-methoxyphenyl)sulfonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared to provide 9.5 mg from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using 4-methoxybenzene-1-sulfonyl chloride as the sulfonylating agent. LCMS: m/e 812.8 $(M+H)^+$, 3.69 min (method 14). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.89 (d, *J*=8.2 Hz, 2H), 7.70 (d, *J*=8.9 Hz, 2H), 7.24 (d, *J*=8.2 Hz, 2H), 7.16 (d, *J*=8.9 Hz, 2H), 5.25 (d, *J*=4.6 Hz, 1H), 4.63 (d, *J*=2.1 Hz, 1H), 4.53 (s, 1H), 3.83 (s, 3H), 2.91 (s, 4H), 2.61 - 2.46 (m, 5H), 2.41 (br. s., 2H), 2.36 - 2.22 (m, 2H), 2.05 (dd, *J*=17.5, 6.3 Hz, 1H), 1.90 - 1.75 (m, 2H), 1.74 - 1.03 (m, 19H), 1.63 (s, 3H), 0.98 (s, 3H), 0.92 (s, 3H), 0.92 (s, 3H), 0.88 (s, 3H), 0.75 (s, 3H).

Example B48

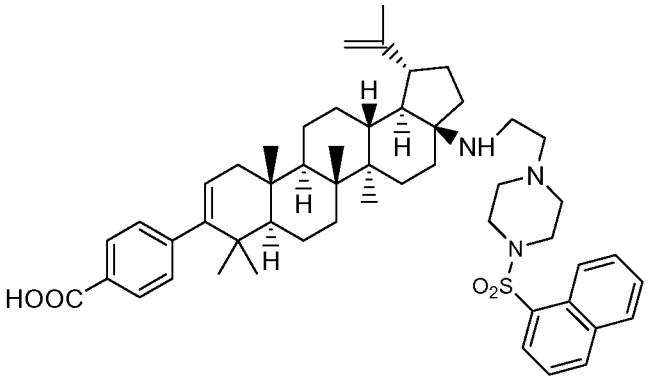
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((2-(4-tosylpiperazin-1-yl)ethyl)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared to provide 4.6 mg from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using 4-methylbenzene-1-sulfonyl chloride as the sulfonylating agent. LCMS: m/e 796.8 $(M+H)^+$, 3.91 min (method 14). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.88 (d, *J*=8.2 Hz, 2H), 7.65 (d, *J*=8.2 Hz, 2H), 7.46 (d, *J*=8.2 Hz, 2H), 7.24 (d, *J*=7.9 Hz, 2H), 5.25 (d, *J*=4.6 Hz, 1H), 4.62 (d, *J*=2.1 Hz, 1H), 4.53 (s, 1H), 2.91 (s, 4H), 2.59 - 2.45 (m, 5H), 2.41 (s, 5H), 2.36 - 2.25 (m, 2H), 2.06 (dd, *J*=17.4, 6.4 Hz, 1H), 1.88 - 1.74 (m, 2H), 1.73 – 0.99 (m, 19H), 1.63 (s, 3H), 0.97 (s, 3H), 0.92 (s, 3H), 0.92 (s, 3H), 0.91 (s, 3H), 0.81 (s, 3H).

Example B49

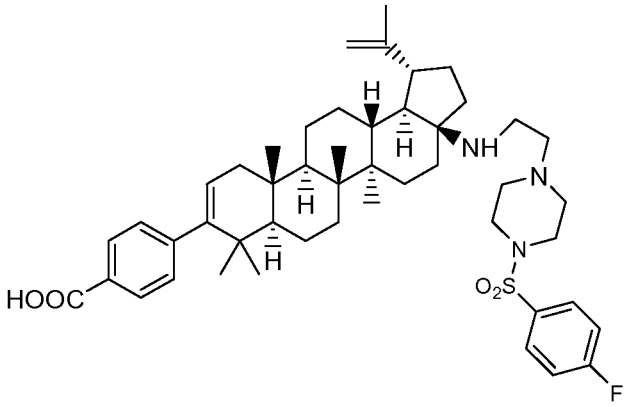
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(naphthalen-1-ylsulfonyl)piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared to provide 3.0 mg from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using naphthalene-1-sulfonyl chloride as the sulfonylating agent. LCMS: m/e 832.8 $(M+H)^+$, 4.00 min (method 14). ^1H NMR (500MHz, DMSO-d_6) δ 8.75 (d, *J*=8.5 Hz, 1H), 8.29 (d, *J*=7.9 Hz, 1H), 8.17 (d, *J*=7.3 Hz, 1H), 8.10 (d, *J*=8.2 Hz, 1H), 7.90 (d, *J*=7.9 Hz, 2H), 7.81 - 7.62 (m, 3H), 7.28 (d, *J*=7.9 Hz, 2H), 5.24 (d, *J*=5.5 Hz, 1H), 4.62 (br. s., 1H), 4.52 (br. s., 1H), 3.08 (br. s., 4H), 2.52 (br. s., 5H), 2.45 - 2.22 (m, 4H), 2.02 (dd, *J*=17.7, 6.1 Hz, 1H), 1.91 - 1.74 (m, 2H), 1.73 – 1.02 (m, 19H), 1.61 (s, 3H), 1.06 (s, 3H), 0.94 (s, 3H), 0.87 (s, 3H), 0.79 (s, 3H), 0.48 (s, 3H).

Example B50

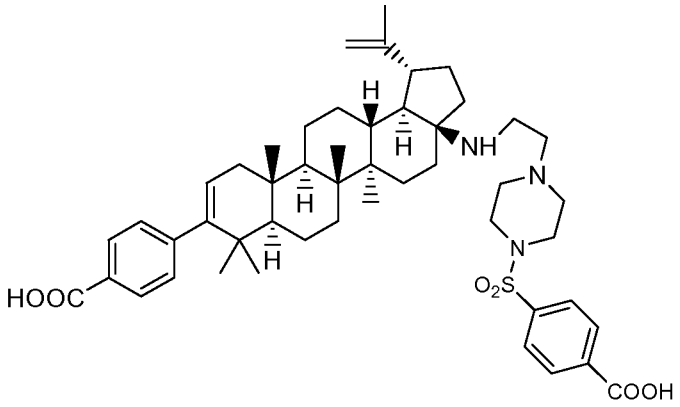
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-((4-fluorophenyl)sulfonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared to provide 5.7 mg from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using 4-fluorobenzene-1-sulfonyl chloride as the sulfonylating agent. LCMS: m/e 800.8 $(M+H)^+$, 4.95 min (method 15). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.93 - 7.80 (m, 4H), 7.50 (t, *J*=8.7 Hz, 2H), 7.24 (d, *J*=7.9 Hz, 2H), 5.25 (d, *J*=4.9 Hz, 1H), 4.64 (d, *J*=2.1 Hz, 1H), 4.53 (s, 1H), 3.05 - 2.84 (m, 4H), 2.64 - 2.47 (m, 5H), 2.40 (br. s., 2H), 2.35 - 2.22 (m, 2H), 2.05 (dd, *J*=17.2, 6.3 Hz, 1H), 1.90 – 0.97 (m, 21H), 1.63 (s, 3H), 0.99 (s, 3H), 0.93 (s, 3H), 0.91 (s, 3H), 0.87 (s, 3H), 0.67 (s, 3H).

Example B51

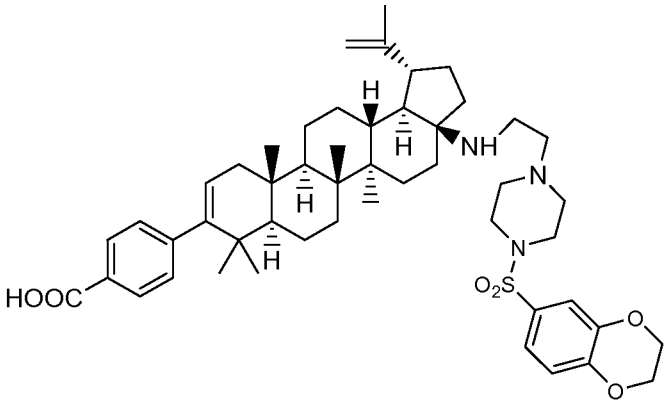
Preparation of 4-((4-(2-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-carboxyphenyl)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-3a-yl)amino)ethyl)piperazin-1-yl)sulfonyl)benzoic acid



The title compound was prepared to provide 10.1 mg from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using 4-(chlorosulfonyl)benzoic acid as the sulfonylating agent. LCMS: m/e 826.8 $(M+H)^+$, 2.75 min (method 14). ^1H NMR (500MHz, DMSO-d_6) δ 8.18 (d, *J*=8.2 Hz, 2H), 7.89 (dd, *J*=8.4, 3.8 Hz, 4H), 7.25 (d, *J*=8.2 Hz, 2H), 5.23 (d, *J*=4.9 Hz, 1H), 4.63 (s, 1H), 4.54 (s, 1H), 3.10 - 2.93 (m, 4H), 2.68 - 2.53 (m, 5H), 2.49 - 2.32 (m, 4H), 2.03 (dd, *J*=17.2, 6.0 Hz, 1H), 1.90 - 1.76 (m, 2H), 1.75 – 0.99 (m, 19H), 1.63 (s, 3H), 0.95 (s, 3H), 0.91 (s, 3H), 0.90 (s, 3H), 0.85 (s, 3H), 0.77 (s, 3H).

Example B52

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)sulfonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound was prepared to provide 13.2 mg from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using 2,3-dihydro-1,4-benzodioxine-6-sulfonyl chloride as the sulfonylating agent. LCMS: m/e 840.8 $(M+H)^+$, 3.66 min (method 14). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.88 (d, *J*=8.2 Hz, 2H), 7.31 - 7.18 (m, 4H), 7.08 (d, *J*=8.2 Hz, 1H), 5.25 (d, *J*=4.6 Hz, 1H), 4.64 (d, *J*=2.1 Hz, 1H), 4.54 (s, 1H), 4.42 - 4.21 (m, 4H), 2.91 (s, 4H), 2.62 - 2.51 (m, 5H), 2.41 (br. s., 2H), 2.36 - 2.26 (m, 2H), 2.06 (dd, *J*=17.4, 6.4 Hz, 1H), 1.90 - 1.76 (m, 2H), 1.75 – 0.88 (m, 19H), 1.64 (s, 3H), 0.98 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H), 0.91 (s, 3H), 0.78 (s, 3H).

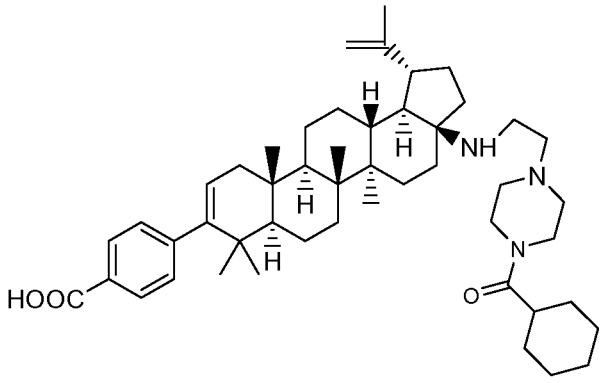
General procedure for the preparation of examples B53-B64

A solution of the corresponding substituted carboxylic acid (acylating agent) (0.039 mmol) and HATU (14.78 mg, 0.039 mmol) in DMF (0.5 mL) was stirred for 10 minutes, then a solution of methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate (17 mg, 0.026 mmol) and DIPEA (0.018 mL, 0.104 mmol) in DMF (0.500 mL) was introduced. The reaction mixture was agitated at 350 rpm on an Innova platform shaker at room temperature overnight. The solvent

was evaporated to provide the dry residue. To the residue in dioxane (0.8 mL) was added the lithium hydroxide monohydrate (8.70 mg, 0.207 mmol) dissolved in water (0.2 mL). The reaction mixture was stirred at 80°C overnight. The solvent was removed and DMF (1.0 mL) was added. The mixture was filtered and the clear solution was purified by HPLC to provide the desired products with yield ranged from 2-31% over two steps.

Example B53

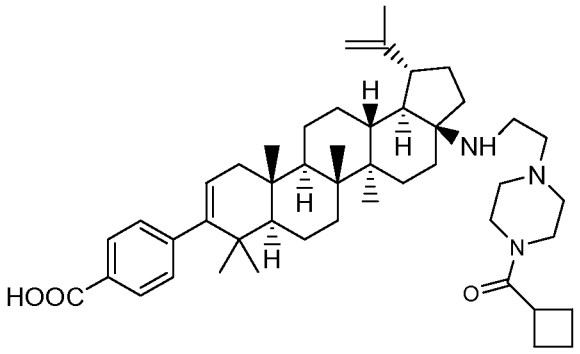
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(cyclohexanecarbonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound (4.9 mg) was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using cyclohexanecarboxylic acid as the acylating agent. LCMS: m/e 752.8 $(M+H)^+$, 3.90 min (method 14). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.85 (d, *J*=8.2 Hz, 2H), 7.19 (d, *J*=8.2 Hz, 2H), 5.24 (d, *J*=4.9 Hz, 1H), 4.70 (s, 1H), 4.56 (s, 1H), 3.49 (br. s., 4H), 2.70 - 2.53 (m, 4H), 2.48 - 2.31 (m, 5H), 2.31 - 2.18 (m, 1H), 2.08 (dd, *J*=17.4, 6.1 Hz, 1H), 1.99 - 1.79 (m, 3H), 1.78 - 1.00 (m, 28H), 1.67 (s, 3H), 1.08 (s., 3H), 0.97 (s, 3H), 0.96 (s, 3H), 0.90 (s, 3H), 0.90 (s, 3H).

Example B54

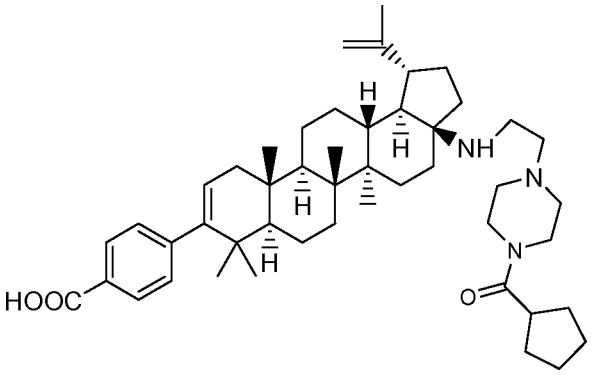
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(cyclobutanecarbonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound (3.1 mg) was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using cyclobutanecarboxylic acid as the acylating agent. LCMS: m/e 724.8 $(M+H)^+$, 3.66 min (method 14). ^{1}H NMR (500MHz, METHANOL-d_4) δ 7.89 (d, *J*=8.2 Hz, 2H), 7.17 (d, *J*=8.2 Hz, 2H), 5.30 (d, *J*=4.6 Hz, 1H), 4.79 (s, 1H), 4.68 (s, 1H), 3.83 - 3.54 (m, 2H), 3.53 - 3.38 (m, 3H), 2.91 (d, *J*=2.1 Hz, 1H), 2.85 - 2.71 (m, 2H), 2.62 (d, *J*=10.1 Hz, 3H), 2.55 - 2.39 (m, 2H), 2.36 - 1.18 (m, 29H), 1.75 (s, 3H), 1.22 (s., 3H), 1.11 (s, 3H), 1.05 (s, 3H), 0.97 (s, 3H), 0.96 (s, 3H).

Example B55

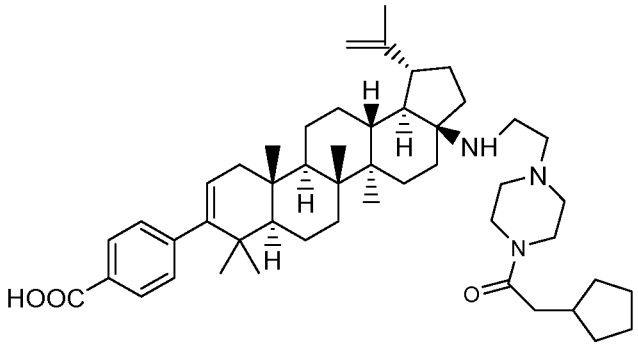
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(cyclopentanecarbonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound (3.1 mg) was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using cyclopentanecarboxylic acid as the acylating agent. LCMS: m/e 738.8 $(M+H)^+$, 3.84 min (method 14). ^{1}H NMR (500MHz, METHANOL-d_4) δ 7.89 (d, *J*=8.2 Hz, 2H), 7.17 (d, *J*=8.2 Hz, 2H), 5.30 (d, *J*=4.6 Hz, 1H), 4.79 (s, 1H), 4.69 (s, 1H), 3.78 - 3.52 (m, 4H), 3.13 - 3.01 (m, 2H), 2.97 - 2.89 (m, 1H), 2.86 - 2.73 (m, 2H), 2.72 - 2.61 (m, 3H), 2.60 - 2.41 (m, 2H), 2.20 - 1.80 (m, 8H), 1.75 (s, 3H), 1.74 - 1.18 (m, 22H), 1.23 (s., 3H), 1.11 (s, 3H), 1.06 (s, 3H), 0.97 (s, 3H), 0.97 (s, 3H).

Example B56

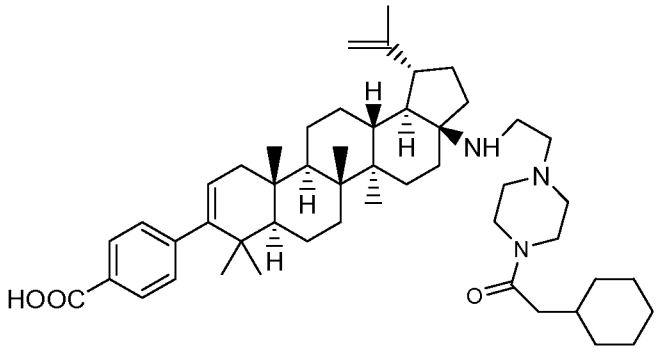
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(2-cyclopentylacetyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound (3.1 mg) was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using cyclopentylacetic acid as the acylating agent. LCMS: m/e 752.9 $(M+H)^+$, 3.93 min (method 14). ^{1}H NMR (500MHz, METHANOL-d_4) δ 7.89 (d, *J*=8.2 Hz, 2H), 7.17 (d, *J*=8.2 Hz, 2H), 5.30 (d, *J*=4.6 Hz, 1H), 4.80 (s, 1H), 4.69 (s, 1H), 3.70 (br. s., 1H), 3.66 - 3.53 (m, 3H), 3.12 - 3.01 (m, 1H), 2.95 - 2.89 (m, 1H), 2.86 - 2.72 (m, 2H), 2.71 - 2.61 (m, 3H), 2.60-2.54 (m, 1H), 2.51 - 2.47 (m, 1H), 2.45 (d, *J*=7.3 Hz, 2H), 2.27 - 1.90 (m, 6H), 1.89 - 1.79 (m, 3H), 1.76 (s, 3H), 1.73 - 1.18 (m, 22H), 1.23 (s, 3H), 1.11 (s, 3H), 1.06 (s, 3H), 0.97 (s, 3H), 0.97 (s, 3H).

Example B57

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(2-cyclohexylacetyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

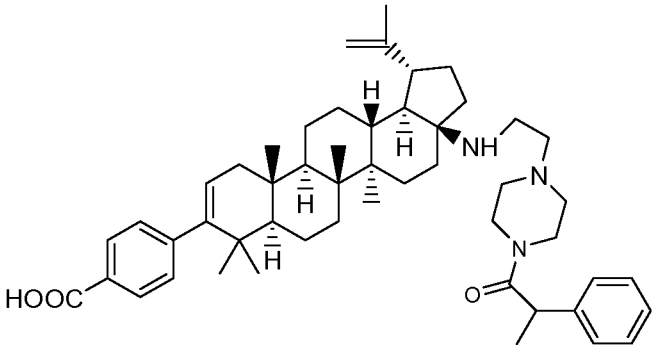


The title compound (3.4 mg) was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described

above using cyclopentylacetic acid as the acylating agent. LCMS: m/e 766.9 $(M+H)^+$, 4.09 min (method 14). ^{1}H NMR (500MHz, METHANOL-d_4) δ 7.89 (d, *J*=8.2 Hz, 2H), 7.17 (d, *J*=8.2 Hz, 2H), 5.30 (d, *J*=4.9 Hz, 1H), 4.79 (s, 1H), 4.69 (s, 1H), 3.72 (dd, *J*=10.5, 6.0 Hz, 1H), 3.67 - 3.53 (m, 3H), 3.11 - 3.01 (m, 1H), 2.92 (d, *J*=10.7 Hz, 1H), 2.87 - 2.72 (m, 2H), 2.71 - 2.60 (m, 3H), 2.60 - 2.53 (m, 1H), 2.51 - 2.41 (m, 1H), 2.31 (d, *J*=6.4 Hz, 2H), 2.20 - 1.90 (m, 5H), 1.84 (td, *J*=12.1, 3.4 Hz, 1H), 1.75 (s, 3H), 1.75 - 1.02 (m, 27H), 1.23 (s, 3H), 1.11 (s, 3H), 1.06 (s, 3H), 0.97 (s, 3H), 0.97 (s, 3H).

Example B58

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(2-phenylpropanoyl)piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

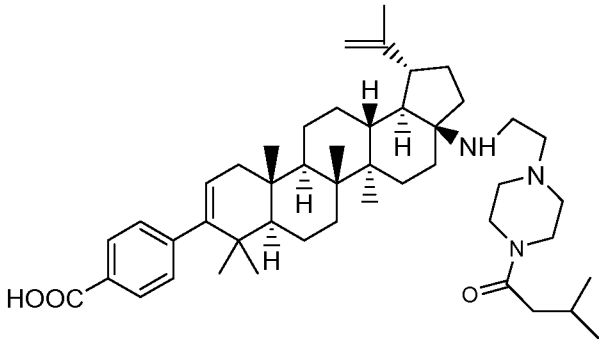


The title compound (4.1 mg) was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using 2-phenylpropionic acid as the acylating agent. LCMS: m/e 774.9 $(M+H)^+$, 3.87 min (method 14). ^{1}H NMR (500MHz, METHANOL-d_4) δ 7.89 (d, *J*=7.0 Hz, 2H), 7.41 - 7.31 (m, 2H), 7.29 - 7.22 (m, 3H), 7.18 (dd, *J*=8.2, 3.1 Hz, 2H), 5.30 (d, *J*=4.9 Hz, 1H), 4.77 (s, 1H), 4.67 (s, 1H), 4.11 (quin, *J*=6.4 Hz, 1H), 3.89 -

3.44 (m, 4H), 2.99 - 2.92 (m, 1H), 2.86 - 2.67 (m, 3H), 2.67 - 2.57 (m, 1H), 2.51 (d, *J*=13.7 Hz, 2H), 2.46 - 2.27 (m, 2H), 2.21 - 2.09 (m, 2H), 2.07 - 1.85 (m, 4H), 1.80 - 1.15 (m, 16H), 1.74 (s, 3H), 1.40 (d, *J*=6.7 Hz, 3H), 1.09 (d, *J*=8.5 Hz, 3H), 1.07 (d, *J*=13 Hz, 3H), 1.04 (s, 3H), 1.01 (s, 3H), 0.98 (s, 3H).

Example B59

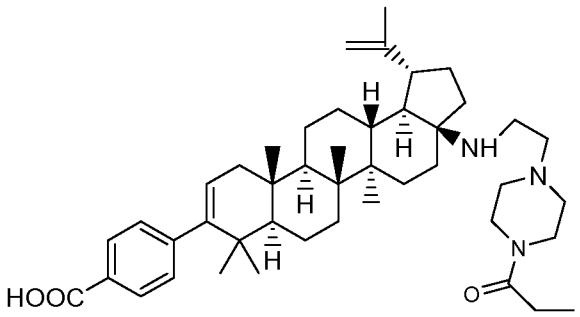
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(3-methylbutanoyl)piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound (3.3 mg) was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using isovaleric acid as the acylating agent. LCMS: m/e 726.8 $(M+H)^+$, 3.71 min (method 14). ^{1}H NMR (500MHz, METHANOL-d_4) δ 7.89 (d, *J*=8.2 Hz, 2H), 7.17 (d, *J*=8.2 Hz, 2H), 5.30 (d, *J*=4.9 Hz, 1H), 4.79 (s, 1H), 4.69 (s, 1H), 3.77 - 3.55 (m, 4H), 3.09 - 3.02 (m, 1H), 2.91 (br. s., 1H), 2.86 - 2.72 (m, 2H), 2.71 - 2.60 (m, 3H), 2.59 - 2.52 (m, 1H), 2.52 - 2.43 (m, 1H), 2.31 (d, *J*=7.3 Hz, 2H), 2.21 - 1.80 (m, 7H), 1.76 (s, 3H), 1.73 - 1.08 (m, 16H), 1.22 (s, 3H), 1.11 (s, 3H), 1.05 (s, 3H), 0.99 (d, *J*=6.4 Hz, 6H), 0.97 (s, 3H), 0.97 (s, 3H).

Example B60

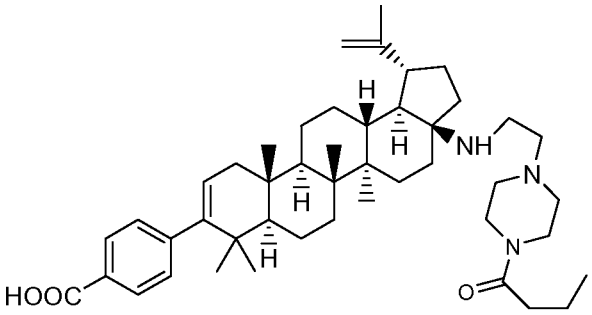
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-3a-((2-(4-propionylpiperazin-1-yl)ethyl)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound (5.5 mg) was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using propionic acid as the acylating agent. LCMS: m/e 698.8 $(M+H)^+$, 3.39 min (method 14). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.87 (d, *J*=8.2 Hz, 2H), 7.22 (d, *J*=7.9 Hz, 2H), 5.25 (d, *J*=4.9 Hz, 1H), 4.70 (s, 1H), 4.56 (s, 1H), 3.52 - 3.43 (m, 4H), 3.11 (br. s., 2H), 2.71 - 2.53 (m, 2H), 2.47 - 2.20 (m, 7H), 2.08 (dd, *J*=17.2, 6.3 Hz, 1H), 1.97 - 1.80 (m, 3H), 1.79 - 1.03 (m, 18H), 1.67 (s, 3H), 1.08 (s, 3H), 0.99 (t, *J*=8.0 Hz, 3H), 0.97 (s, 3H), 0.96 (s, 3H), 0.90 (s, 3H), 0.90 (s, 3H).

Example B61

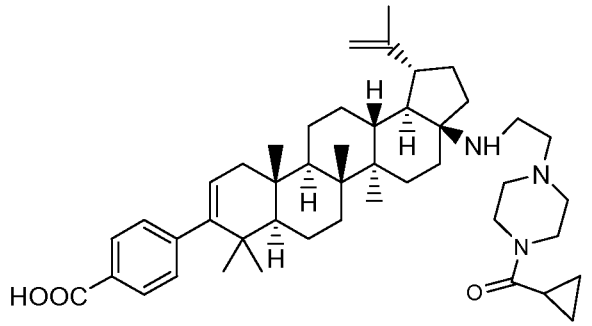
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-butyrylpiperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound (1.2 mg) was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using butyric acid as the acylating agent. LCMS: m/e 712.8 $(M+H)^+$, 4.97 min (method 15). ^{1}H NMR (500MHz, METHANOL-d_4) δ 7.89 (d, *J*=8.2 Hz, 2H), 7.16 (d, *J*=8.2 Hz, 2H), 5.30 (d, *J*=4.6 Hz, 1H), 4.78 (s, 1H), 4.68 (s, 1H), 3.79 - 3.55 (m, 4H), 3.12 - 2.98 (m, 1H), 2.97 - 2.82 (m, 2H), 2.78 (td, *J*=10.9, 5.0 Hz, 1H), 2.71 - 2.61 (m, 3H), 2.60 - 2.54 (m, 1H), 2.52 - 2.44 (m, 1H), 2.40 (t, *J*=7.5 Hz, 2H), 2.19 - 1.80 (m, 6H), 1.75 (s, 3H), 1.73 - 1.04 (m, 18H), 1.23 (s, 3H), 1.11 (s, 3H), 1.05 (s, 3H), 0.99 (t, *J*=7.5 Hz, 3H), 0.97 (s, 3H), 0.97 (s, 3H).

Example B62

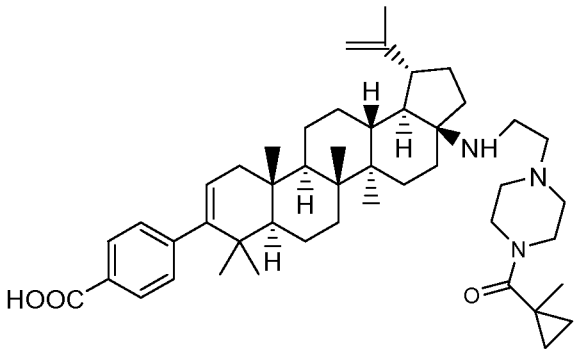
Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(cyclopropanecarbonyl)piperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid



The title compound (0.9 mg) was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using cyclopropanecarboxylic acid as the acylating agent. LCMS: m/e 710.8 $(M+H)^+$, 4.41 min (method 15). ^{1}H NMR (500MHz, METHANOL-d_4) δ 7.88 (d, *J*=7.9 Hz, 2H), 7.16 (d, *J*=7.9 Hz, 2H), 5.30 (d, *J*=4.9 Hz, 1H), 4.78 (s, 1H), 4.67 (s, 1H), 3.84 (br. s., 2H), 3.77 - 3.50 (m, 2H), 3.09 - 2.97 (m, 1H), 2.94 - 2.81 (m, 2H), 2.77 (td, *J*=10.5, 5.3 Hz, 1H), 2.73 - 2.57 (m, 4H), 2.48 (br. s., 1H), 2.21 - 1.82 (m, 8H), 1.75 (s, 3H), 1.73 - 1.07 (m, 15H), 1.24 (s, 3H), 1.10 (s, 3H), 1.06 (s, 3H), 0.97 (s, 3H), 0.97 (s, 3H), 0.93 - 0.87 (m, 2H), 0.87 - 0.79 (m, 2H).

Example B63

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(4-(1-methylcyclopropanecarbonyl)piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

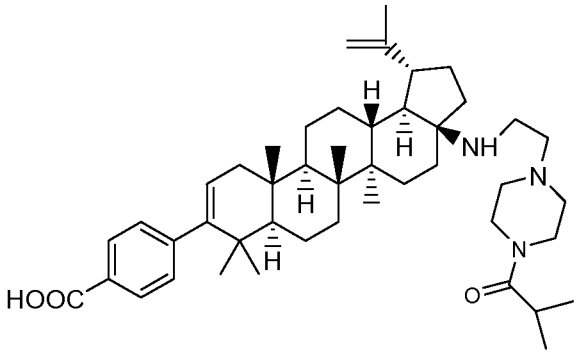


The title compound (0.9 mg) was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-

cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using 1-methylcyclopropane-1-carboxylic acid as the acylating agent. LCMS: m/e 724.8 $(M+H)^+$, 4.49 min (method 15). ^{1}H NMR (500MHz, METHANOL-d_4) δ 7.89 (d, *J*=8.2 Hz, 2H), 7.16 (d, *J*=8.2 Hz, 2H), 5.30 (d, *J*=4.6 Hz, 1H), 4.78 (s, 1H), 4.67 (s, 1H), 3.90 - 3.63 (m, 4H), 3.09 - 2.98 (m, 1H), 2.96 - 2.82 (m, 2H), 2.81 - 2.73 (m, 1H), 2.71 - 2.61 (m, 3H), 2.54 (br. s., 2H), 2.24 - 2.12 (m, 1H), 2.11 - 1.82 (m, 5H), 1.75 (s, 3H), 1.72 - 1.14 (m, 16H), 1.32 (s., 3H), 1.23 (s., 3H), 1.11 (s, 3H), 1.06 (s, 3H), 0.97 (s, 3H), 0.97 (s, 3H), 0.93 - 0.88 (m, 2H), 0.68 - 0.58 (m, 2H).

Example B64

Preparation of 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-isobutyrylpiperazin-1-yl)ethyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoic acid

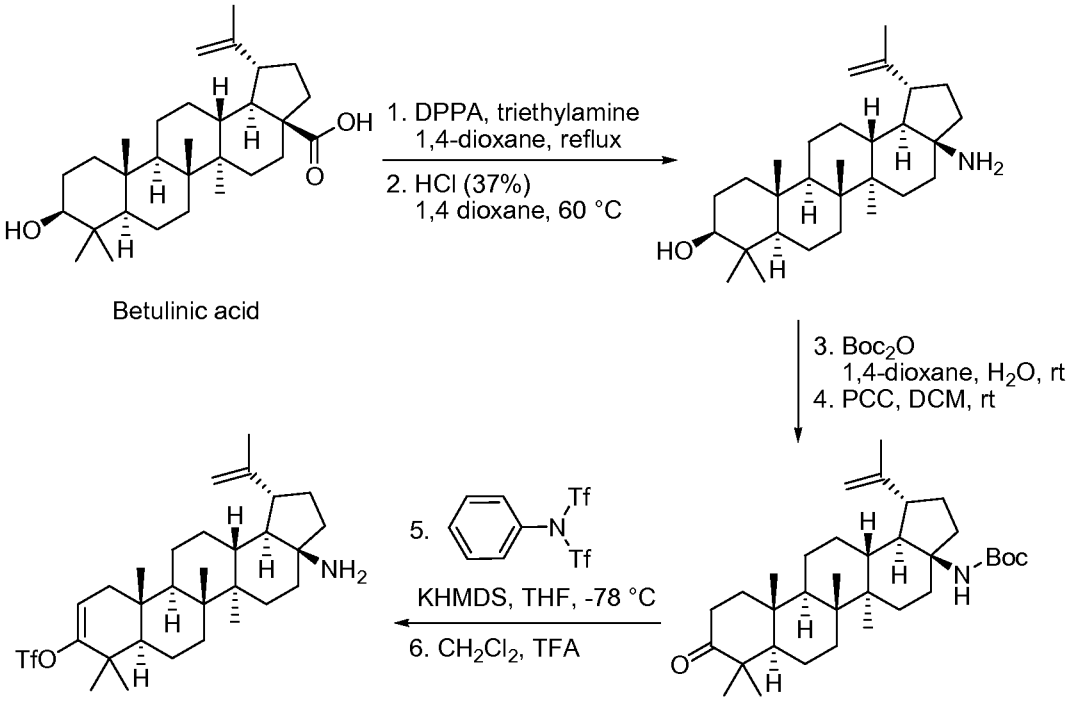


The title compound (0.4 mg) was prepared from methyl 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-3a-((2-(piperazin-1-yl)ethyl)amino)-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl)benzoate following the general procedure as described above using isobutyric acid as the acylating agent. LCMS: m/e 712.8 $(M+H)^+$, 4.46 min (method 15). ^{1}H NMR (500MHz, METHANOL-d_4) δ 7.88 (d, *J*=8.2 Hz, 2H), 7.15 (d, *J*=7.9 Hz, 2H), 5.30 (d, *J*=4.9 Hz, 1H), 4.78 (s, 1H), 4.67 (s, 1H), 3.77 - 3.54 (m, 4H), 2.97 (dt, *J*=13.4, 6.6 Hz, 2H), 2.86 - 2.71 (m, 3H), 2.70 - 2.51 (m, 4H), 2.46

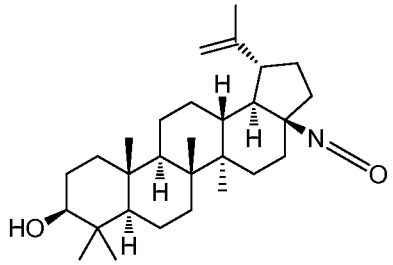
(br. s., 1H), 2.15 (dd, *J*=17.1, 6.4 Hz, 1H), 2.08 - 1.82 (m, 5H), 1.75 (s, 3H), 1.73 - 1.18 (m, 16H), 1.22 (s, 3H), 1.11 (d, *J*=6.7 Hz, 6H), 1.10 (s, 3H), 1.05 (s, 3H), 0.97 (s., 3H), 0.97 (s., 3H),

Example B65

Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate

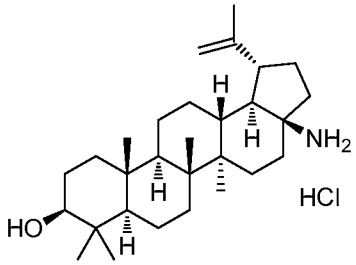


Step 1. Preparation of (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-9-ol



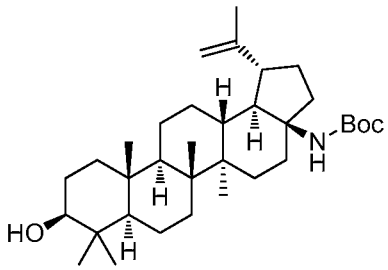
To a suspension of betulinic acid (10 g, 21.90 mmol) in 1,4-Dioxane (100 mL) was added triethylamine (9.16 mL, 65.7 mmol) and diphenyl phosphorazidate (7.08 mL, 32.8 mmol). The mixture was heated to reflux. Upon heating, all solids dissolved. After heating the mixture for 26h, the mixture was cooled to rt and was concentrated under reduced pressure. The residue was diluted with 100 mL of water and was extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried with sodium sulfate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography in silica gel using a 0-15% EtOAc in hexanes gradient and a Thomson 240g silica gel column. The fractions containing the expected product were combined and concentrated under reduced pressure. A second batch of less-pure product was concentrated and was repurified using a Thomson 240g column and the same gradient The fractions containing the expected product were combined with the first batch to give (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-9-ol (7.76 g, 17.10 mmol, 78 % yield) as a white solid. ^{1}H NMR (400MHz, *chloroform-d*) δ = 4.75 (s, 1H), 4.67 - 4.62 (m, 1H), 3.20 (dt, *J*=11.3, 5.6 Hz, 1H), 2.55 (td, *J*=10.9, 5.9 Hz, 1H), 2.17 - 2.03 (m, 1H), 1.92 - 1.76 (m, 5H), 1.69 (s, 3H), 1.06 (s, 3H), 0.98 (s, 3H), 0.95 (s, 3H), 0.85 (s, 3H), 0.78 (s, 3H), 1.74 - 0.66 (m, 19H).

Step 2. Preparation of (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-9-ol, HCl



To a solution of (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-isocyanato-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-9-ol (7.76 g, 17.10 mmol) in 1,4-dioxane (100 mL) was added HCl (37%) (21.07 mL, 257 mmol). The mixture was heated to 60 °C for 15h of heating then was cooled to rt and was concentrated under reduced pressure. The residue was dissolved in dichloromethane and methanol and was concentrated two additional times to give (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-9-ol, HCl (7.75 g, 16.70 mmol, 98 % yield) as an off-white foam. The crude product was used in the next step with no purification.

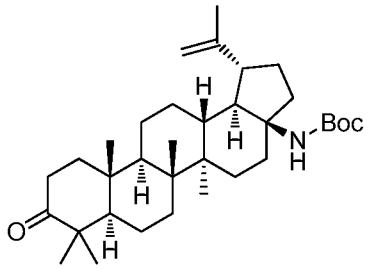
Step 3. Preparation of tert-butyl ((1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-9-hydroxy-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-3a-yl)carbamate



To a solution of (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-9-ol, HCl (7.76 g, 16.72 mmol) in 1,4-Dioxane (100 mL) was added water (25 mL), sodium bicarbonate (4.21 g, 50.2 mmol) and Boc anhydride (5.82 mL, 25.08 mmol). The mixture was stirred at rt for 16h then the mixture was diluted with 100 mL of water and was extracted with ethyl acetate (3 x 100 mL). The combined organic

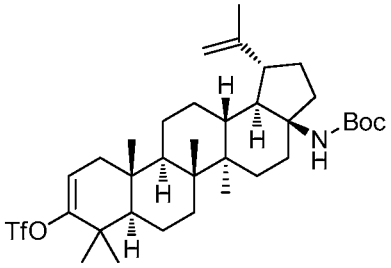
layers were washed with brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure to give tert-butyl ((1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-9-hydroxy-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-3a-yl)carbamate as an off-white foam. ^{1}H NMR (500MHz, *chloroform-d*) δ = 4.74 (d, *J*=1.6 Hz, 1H), 4.64 - 4.62 (m, 1H), 4.34 (br. s., 1H), 3.24 - 3.18 (m, 1H), 2.63 - 2.35 (m, 3H), 2.06 - 1.93 (m, 1H), 1.71 (s, 3H), 1.46 (s, 9H), 1.04 (s, 3H), 0.99 (s, 3H), 0.98 (s, 3H), 0.86 (s, 3H), 0.79 (s, 3H), 1.77 - 0.68 (m, 22H).

Step 4. Preparation of tert-butyl ((1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-3a-yl)carbamate



To a solution of the resulting tert-butyl ((1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-9-hydroxy-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-3a-yl)carbamate in dichloromethane (100 mL) was added pyridinium chlorochromate (4.69 g, 21.74 mmol). The mixture was stirred at rt for 5h then an additional 1.0g of PCC was added and the mixture was stirred at rt for 1h. The mixture was filtered through a plug of silica gel and celite which was washed with a solution of 25% ethyl acetate in hexanes. The filtrate was concentrated under reduced pressure to give tert-butyl ((1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-3a-yl)carbamate as a light-yellow foam. ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 4.74 (d, *J*=1.7 Hz, 1H), 4.63 (t, *J*=1.7 Hz, 1H), 4.34 (br. s., 1H), 2.65 - 2.34 (m, 5H), 2.05 - 1.88 (m, 2H), 1.71 (s, 3H), 1.47 (s, 9H), 1.10 (s, 3H), 1.08 (s, 3H), 1.05 (s, 3H), 0.99 (s, 3H), 0.96 (s, 3H), 1.76 - 0.93 (m, 18H).

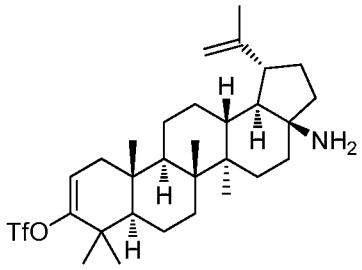
Step 5. Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((tert-butoxycarbonyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate



A solution of the resulting tert-butyl ((1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-1H-cyclopenta[a]chrysen-3a-yl)carbamate in THF (100 mL) was cooled to -78 °C. To the solution was added KHMDS (0.91M in THF) (40.4 mL, 36.8 mmol). The mixture was stirred for 20 minutes at -78 °C then a solution of 1,1,1-trifluoro-N-phenyl-N-(trifluoromethyl)sulfonyl methanesulfonamide (7.47 g, 20.90 mmol) in THF (100 mL) was added via canula. The mixture was stirred at -78 °C for 5h then was quenched with 100 mL of water and was extracted with ethyl acetate (3 x 75 mL). The combined organic layers were dried with magnesium sulfate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was taken up in a small amount of DCM and methanol and the yellow solids that formed were removed by filtration. The filtrate was again concentrated and treated with methanol and the solids that formed were again removed by filtration. The filtrate was concentrated and was adsorbed to silica gel and was then purified by flash chromatography using a 0-50% ethyl acetate in hexanes gradient and a Thomson 240g silica gel column. The fractions containing the deprotected product were combined and were concentrated under reduced pressure to give a mixture of products The expected product was repurified by flash chromatography using a 0-10% EtOAc in hexanes gradient and a 240g Thomson silica gel column. The fractions containing the expected product were combined and were concentrated under reduced pressure to give (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((tert-butoxycarbonyl)amino)-

5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (1.31g, 1.99 mmol, 11.9% over 3 steps). ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 5.57 (dd, *J*=6.7, 1.8 Hz, 1H), 4.73 (s, 1H), 4.62 (s, 1H), 4.32 (br. s., 1H), 2.64 - 2.31 (m, 3H), 2.16 (dd, *J*=17.0, 6.8 Hz, 1H), 2.04 - 1.94 (m, 1H), 1.70 (s, 3H), 1.45 (s, 9H), 1.13 (s, 3H), 1.06 (s, 3H), 1.03 (s, 3H), 0.97 (s, 3H), 0.93 (s, 3H), 1.82 - 0.86 (m, 18H).

Step 6. Preparation of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate



To a solution of (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((tert-butoxycarbonyl)amino)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (0.2 g, 0.304 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (0.5 mL, 6.49 mmol). The mixture was stirred at rt for 1.5h then was concentrated under reduced pressure. The residue was diluted with saturated aqueous sodium bicarbonate (20 mL) and was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried with Na_2SO_4. The drying agent was removed by filtration and the filtrate was concentrated and adsorbed to silica gel then was purified by flash chromatography using a 12-100% ethyl acetate in hexanes gradient and a 12g Thomson silica gel column. The fractions containing the expected product were combined and were concentrated under reduced pressure to give (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentamethyl-

1-(prop-1-en-2-yl)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-cyclopenta[a]chrysen-9-yl trifluoromethanesulfonate (0.109 g, 0.195 mmol, 64.3 % yield) as an off-white solid. ^{1}H NMR (500MHz, *chloroform-d*) δ = 5.57 (dd, *J*=6.8, 1.9 Hz, 1H), 4.73 (d, *J*=1.6 Hz, 1H), 4.63 - 4.60 (m, 1H), 2.54 (td, *J*=10.9, 5.3 Hz, 1H), 2.17 (dd, *J*=17.1, 6.9 Hz, 1H), 2.08 - 1.99 (m, 1H), 1.70 (s, 3H), 1.13 (s, 3H), 1.08 (s, 3H), 1.03 (s, 3H), 0.97 (s, 3H), 0.93 (s, 3H), 1.82 - 0.91 (m, 20H).

Biology Data for the Examples

- "μM" means micromolar;
- "mL" means milliliter;
- "μl" means microliter;
- "mg" means milligram;
- "μg" means microgram;

The materials and experimental procedures used to obtain the results reported in Tables 1-2 are described below.

HIV cell culture assay - MT-2 cells and 293T cells were obtained from the NIH AIDS Research and Reference Reagent Program. MT-2 cells were propagated in RPMI 1640 media supplemented with 10% heat inactivated fetal bovine serum, 100 μg/ml penicillin G and up to 100 units/ml streptomycin. The 293T cells were propagated in DMEM media supplemented with 10% heat inactivated fetal bovine serum (FBS), 100 units/ml penicillin G and 100 μg/ml streptomycin. The proviral DNA clone of NL_{4-3} was obtained from the NIH AIDS Research and Reference Reagent Program. A recombinant NL_{4-3} virus, in which a section of the nef gene from NL4-3 was replaced with the *Renilla* luciferase gene, was used as a reference virus. In addition, residue Gag P373 was converted to P373S. Briefly, the recombinant virus was prepared by transfection of the altered proviral clone of NL_{4-3}. Transfections were performed in 293T cells using LipofectAMINE PLUS from Invitrogen (Carlsbad, CA), according to manufacturer's instruction. The virus was titered in MT-2 cells using luciferase enzyme activity as a marker. Luciferase was quantitated using the Dual Luciferase kit

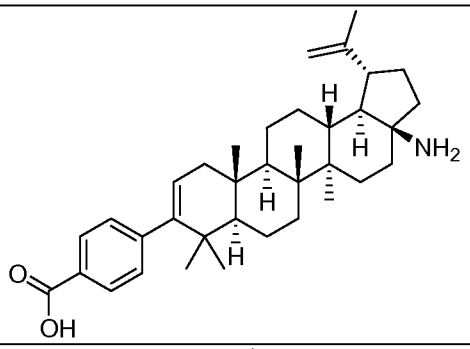
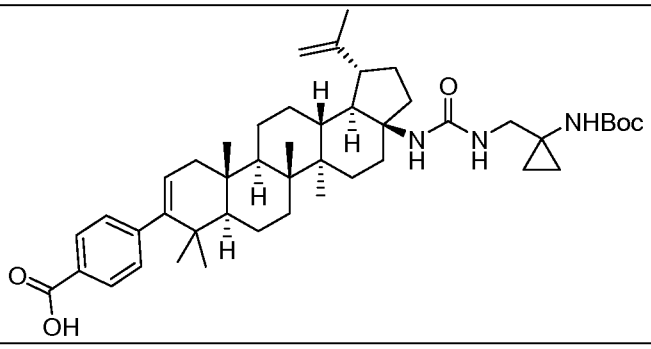
from Promega (Madison, WI), with modifications to the manufacturer's protocol. The diluted Passive Lysis solution was pre-mixed with the re-suspended Luciferase Assay Reagent and the re-suspended Stop & Glo Substrate (2:1:1 ratio). Fifty (50) μL of the mixture was added to each aspirated well on assay plates and luciferase activity was measured immediately on a Wallac TriLux (Perkin-Elmer). Antiviral activities of inhibitors toward the recombinant virus were quantified by measuring luciferase activity in cells infected for 4-5 days with NLRluc recombinants in the presence serial dilutions of the inhibitor. The EC_{50} data for the compounds is shown in Table 2. Table 1 is the key for the data in Table 2.

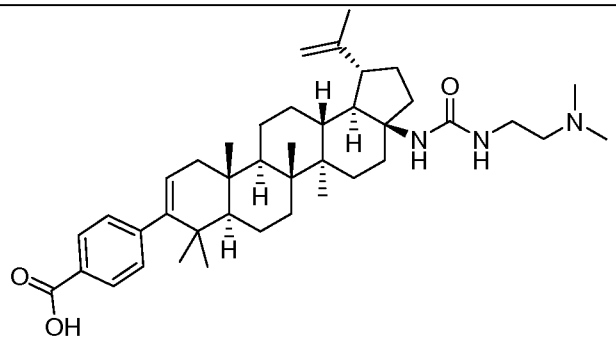
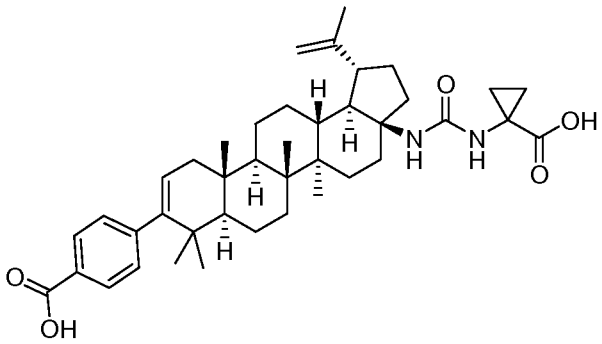
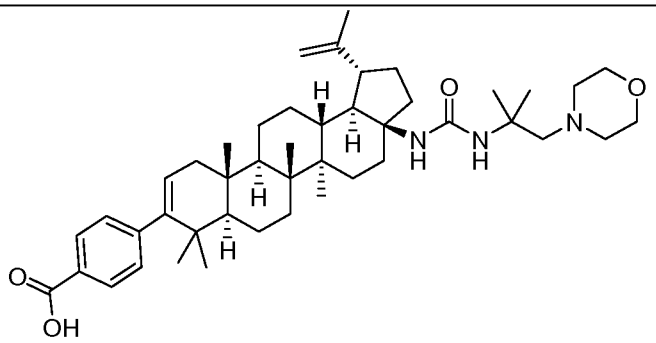
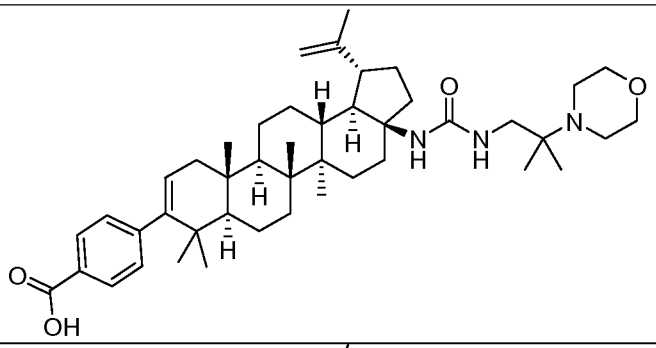
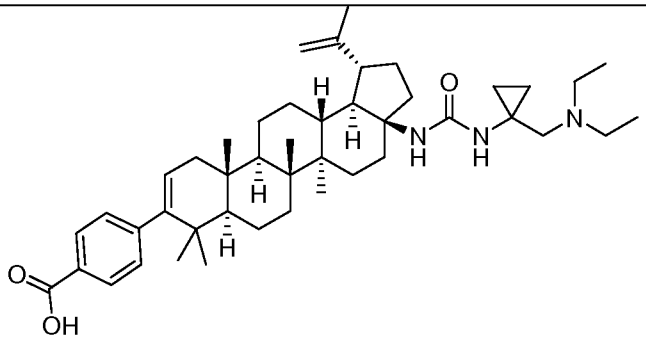
Results

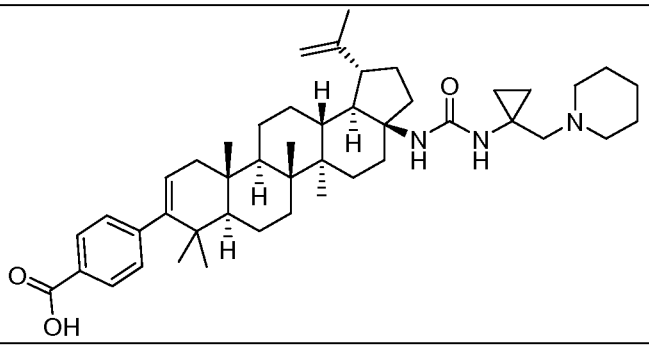
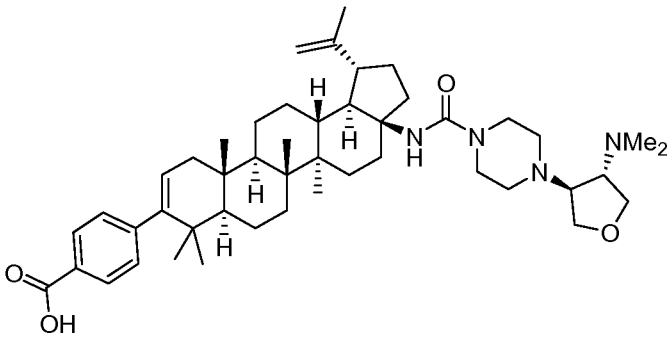
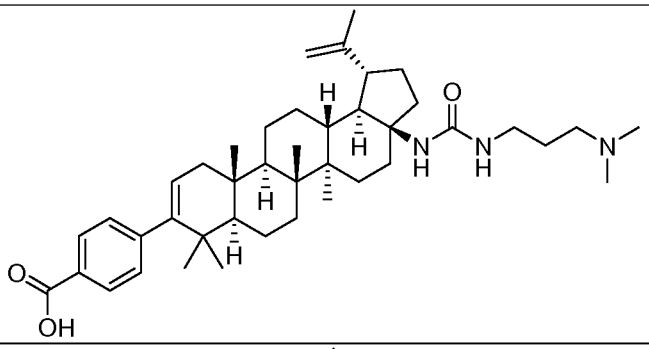
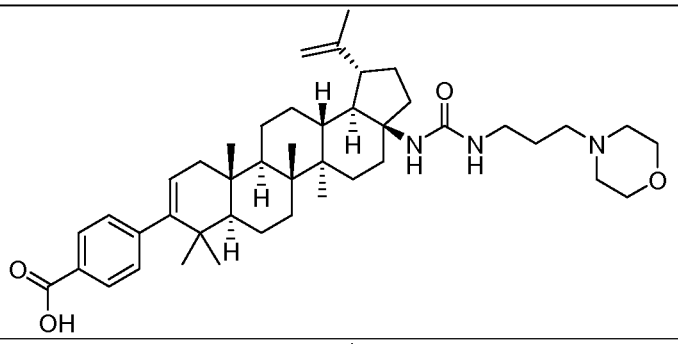
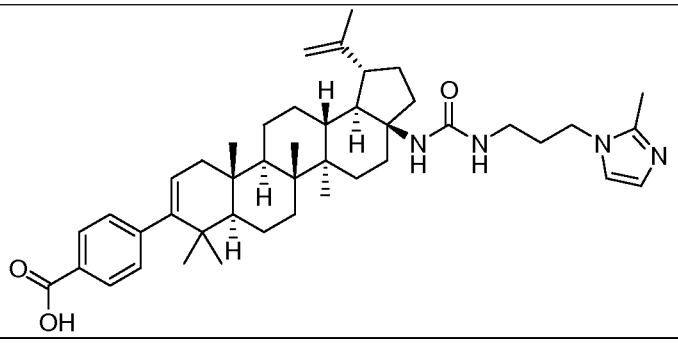
Table 1. Biological Data Key for EC_{50}

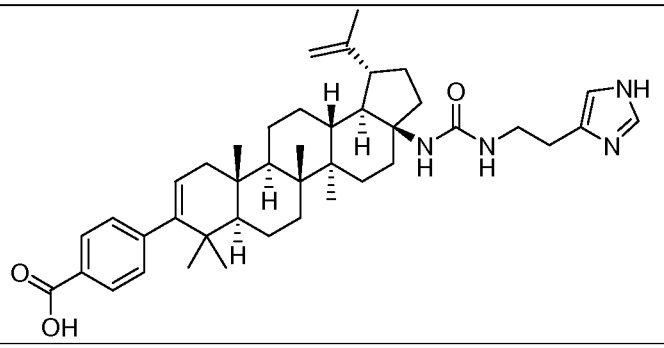
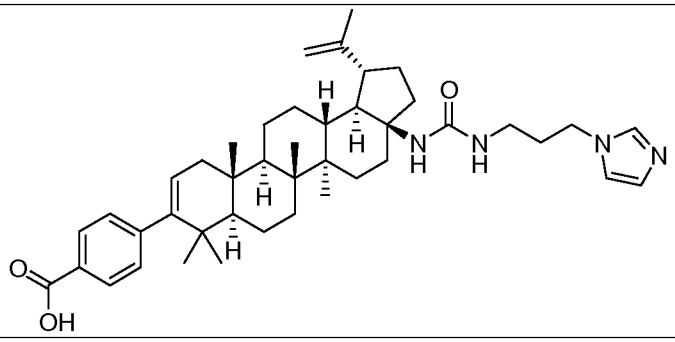
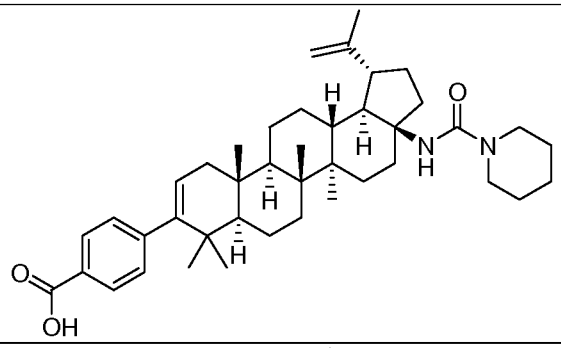
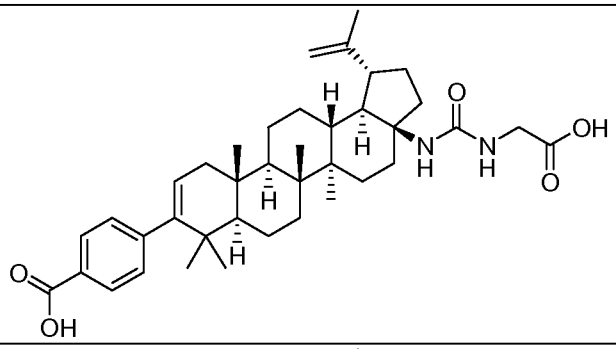
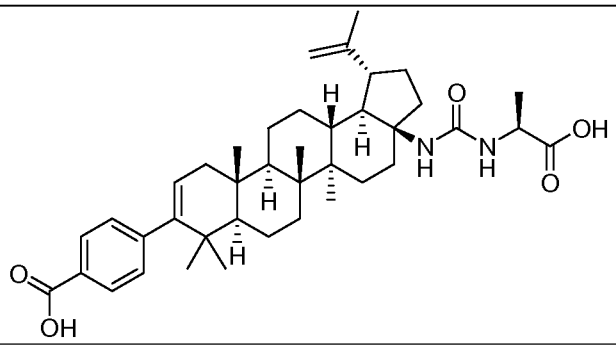
Compounds with EC_{50} >0.1 μM	Compounds with EC_{50} < 0.1 μM
Group "B"	Group "A"

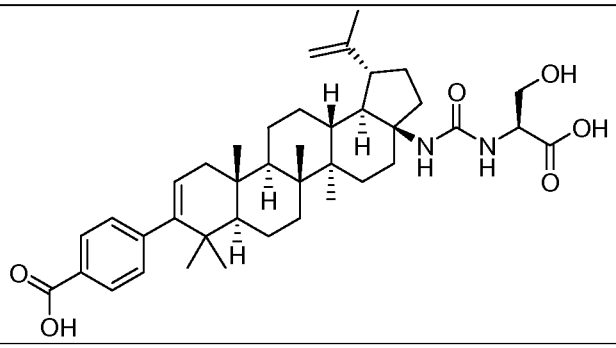
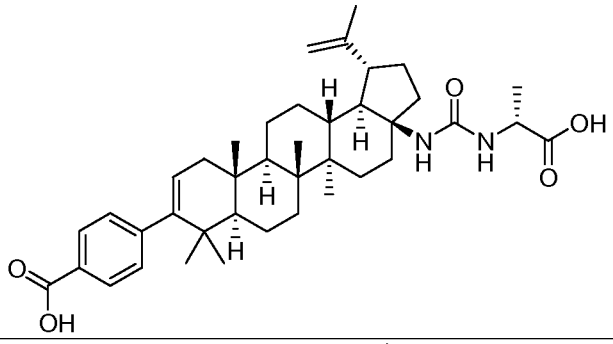
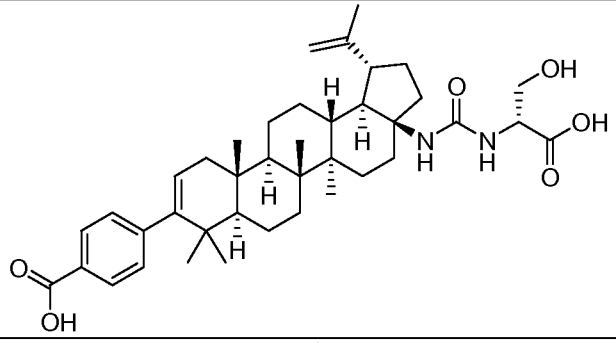
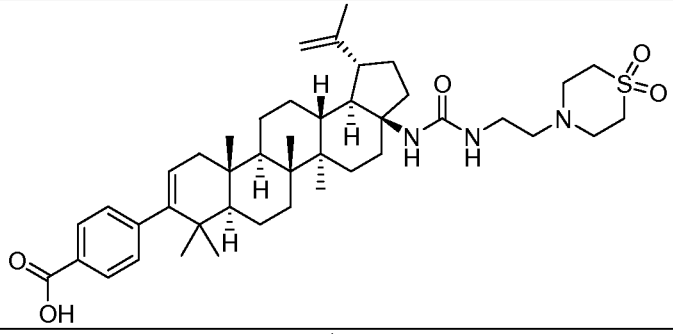
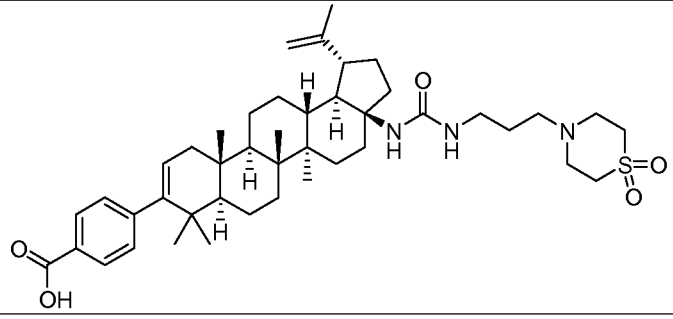
Table 2

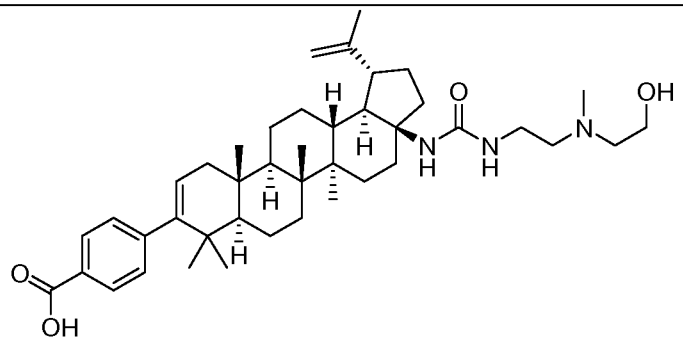
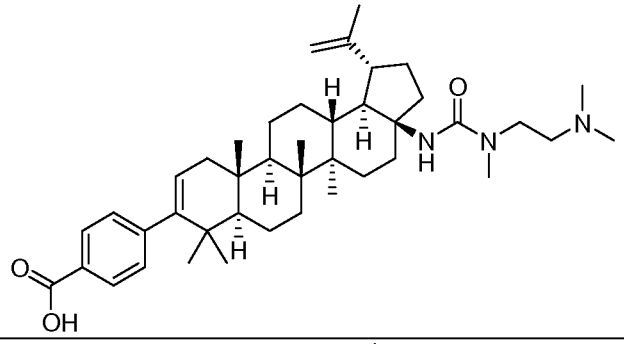
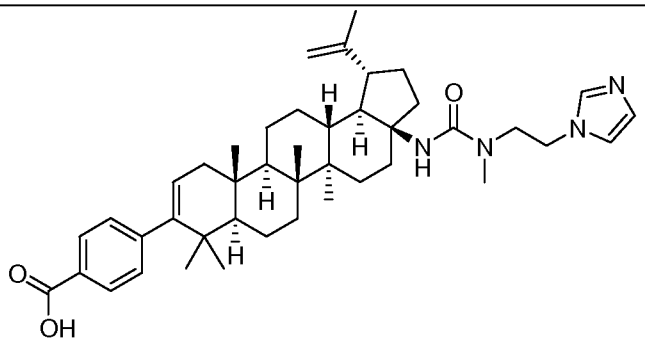
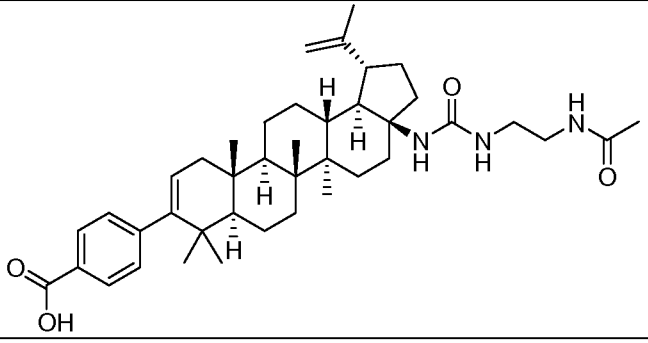
Example #	Structure	EC_{50} (μM)
1		A
2		A

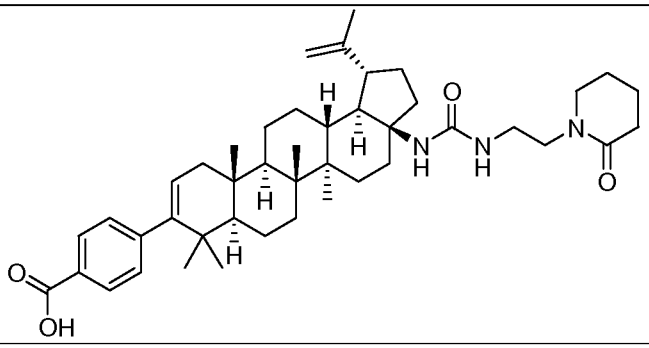
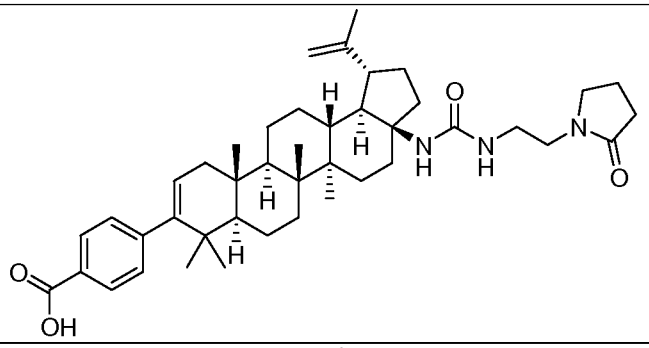
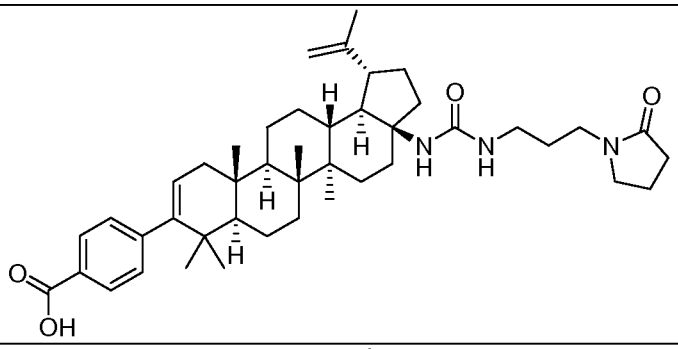
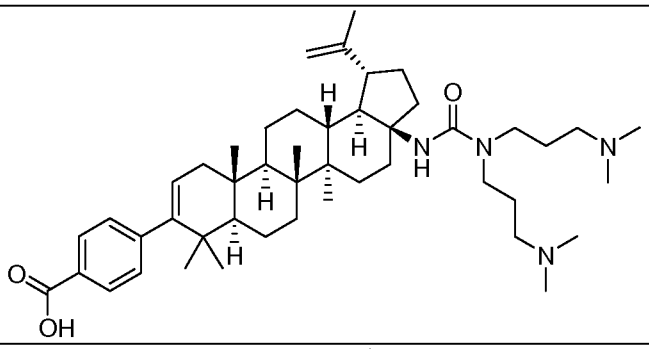
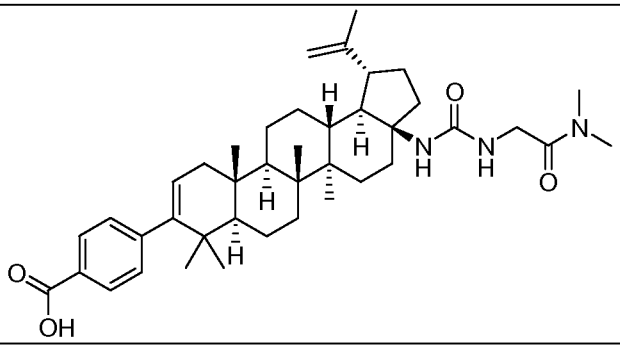
3		0.004
4		B
5		A
6		A
7		A

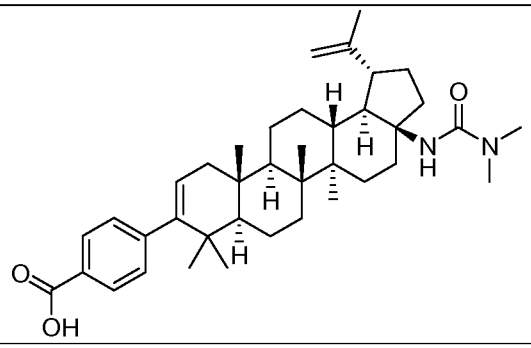
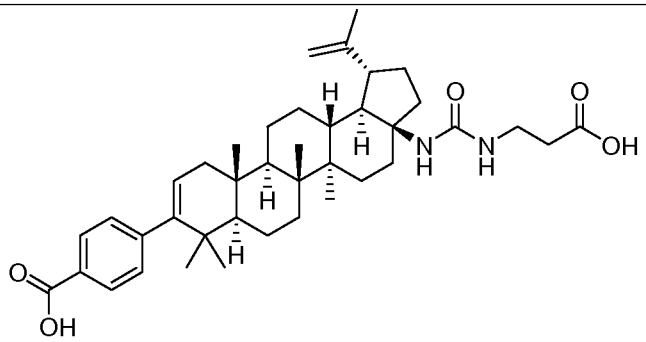
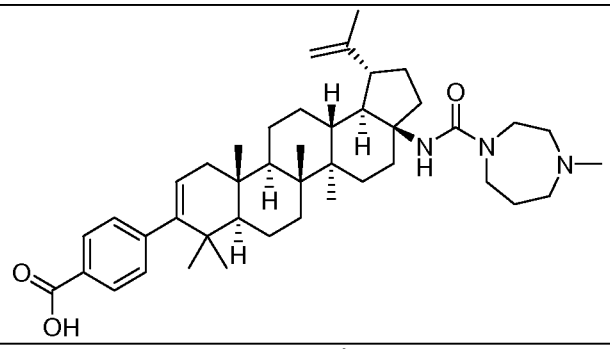
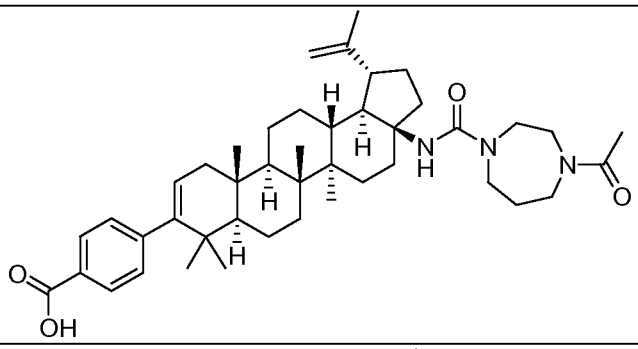
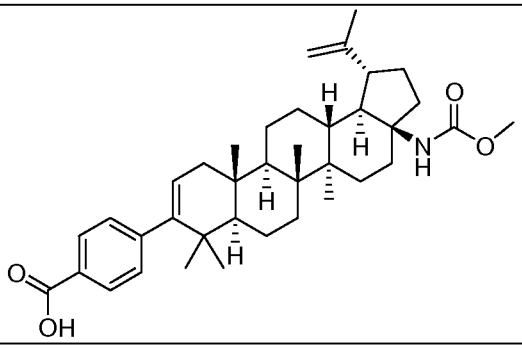
8		A
9		0.003
10		A
11		A
12		A

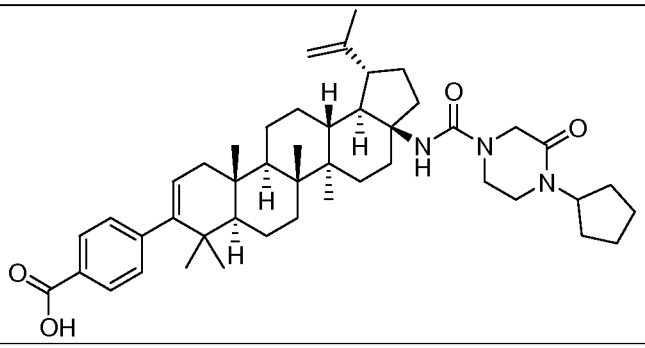
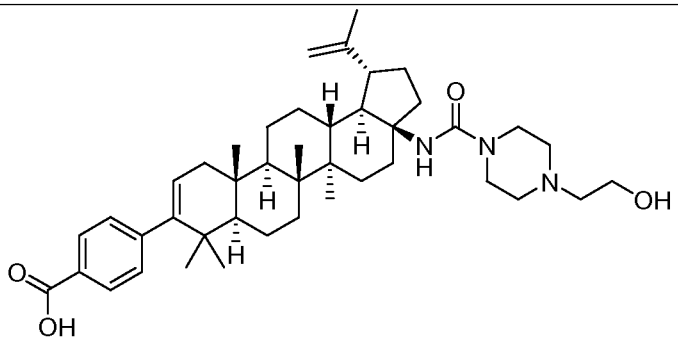
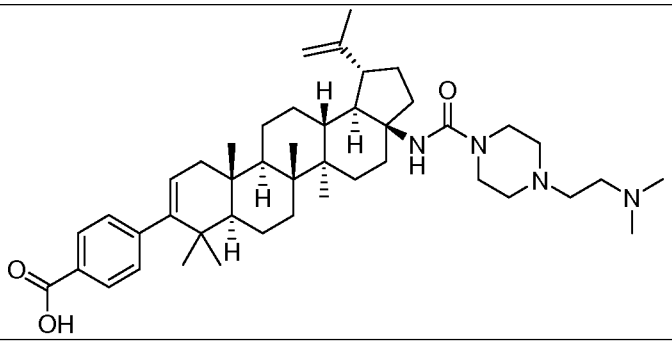
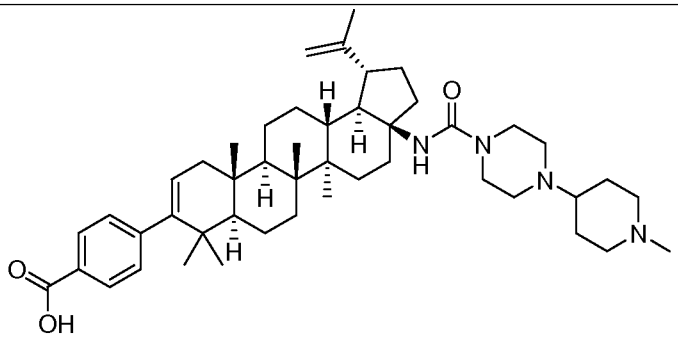
13		A
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16		A
17		A

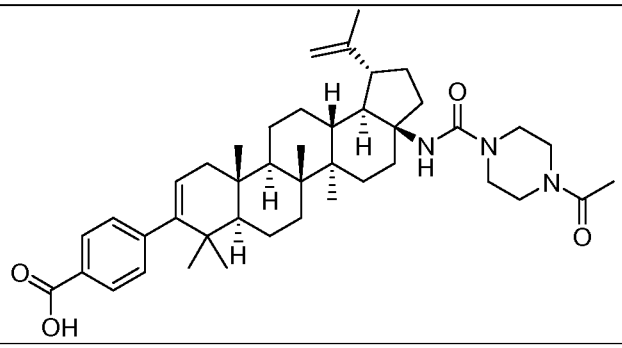
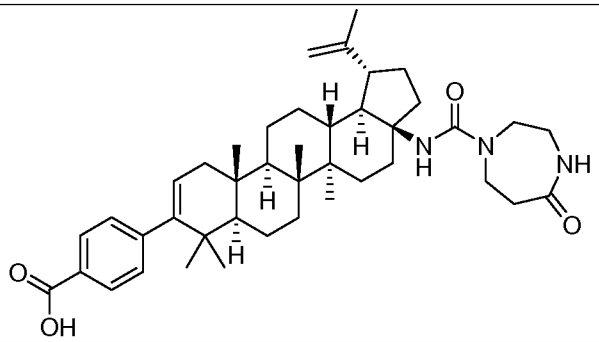
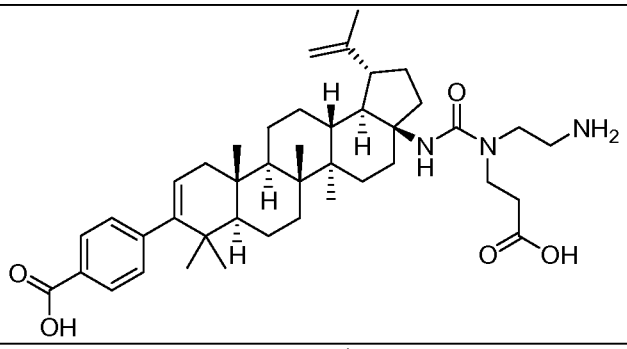
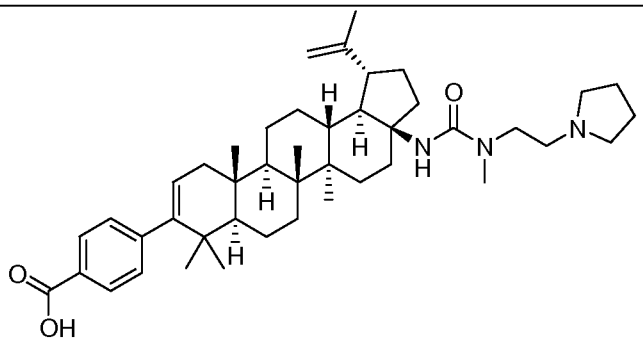
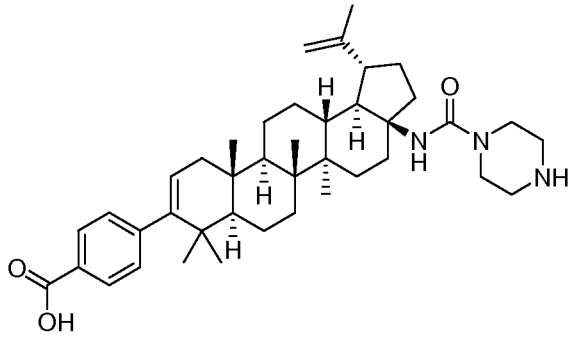
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21		A
22		A

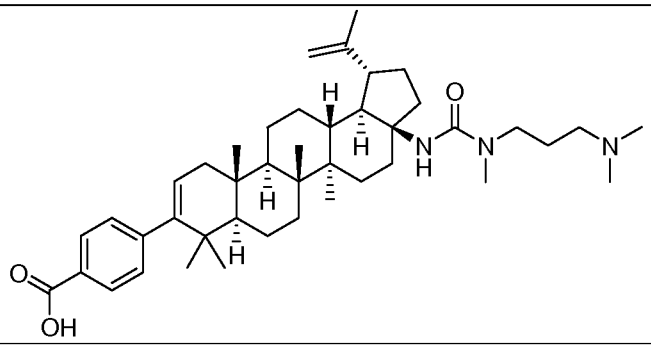
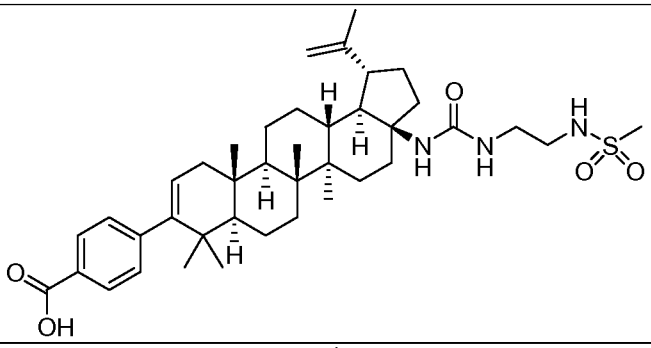
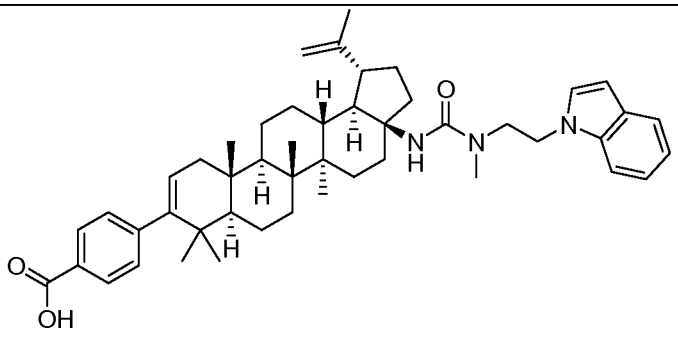
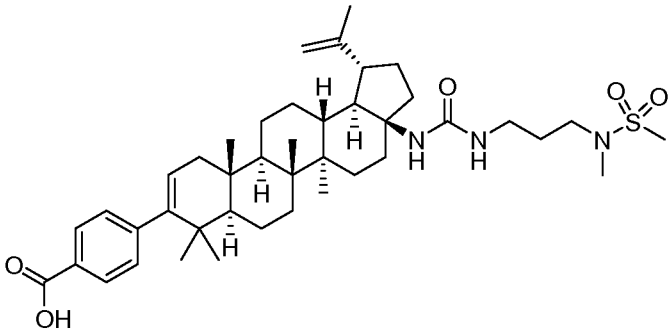
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25		A
26		A

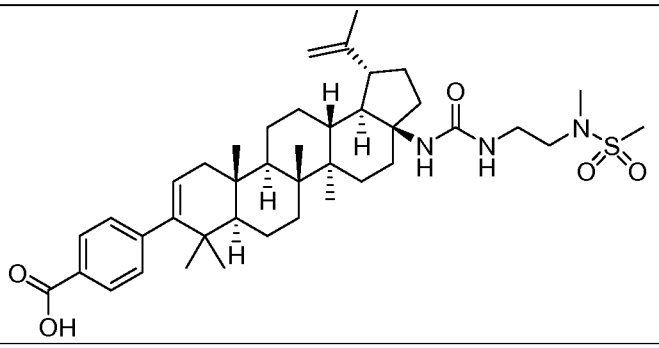
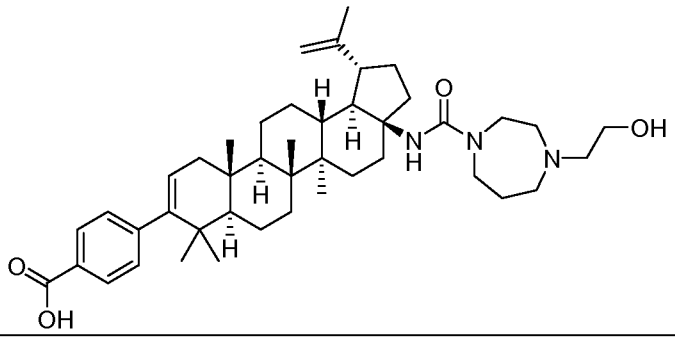
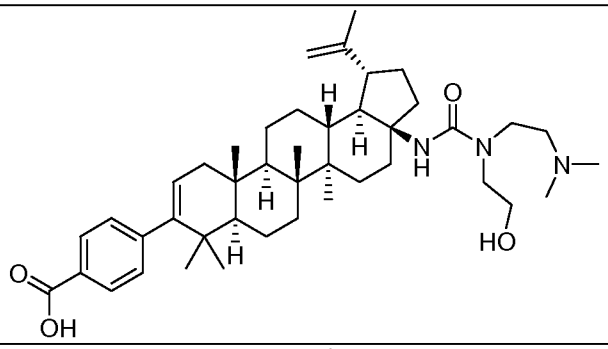
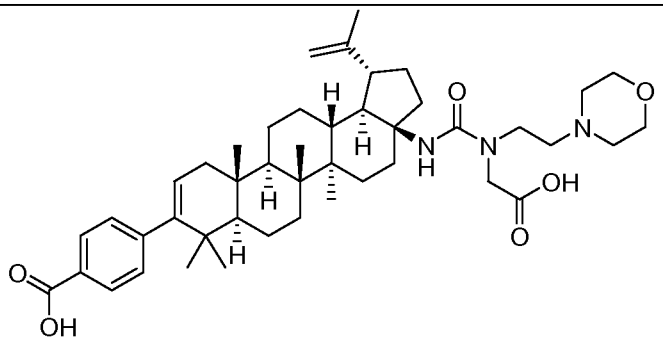
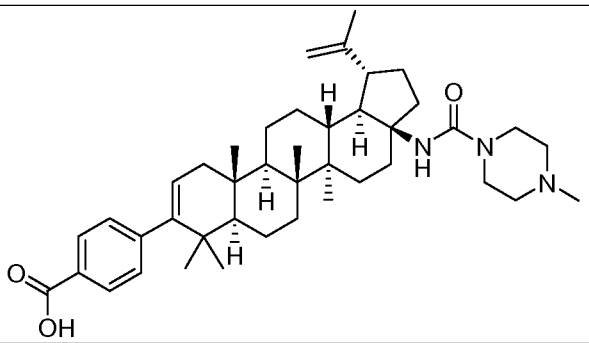
27		A
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29		0.01
30		A
31		A

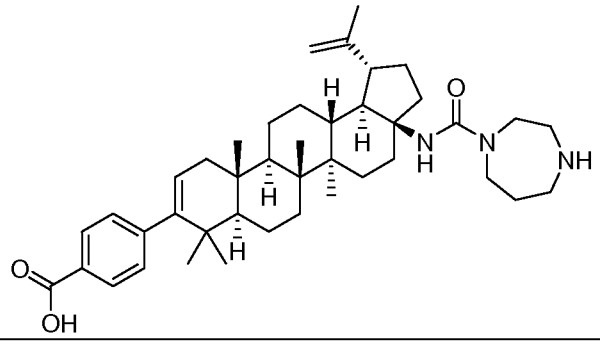
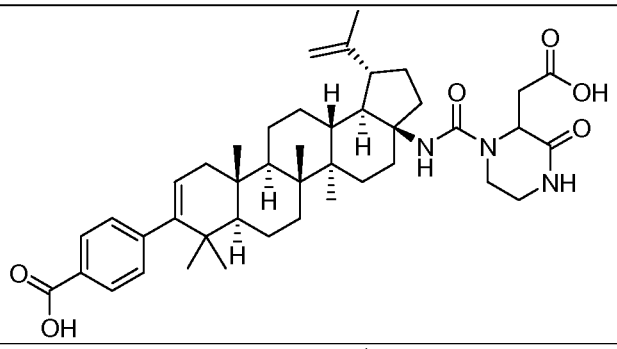
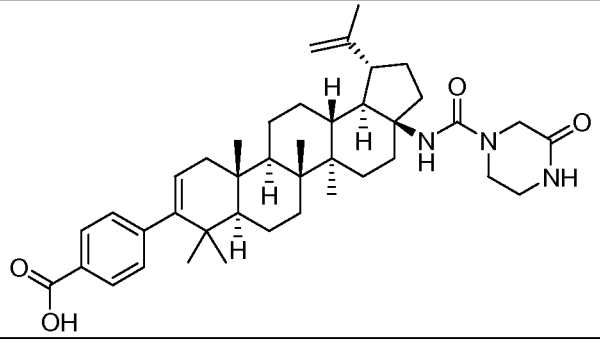
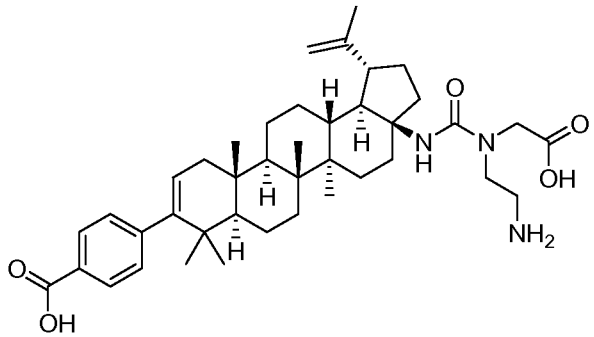
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33		A
34		0.002
35		A
36		A

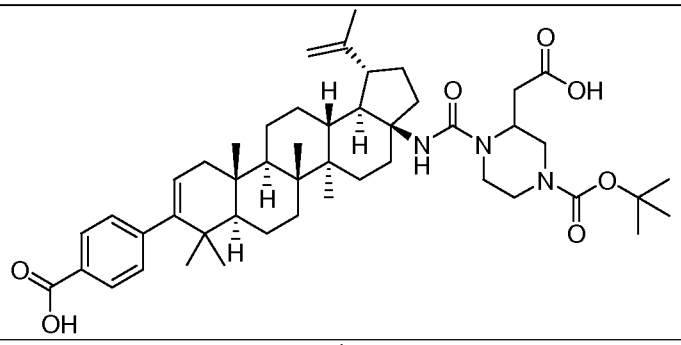
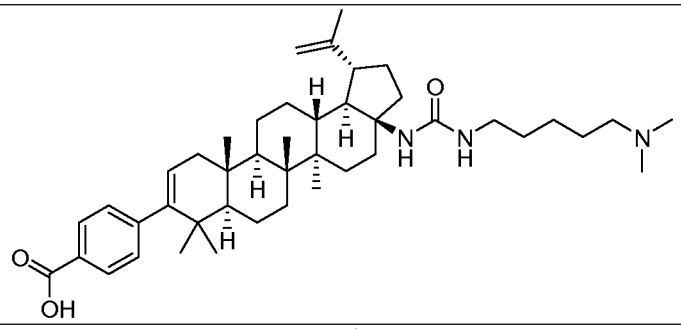
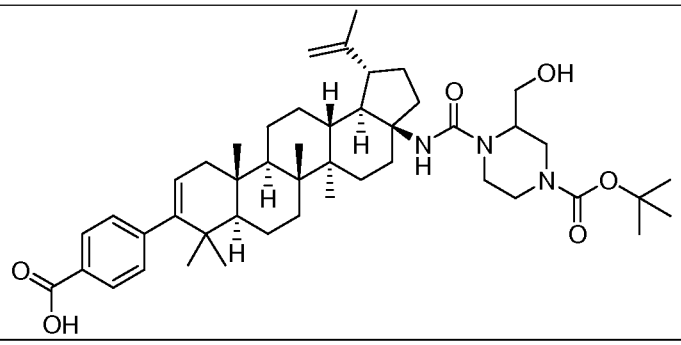
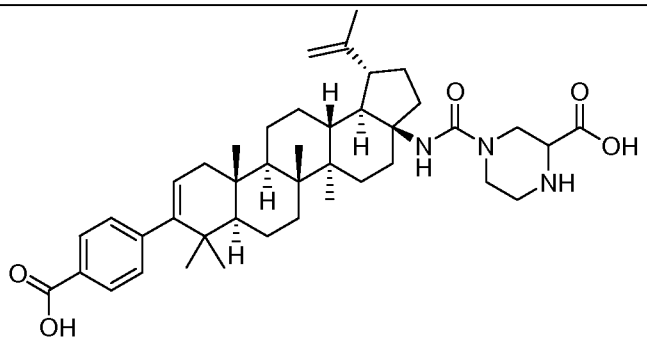
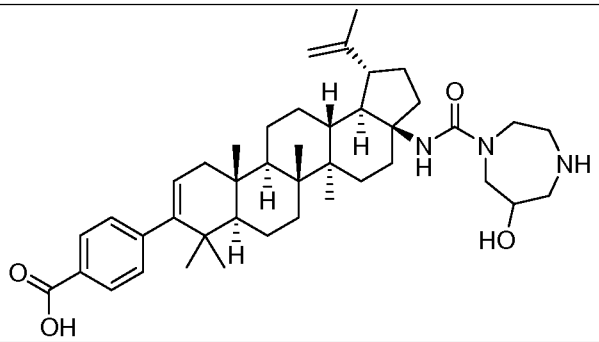
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38		A
39		A
40		A
41		A

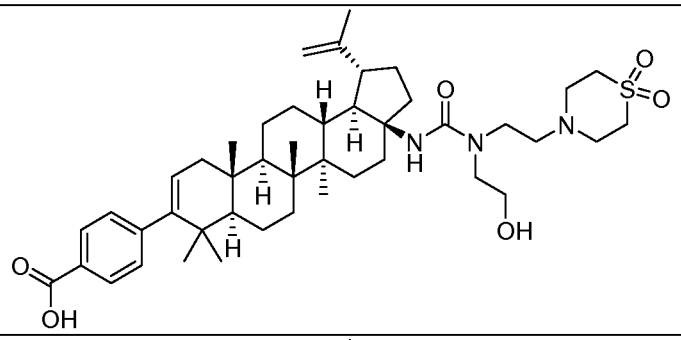
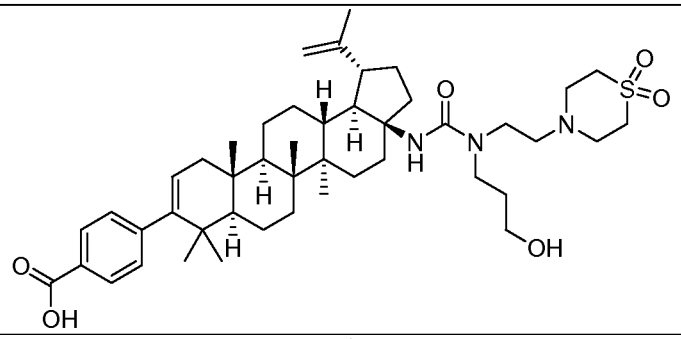
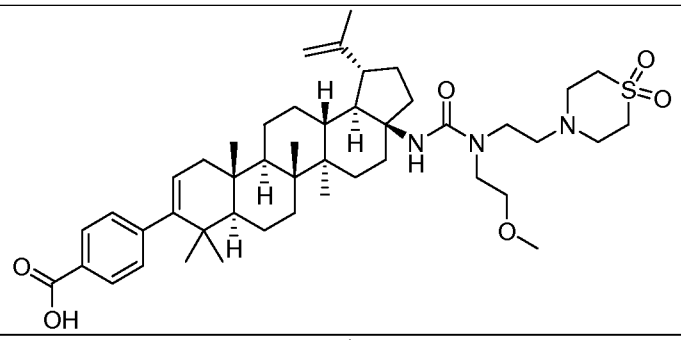
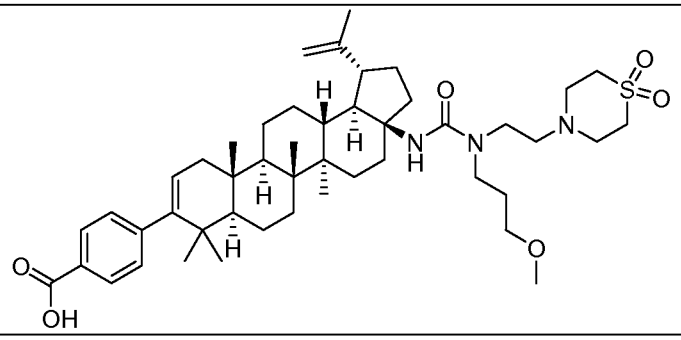
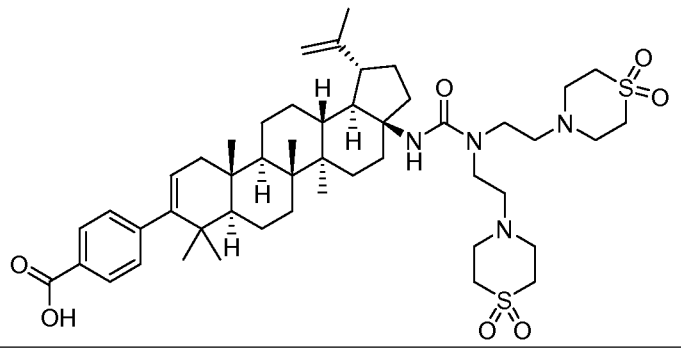
		
42		A
43		0.03
44		A
45		A

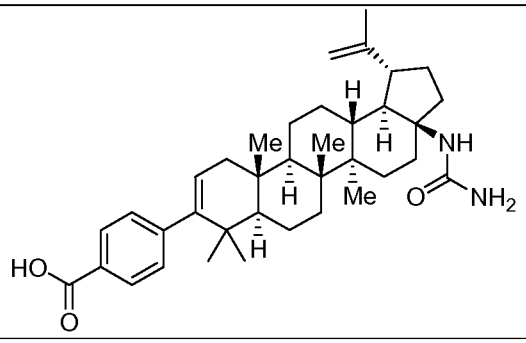
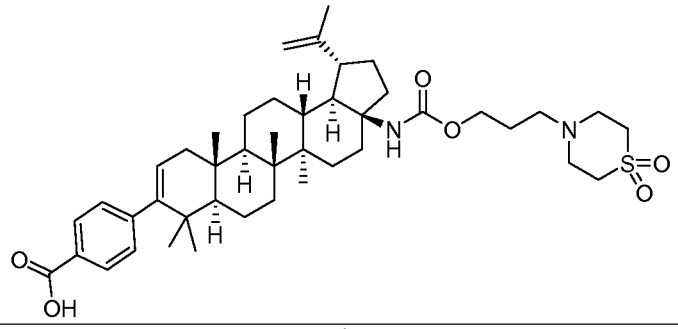
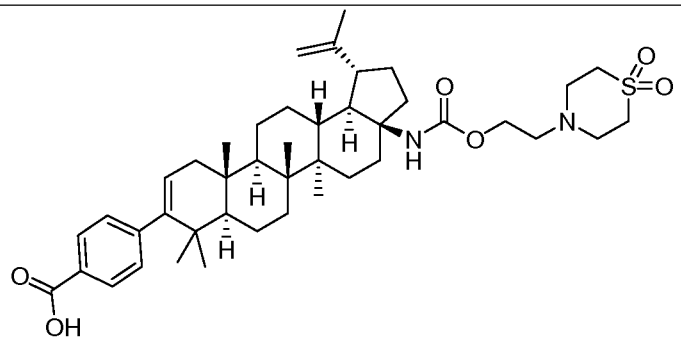
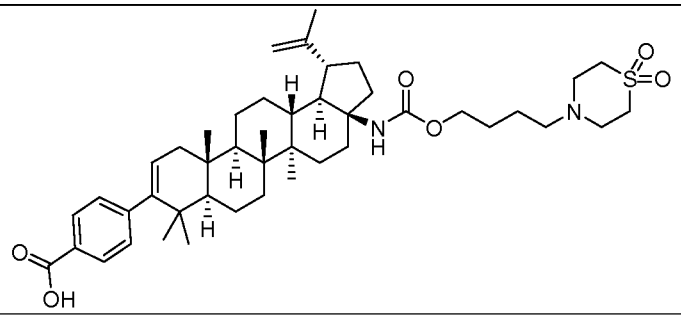
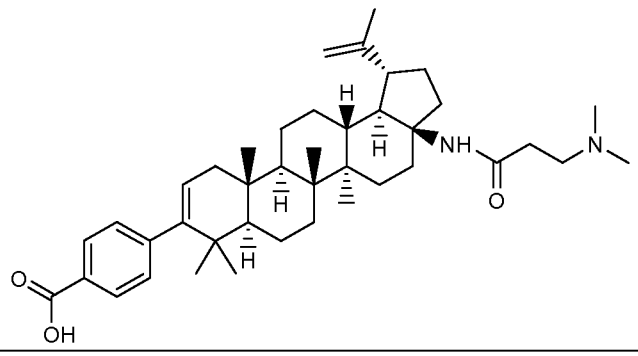
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47		A
48		A
49		A

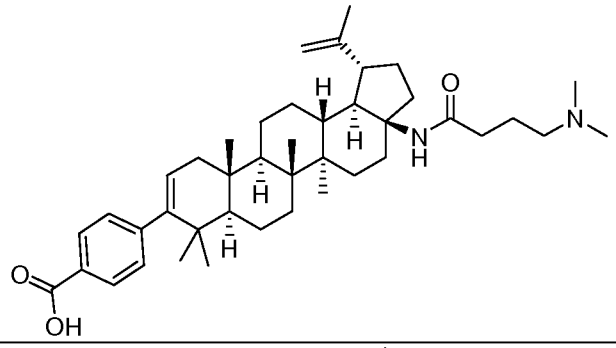
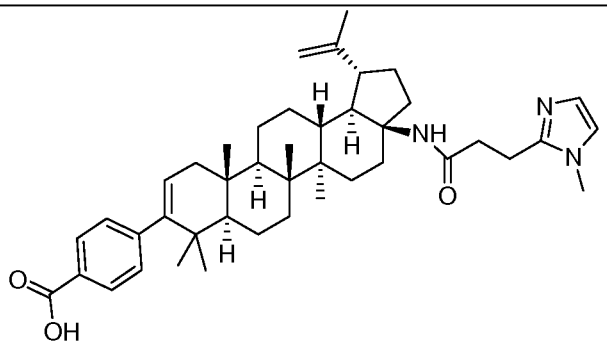
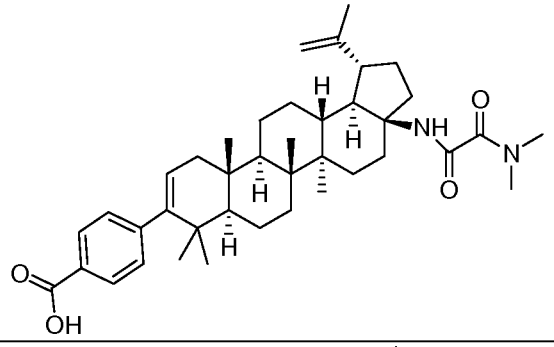
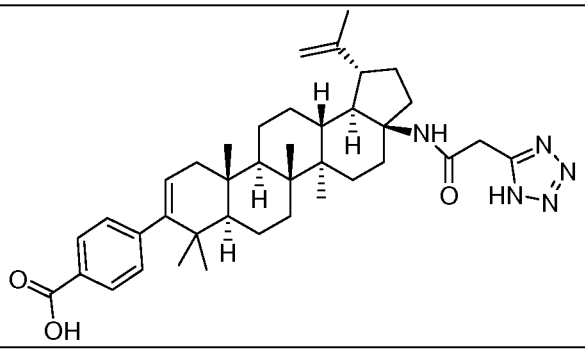
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53		A
54		A

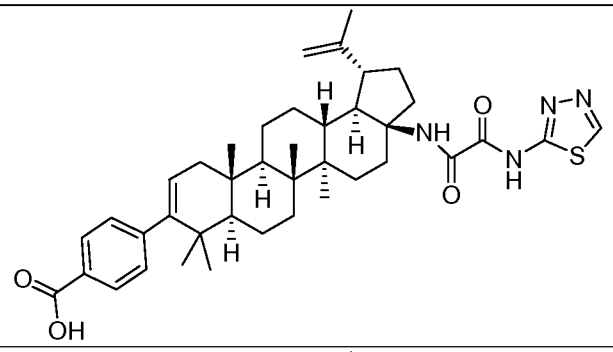
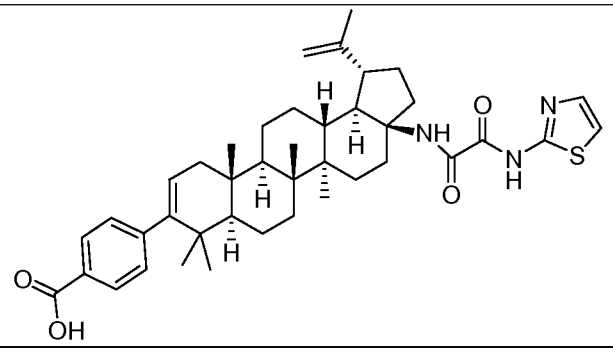
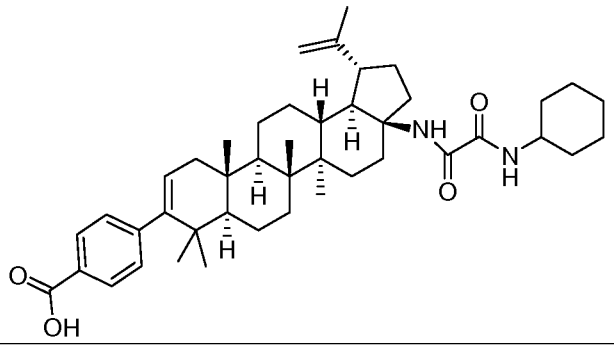
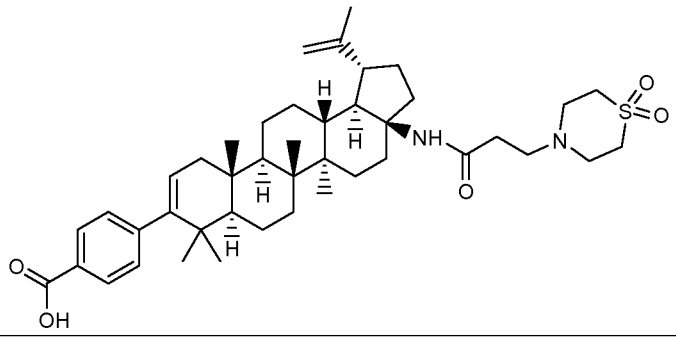
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57		A
58		A
59		A

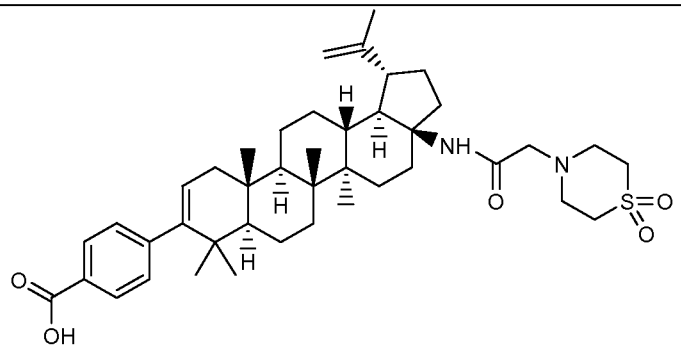
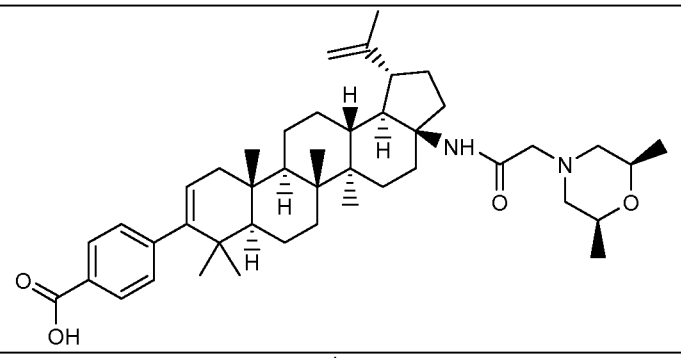
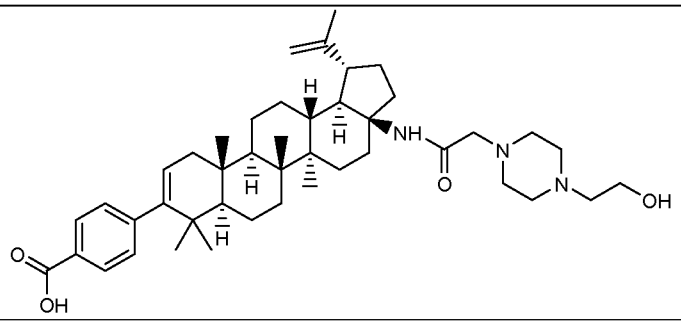
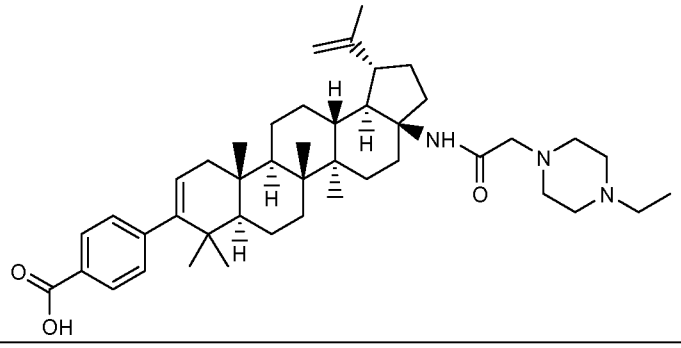
		
60		A
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63		A
64		A

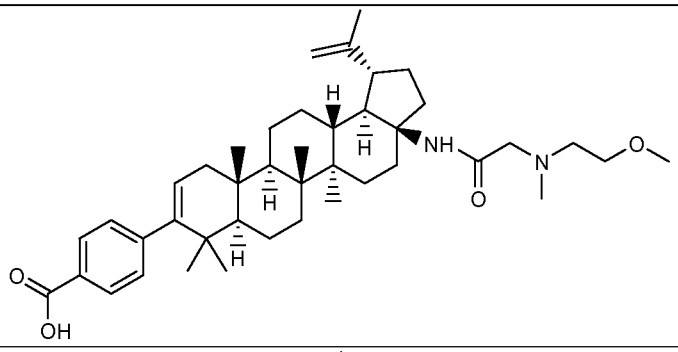
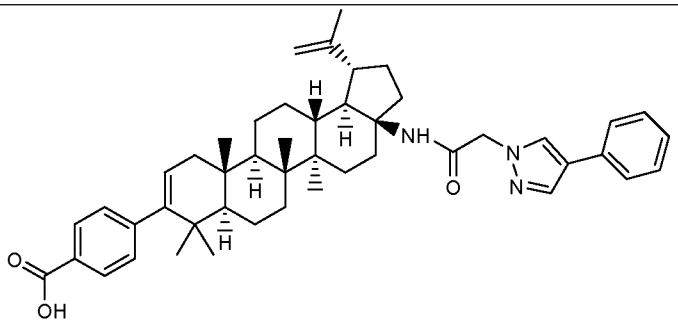
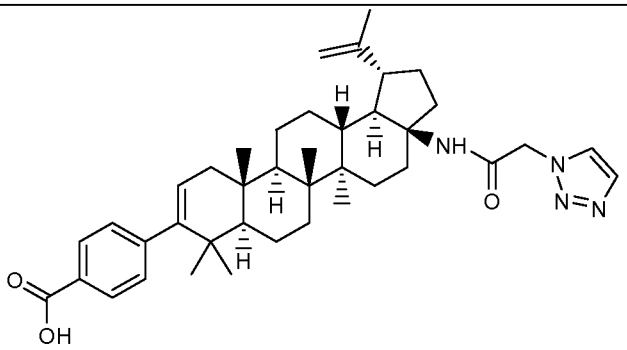
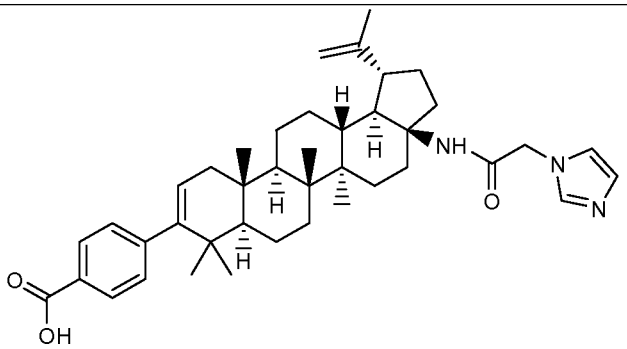
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67		A
68		A
69		A

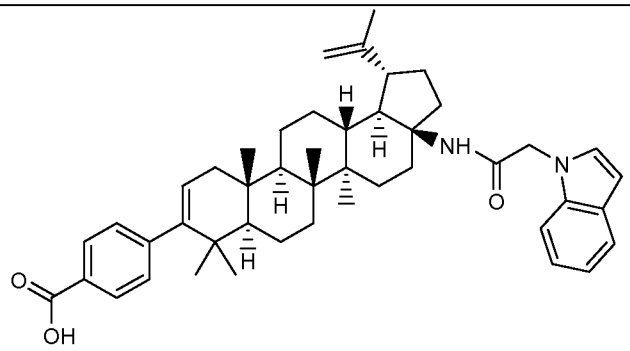
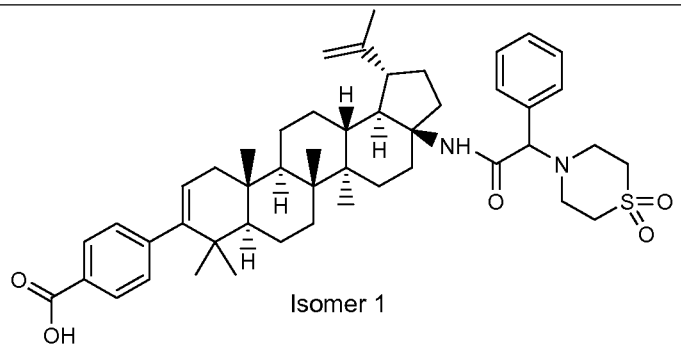
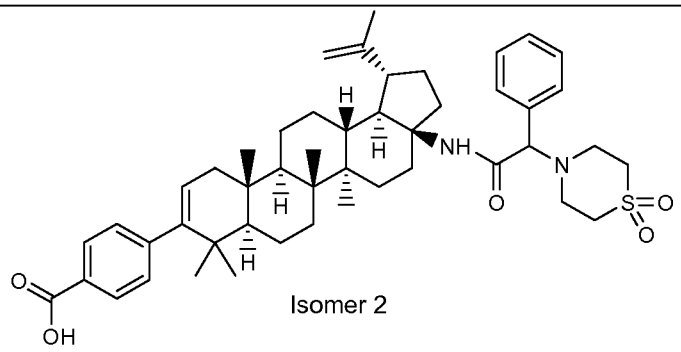
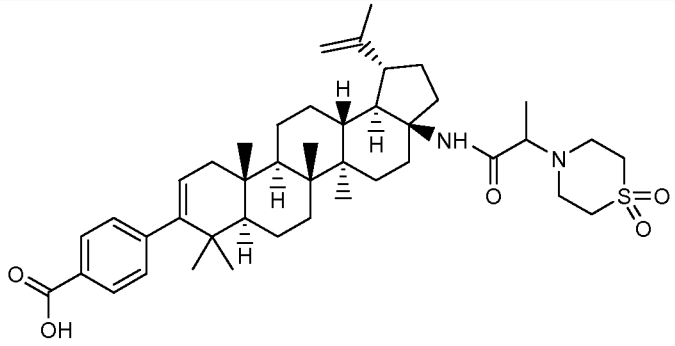
69-1		A
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71		A
72		A
73		A

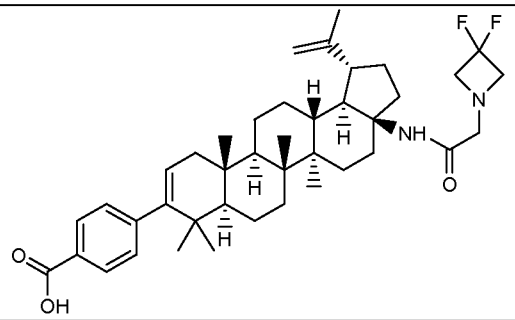
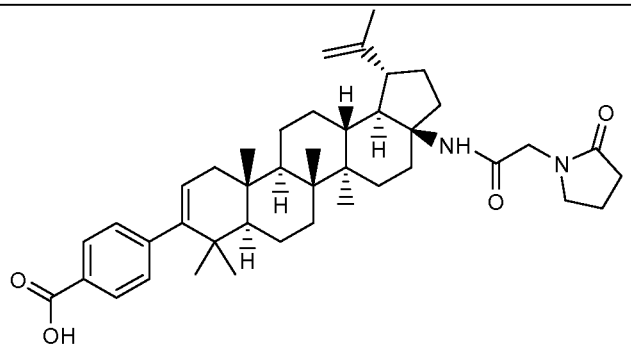
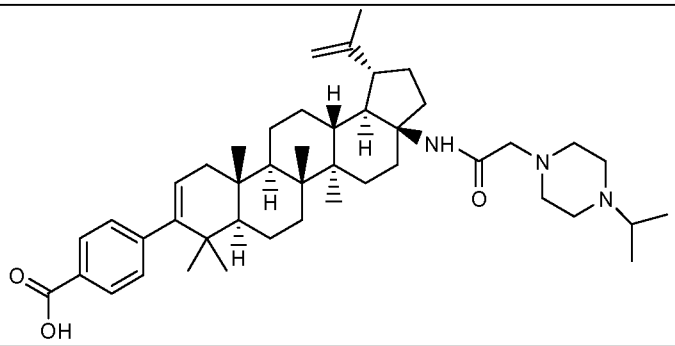
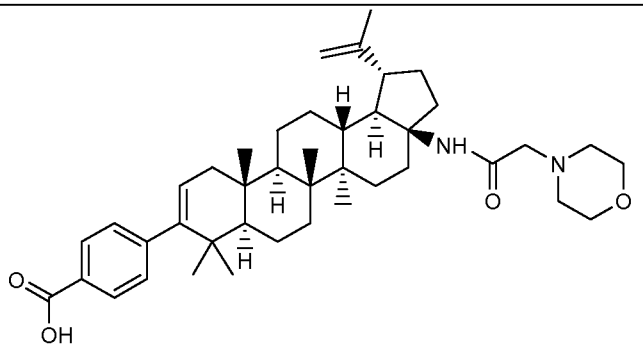
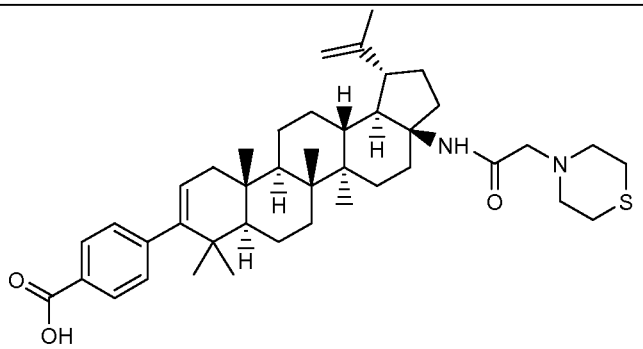
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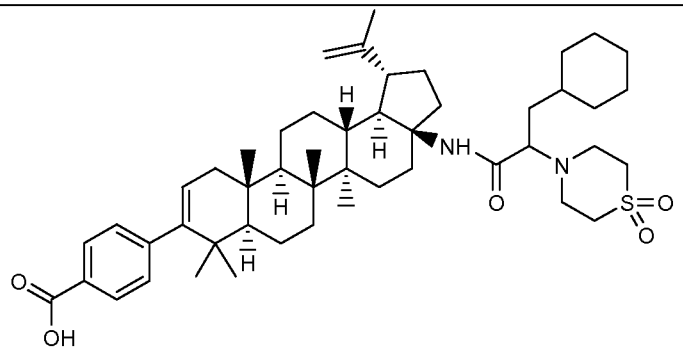
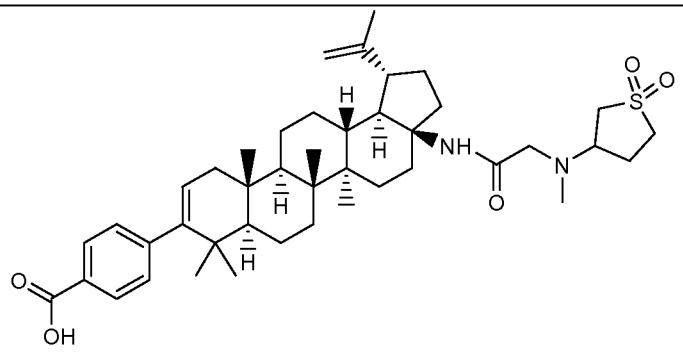
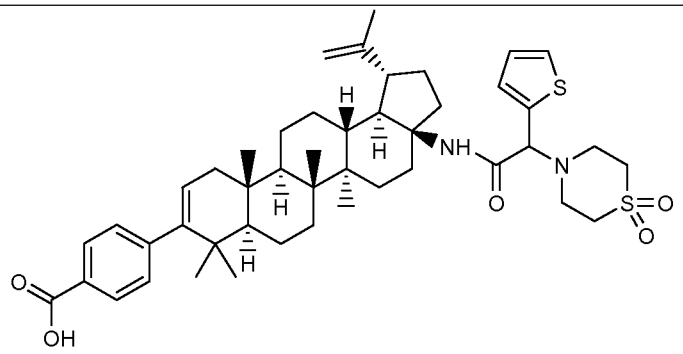
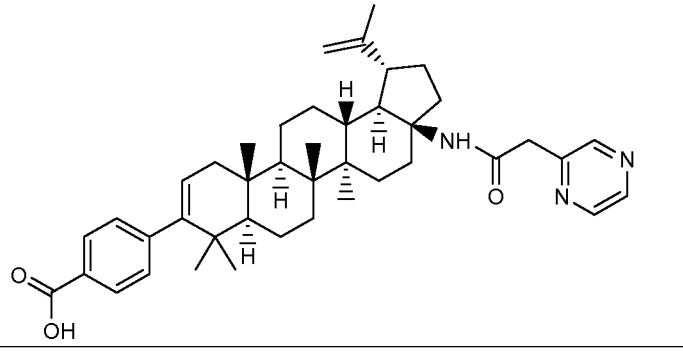
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81		A

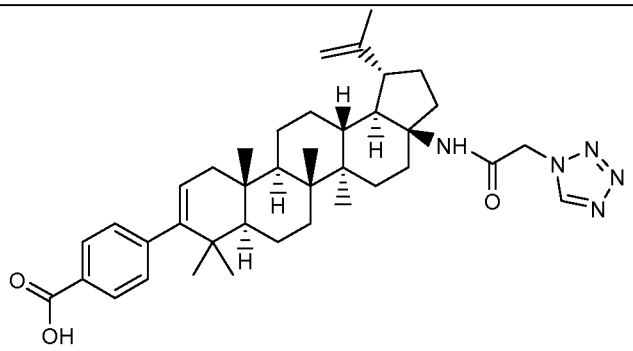
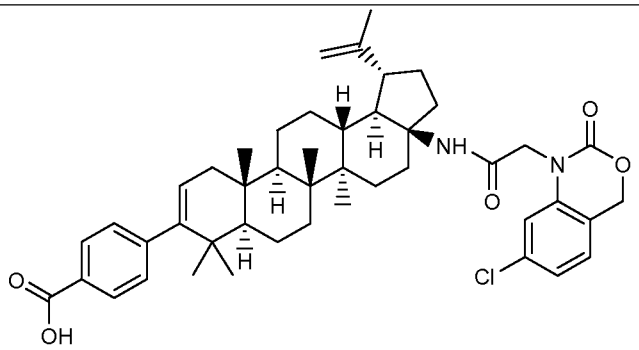
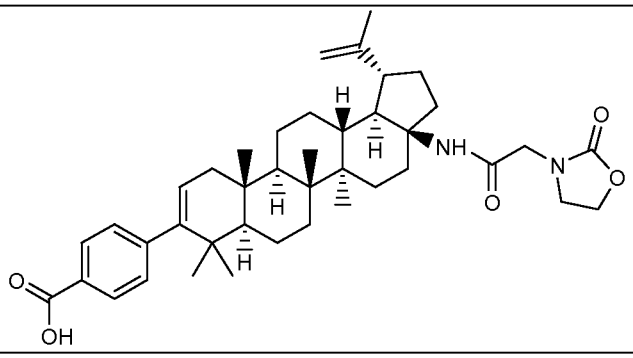
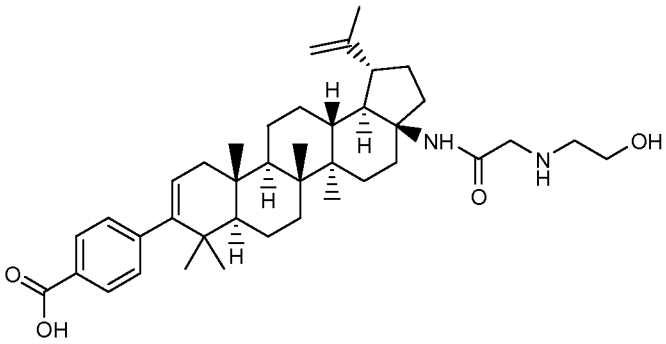
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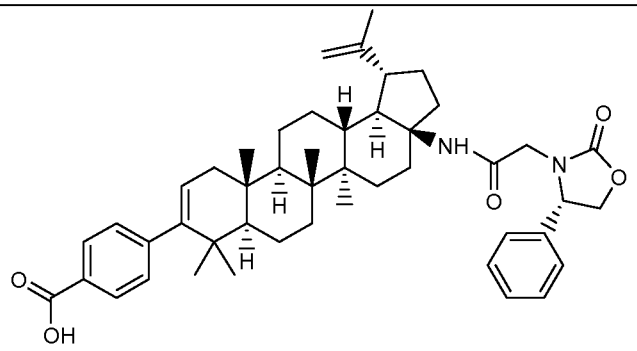
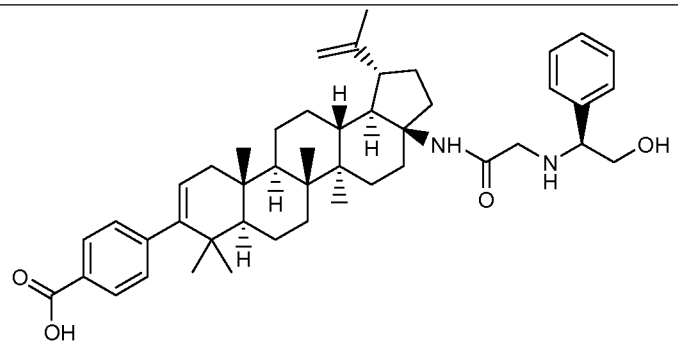
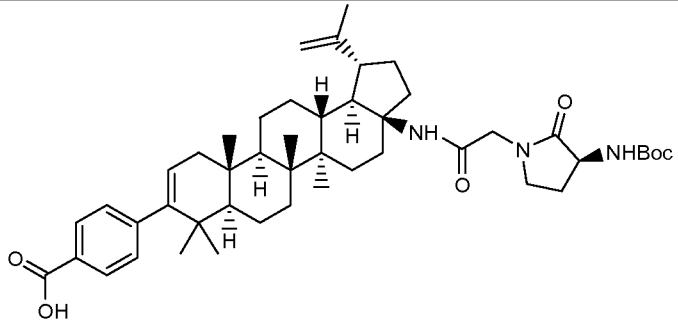
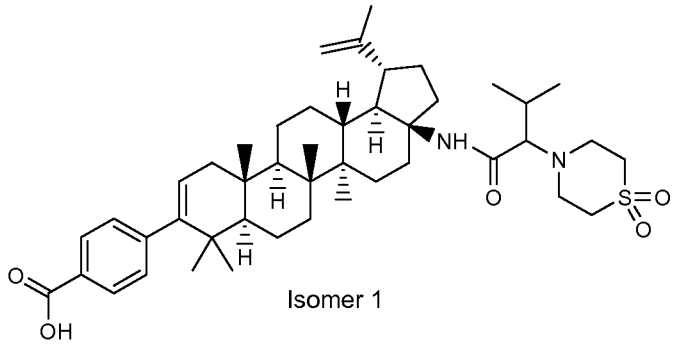
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87		A
88		A
89		A
90		0.02

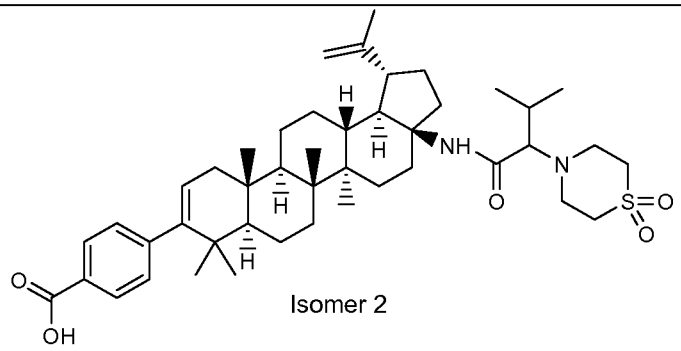
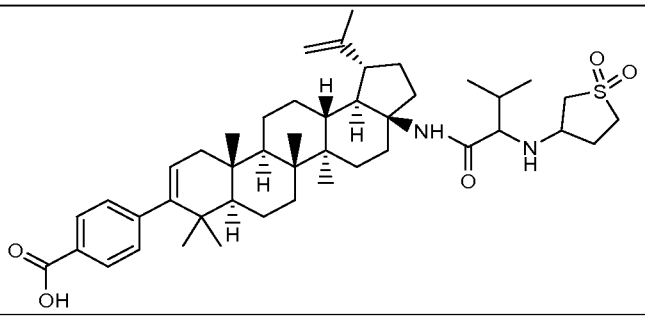
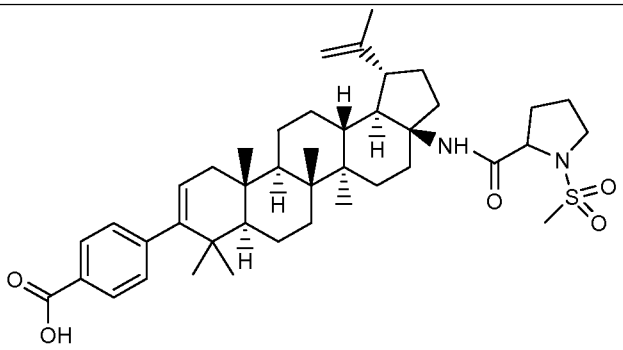
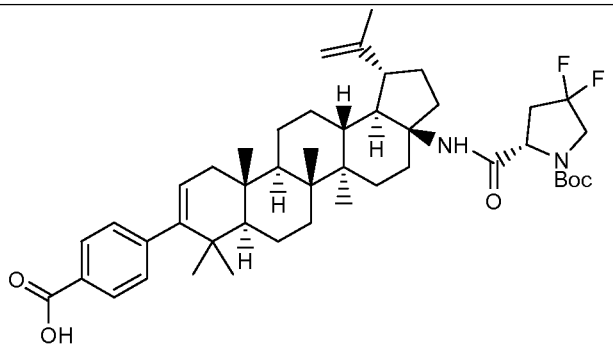
		
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92	 Isomer 2	A
93		A

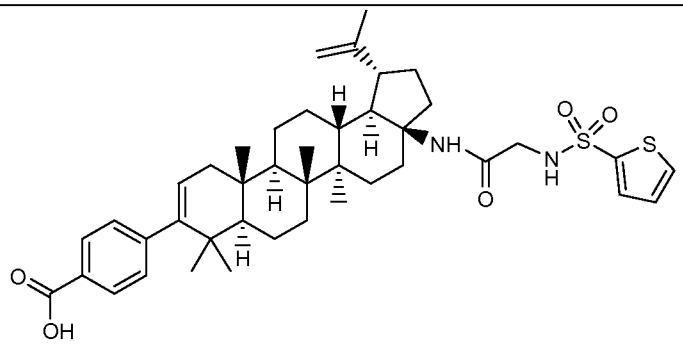
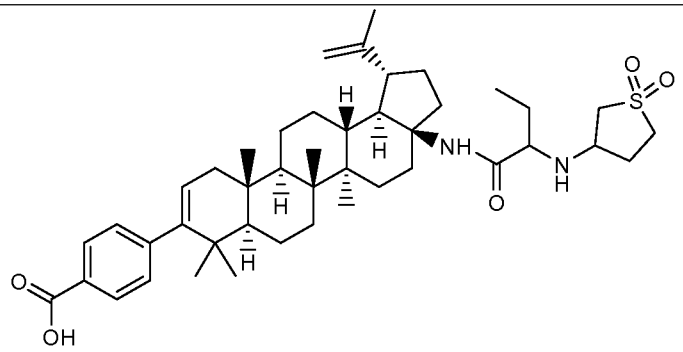
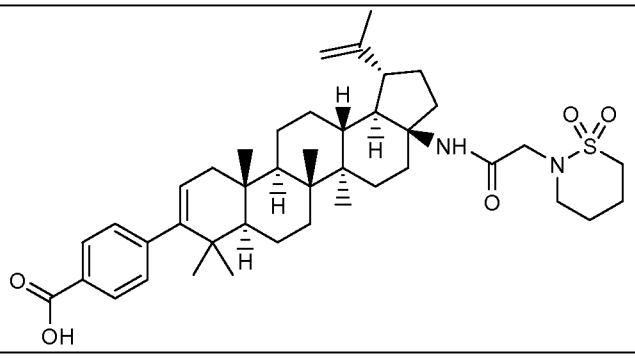
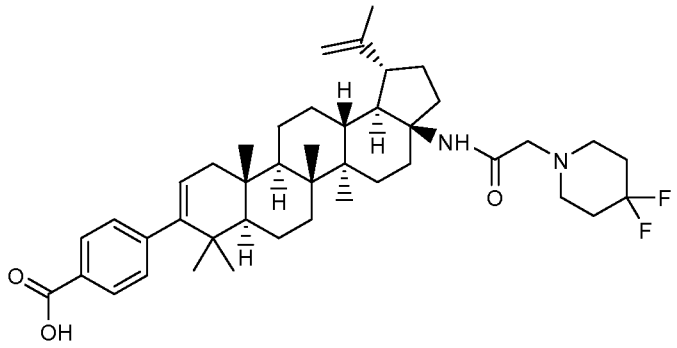
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99		A

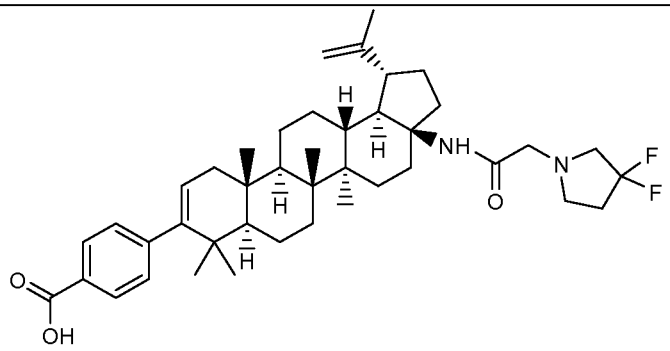
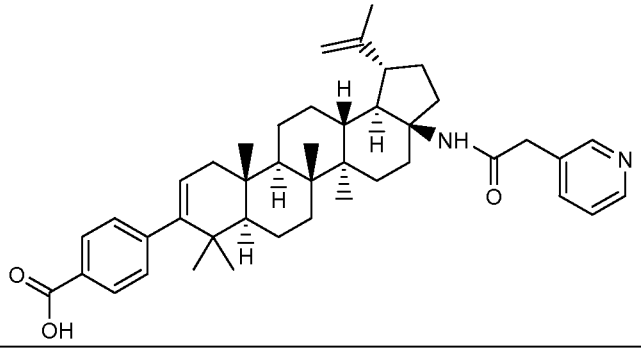
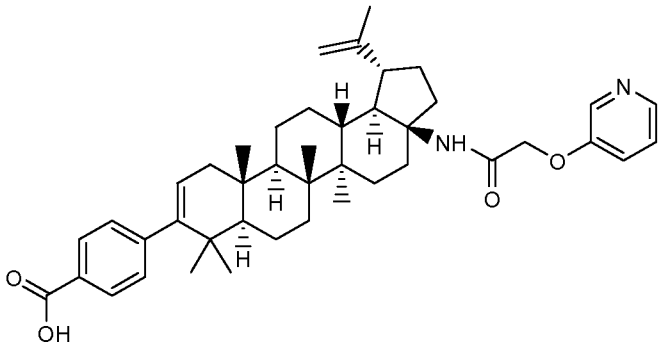
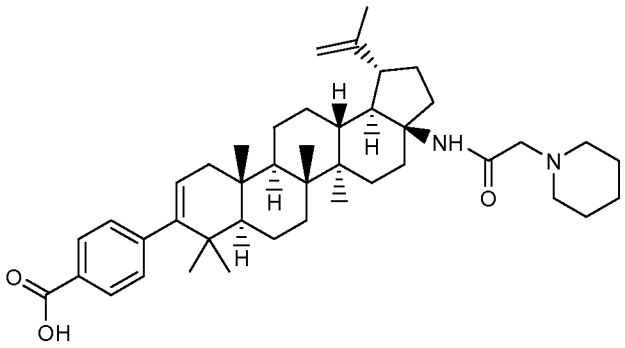
		
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102		A

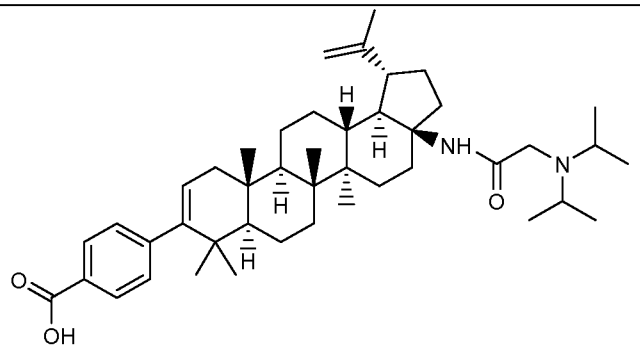
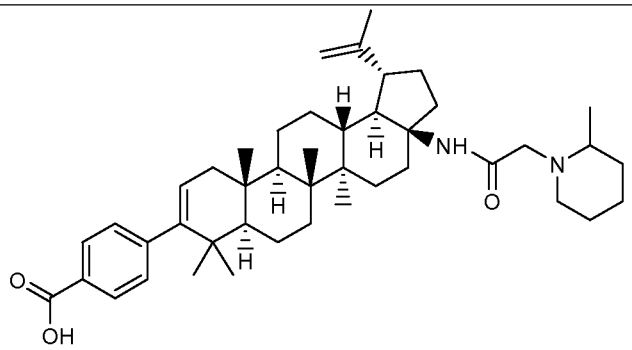
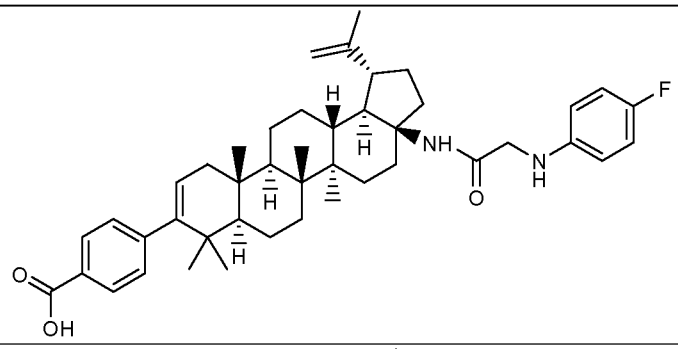
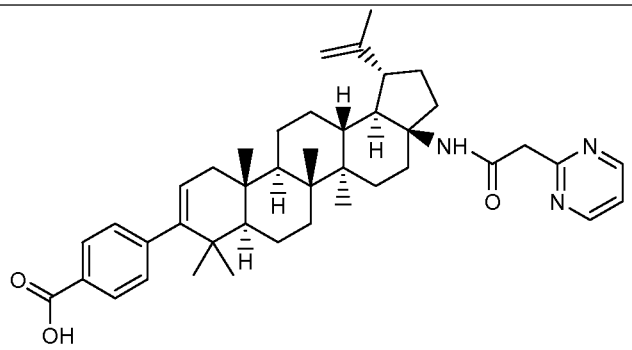
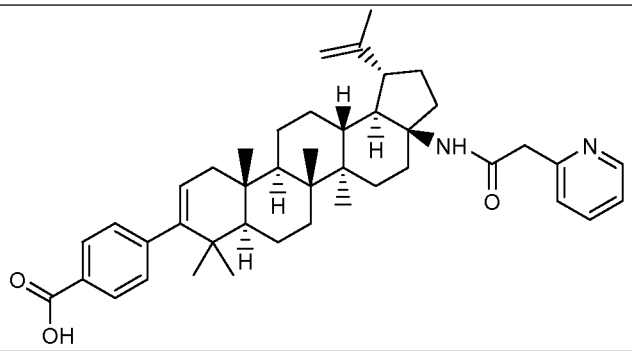
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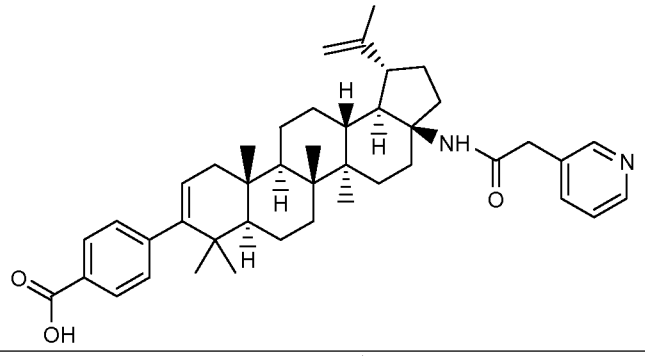
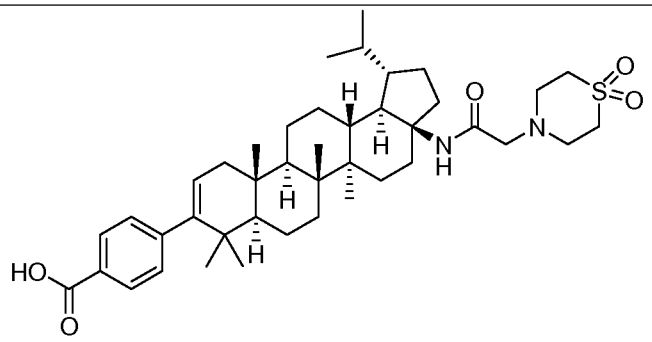
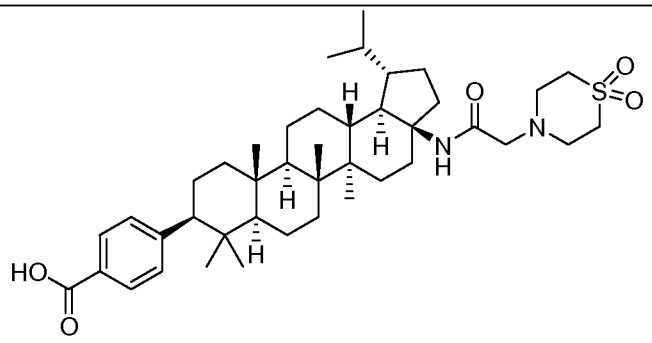
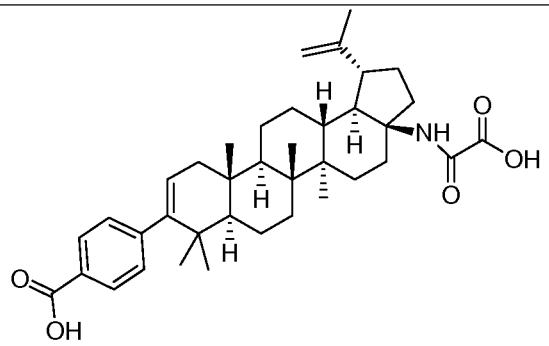
		
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110	 Isomer 1	A

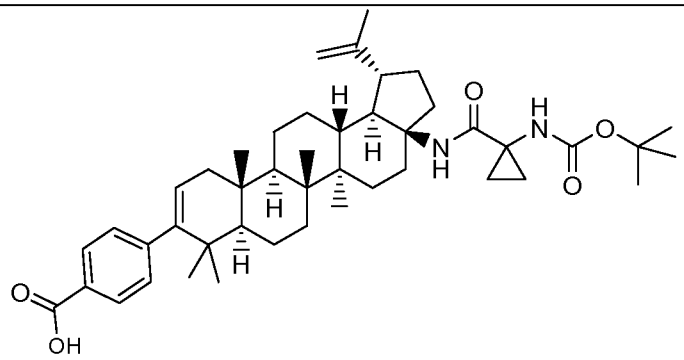
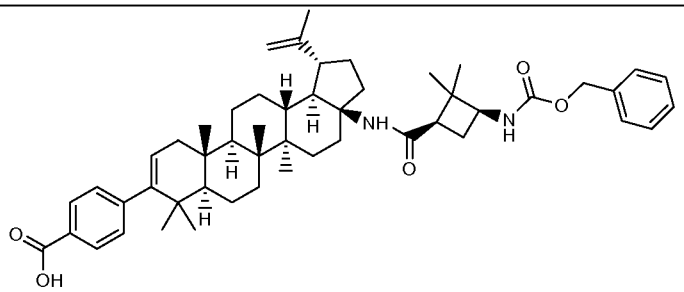
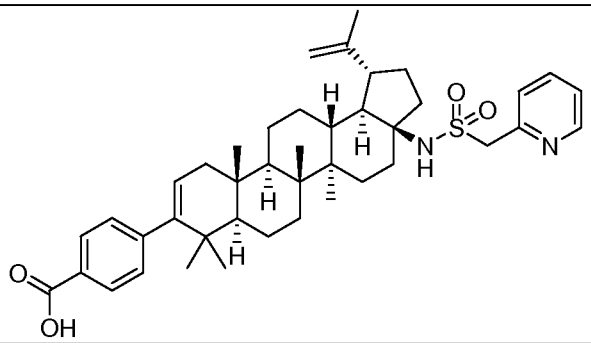
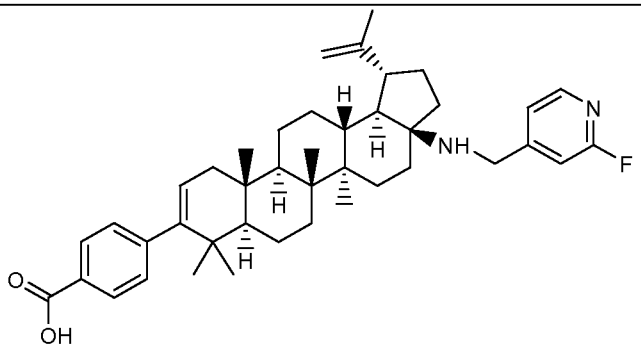
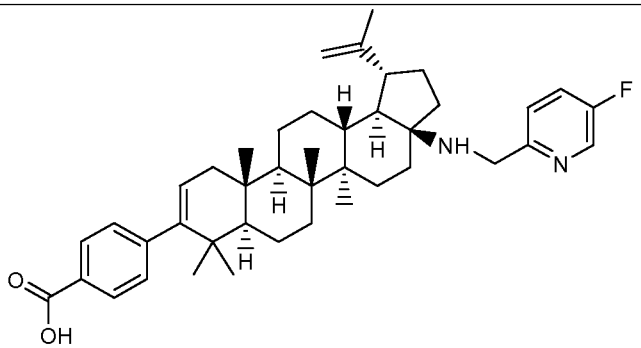
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115		A

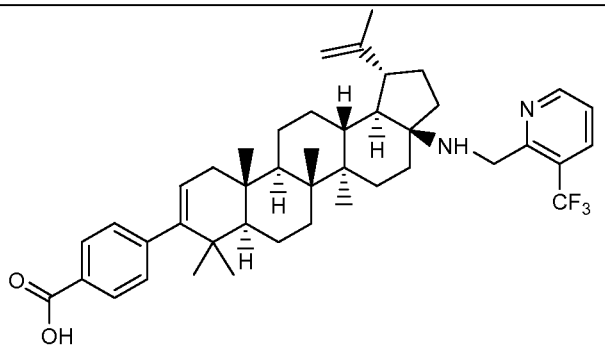
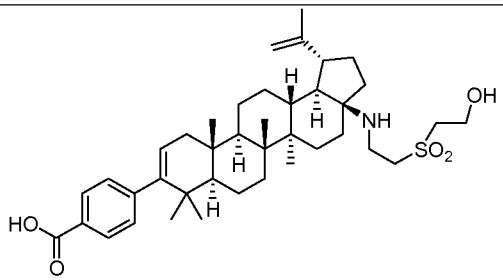
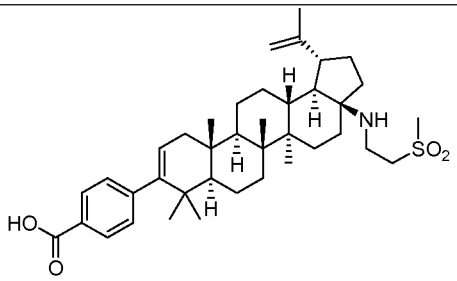
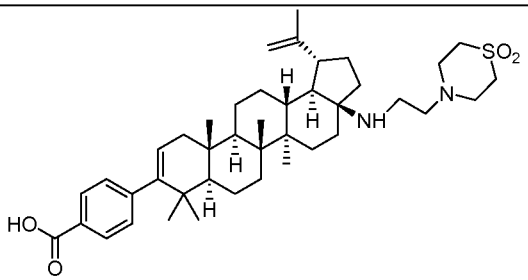
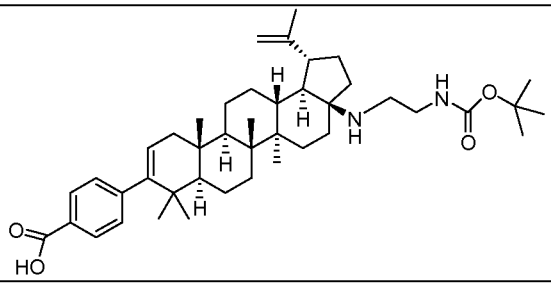
		
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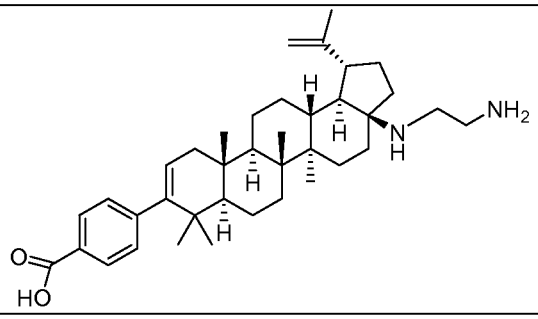
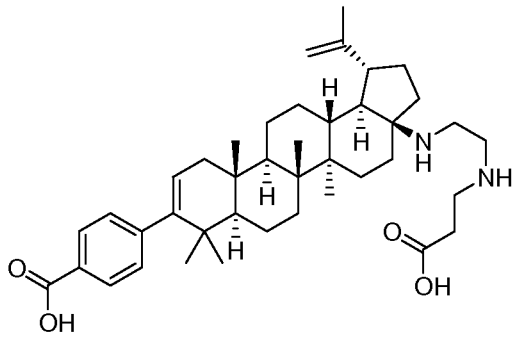
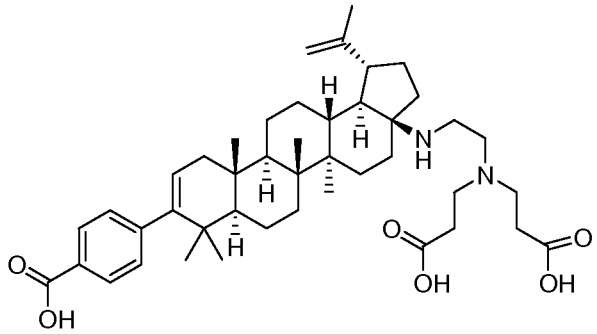
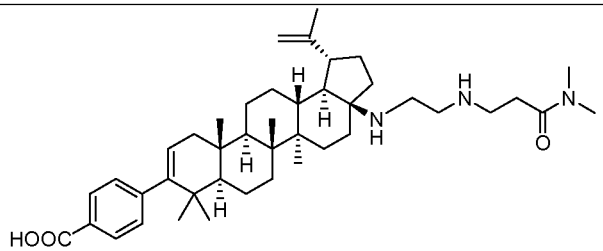
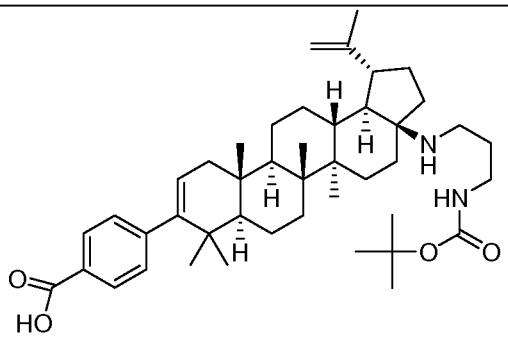
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123		A

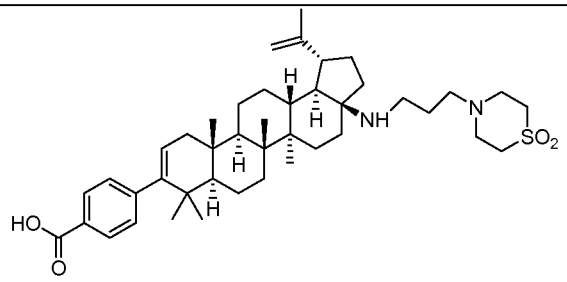
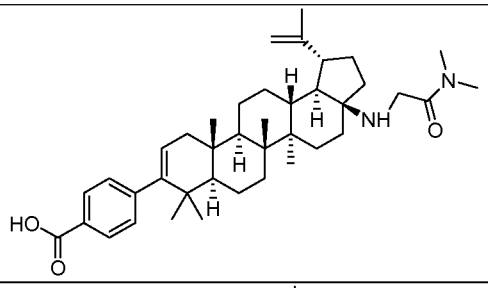
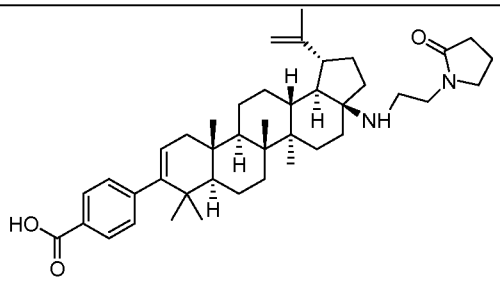
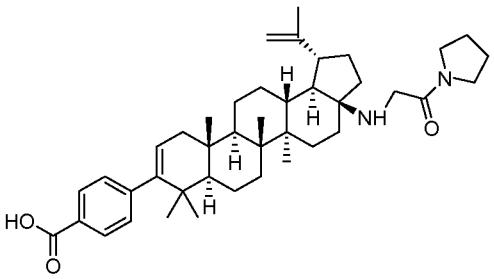
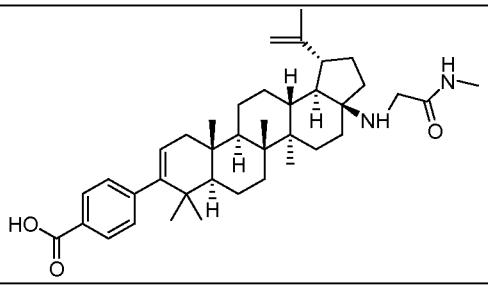
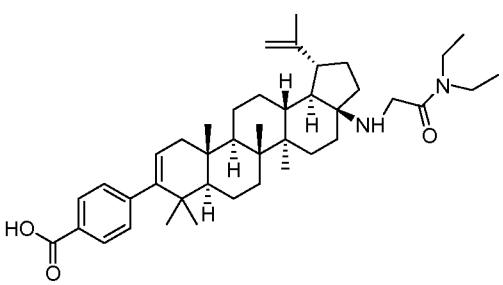
		
124		A
125		A
126		A
127		A

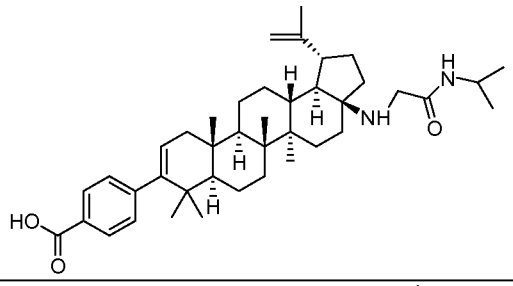
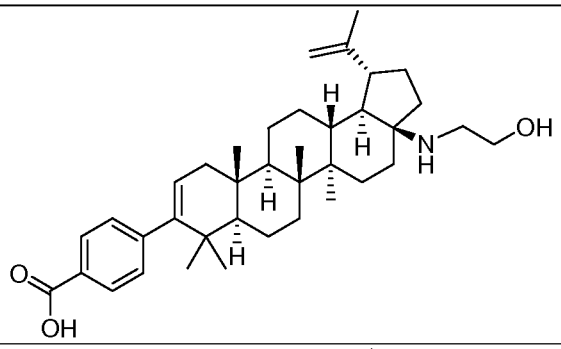
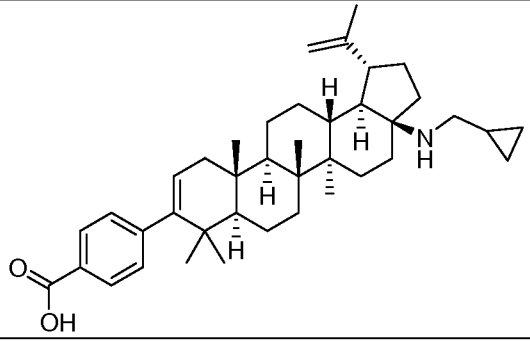
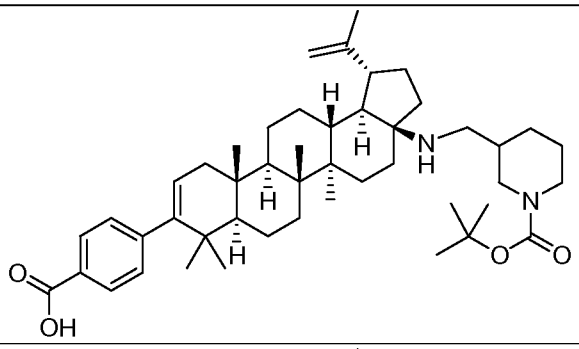
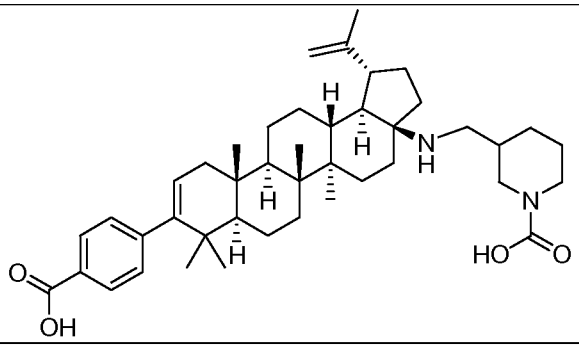
128		A
129		A
130		A
130-1		B

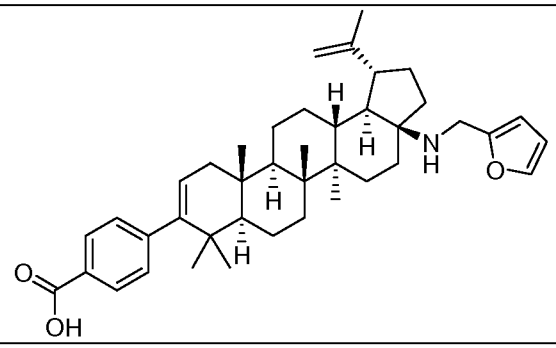
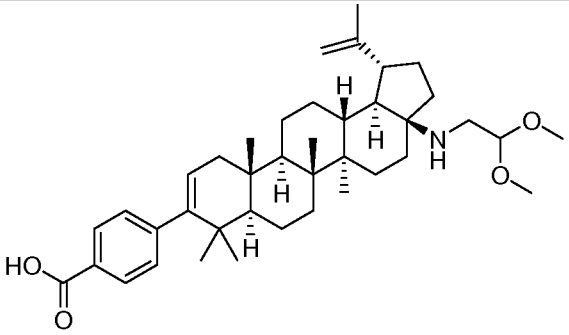
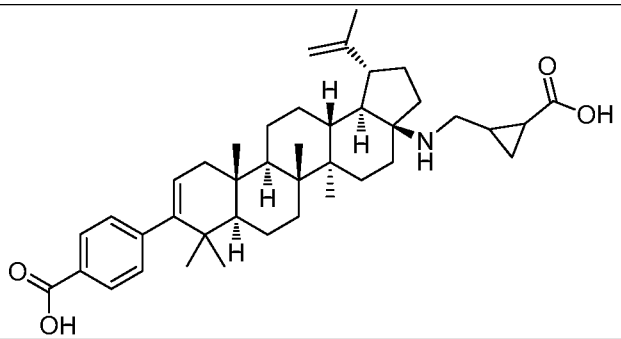
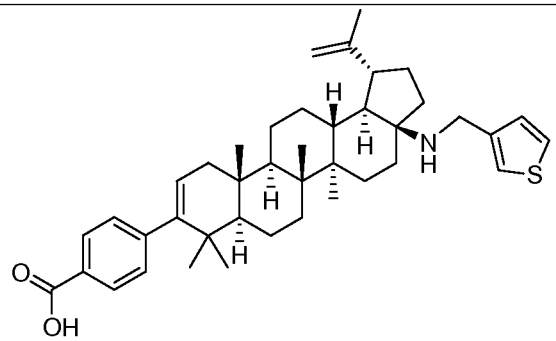
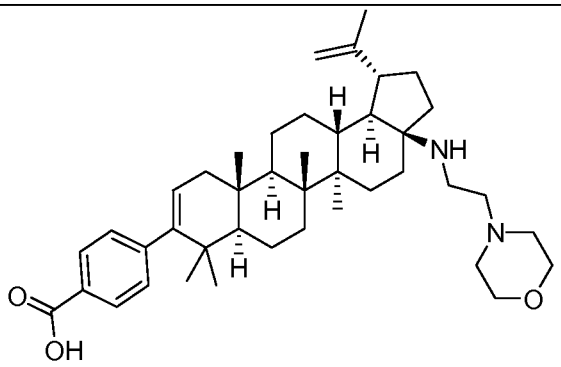
130-2		A
130-3		A
131		A
132		A
133		0.03

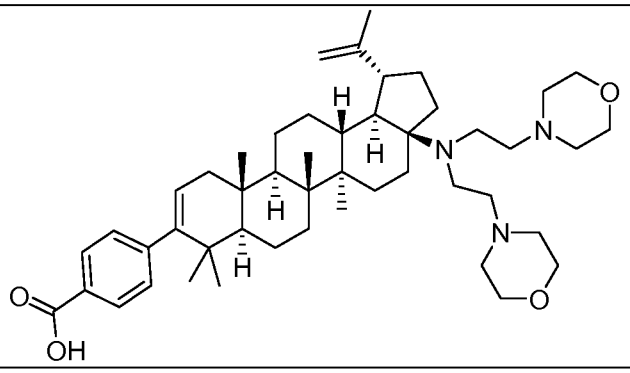
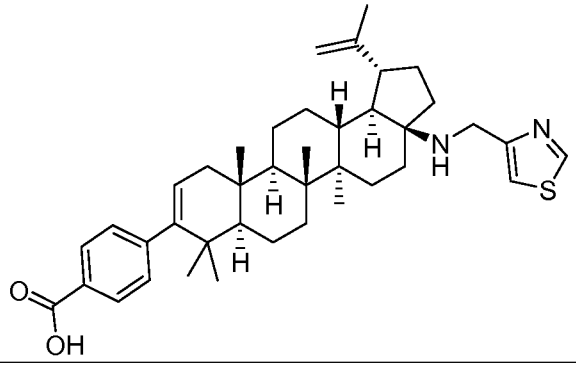
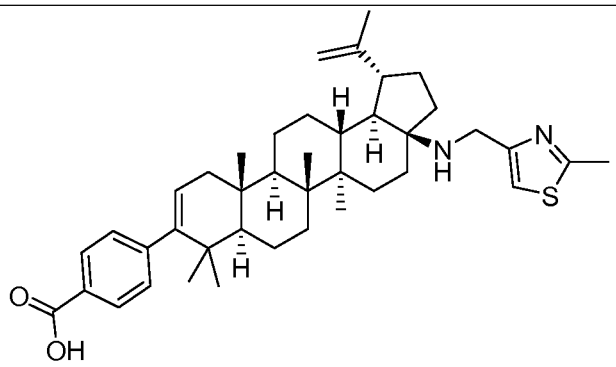
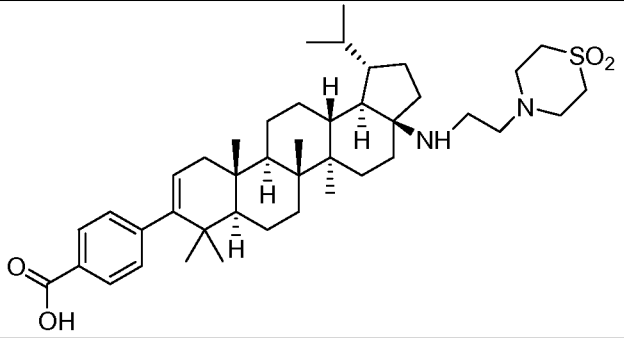
134		0.10
135		A
136		A
137		A
138		A
139		A

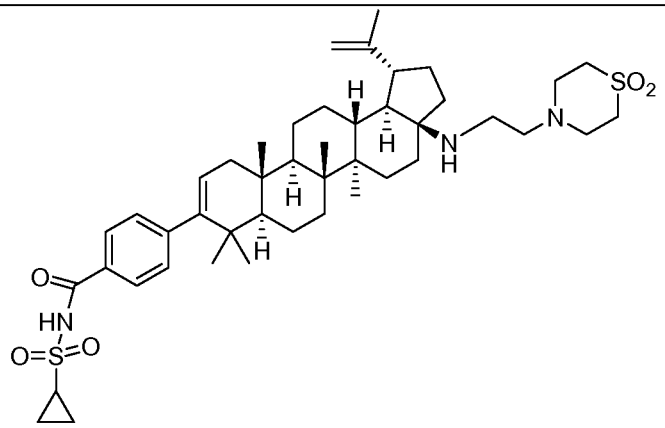
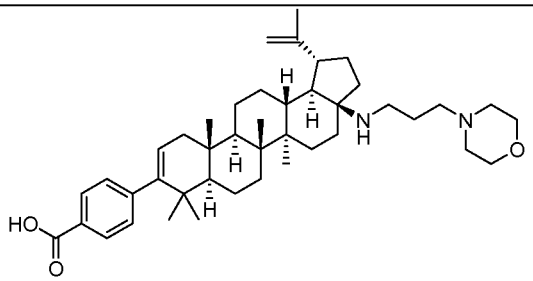
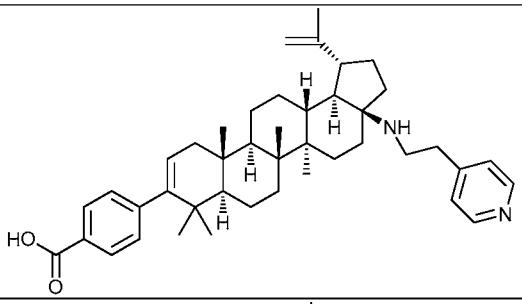
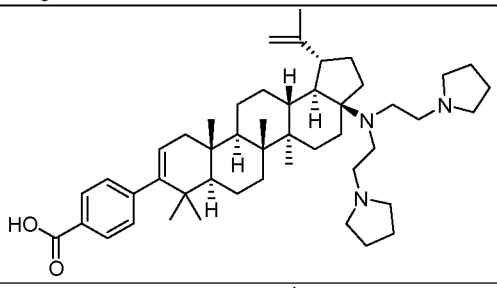
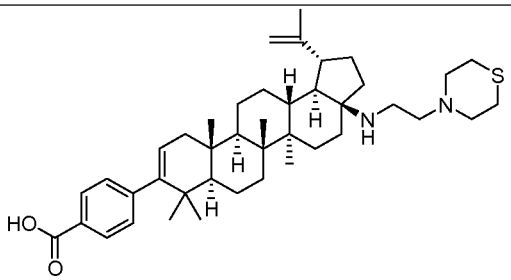
		
140		0.009
141		A
142		A
143		A

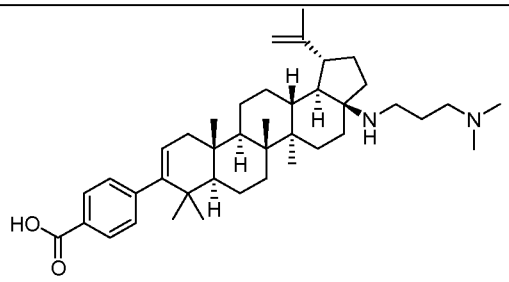
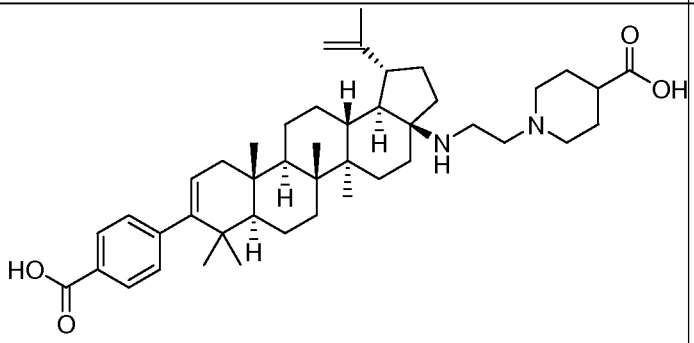
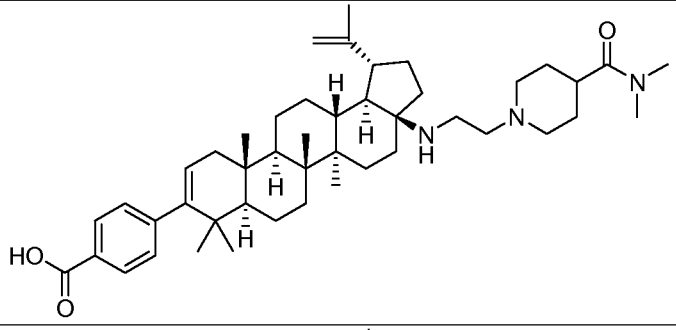
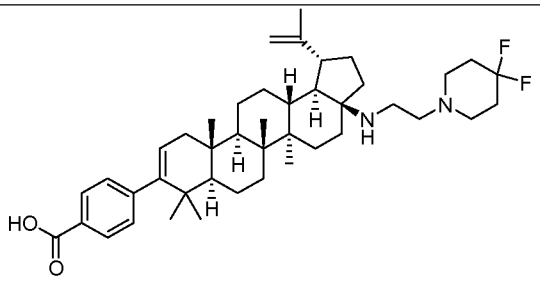
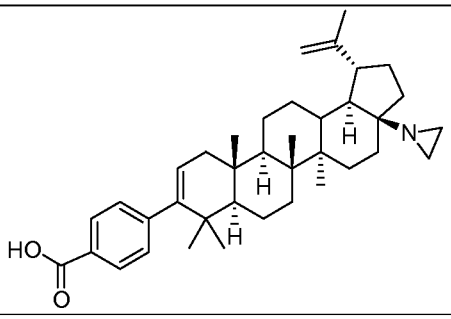
144		A
145		A
146		A
147		A
148		A
149		A

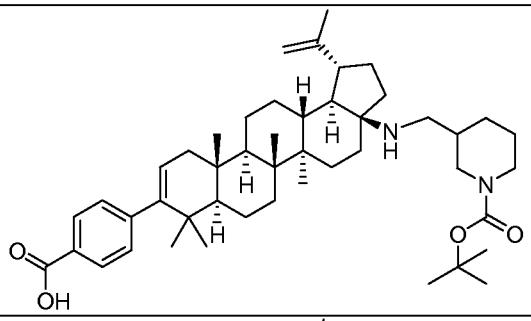
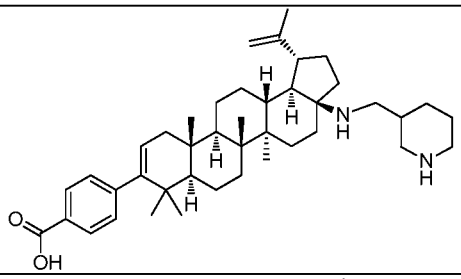
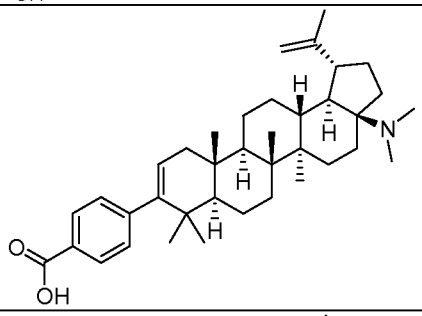
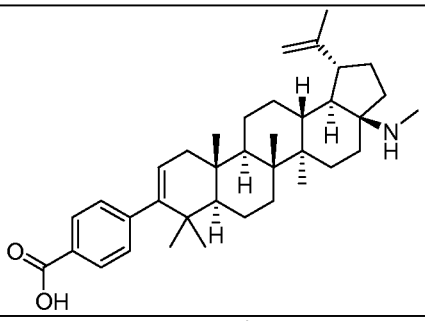
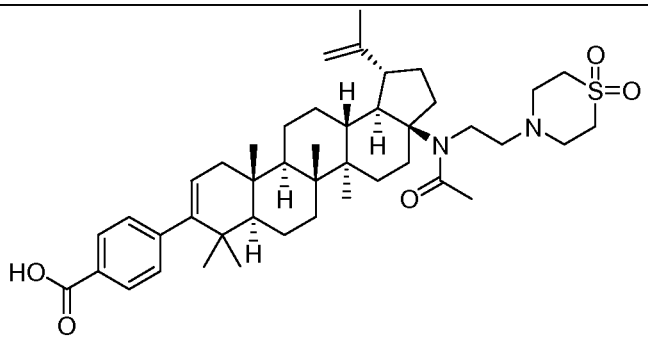
150		A
151		A
152		A
153		B
154		A

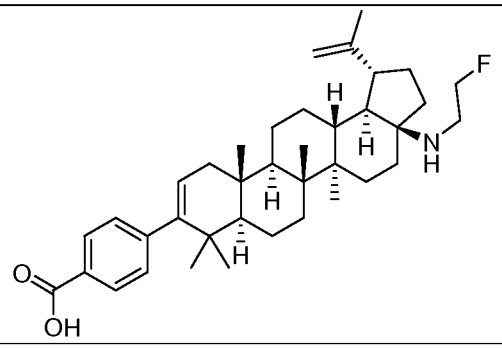
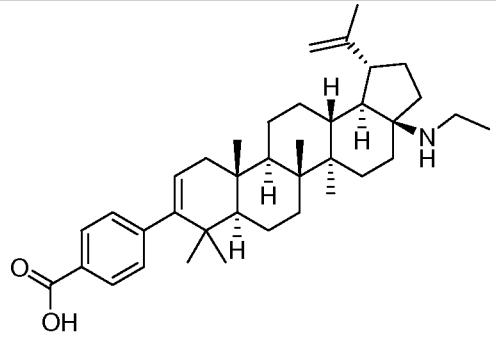
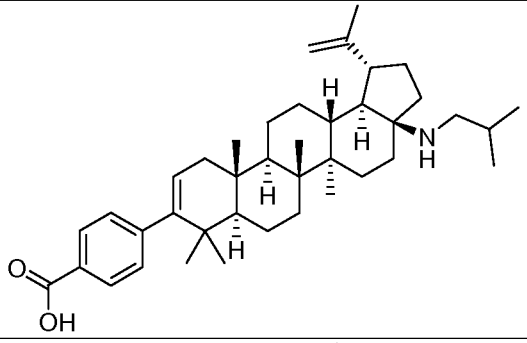
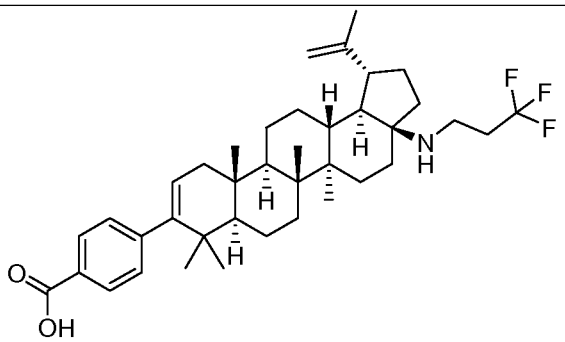
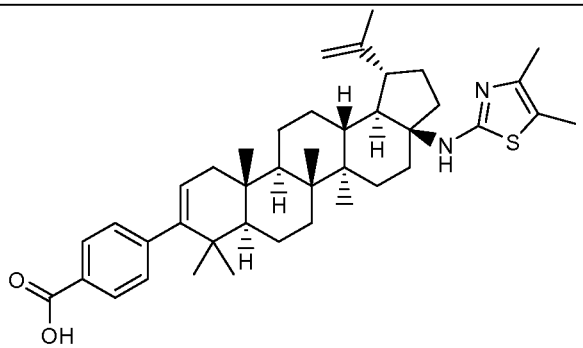
155		A
156		0.12
157		A
158		A
159		A

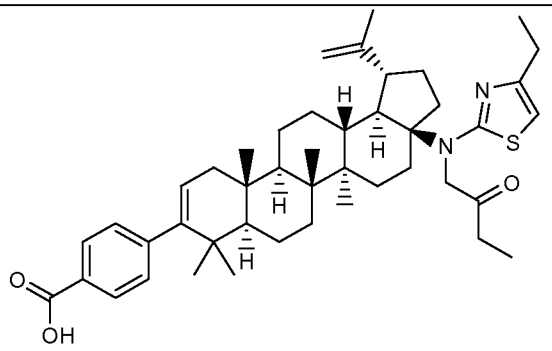
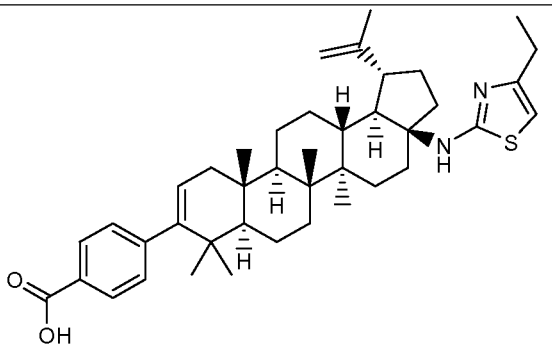
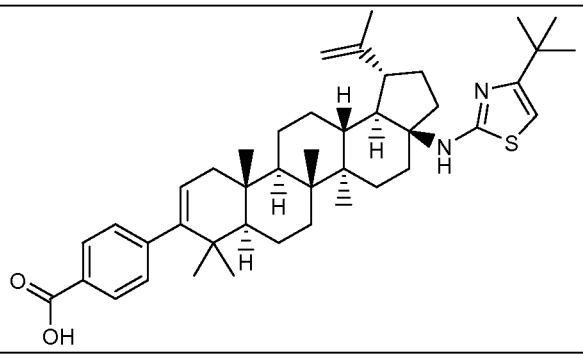
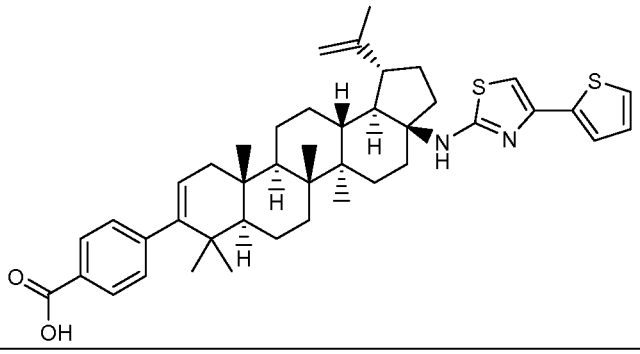
160		A
161		A
162		A
163		A

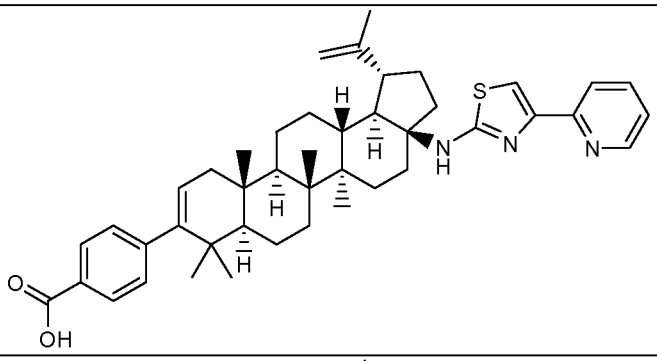
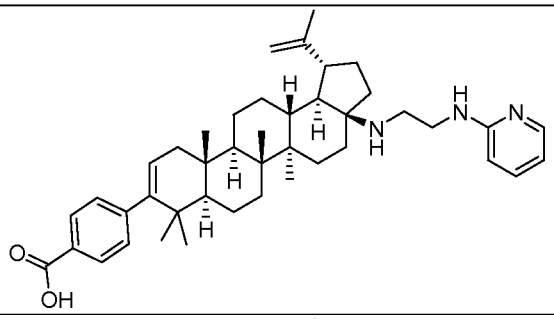
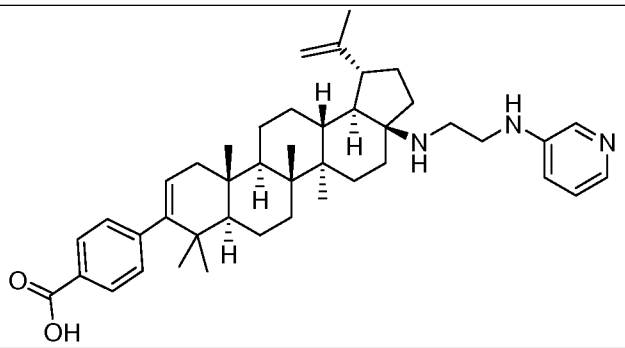
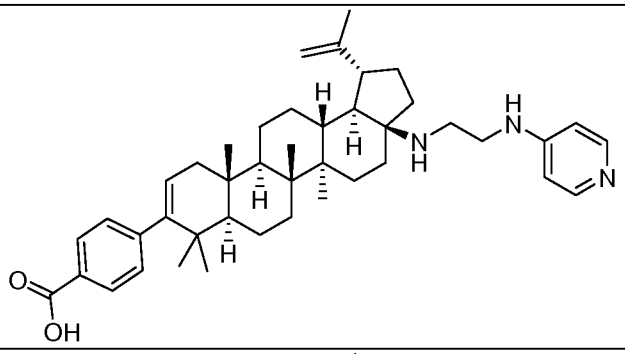
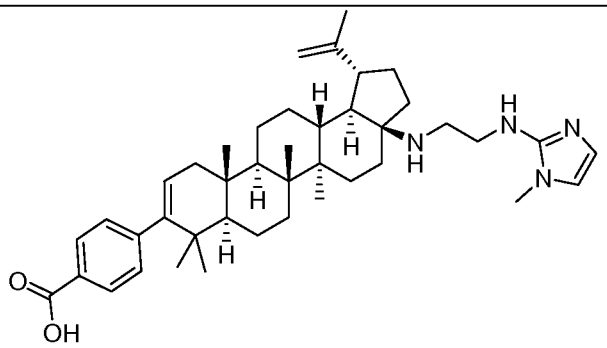
164		A
165		A
166		A
167		0.004
168		A

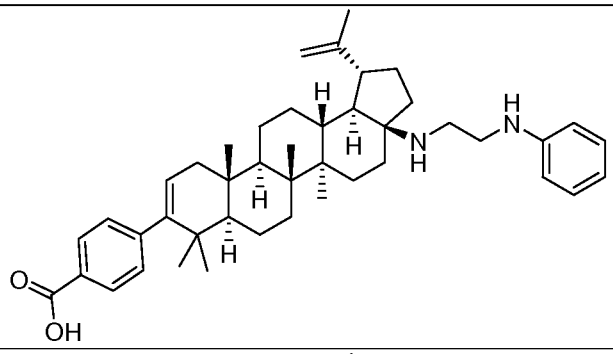
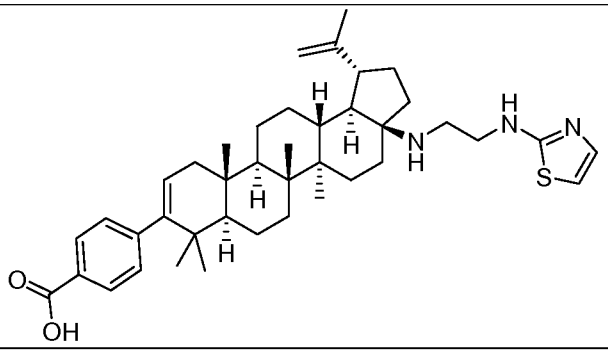
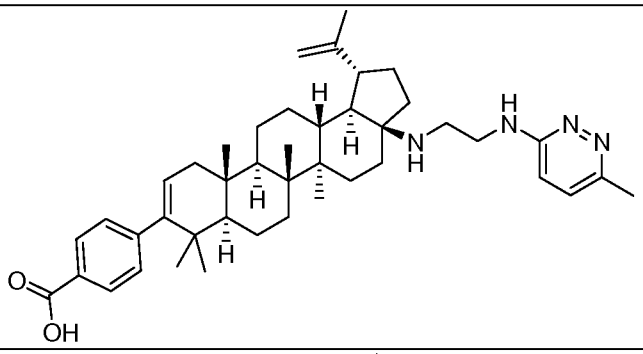
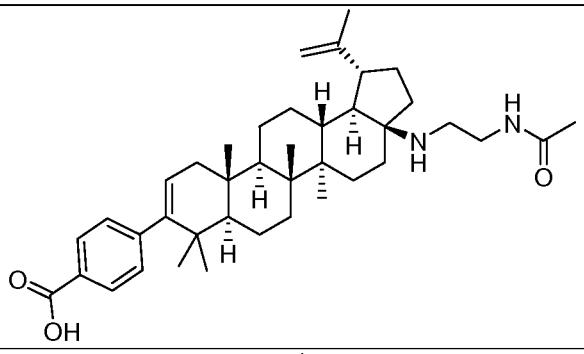
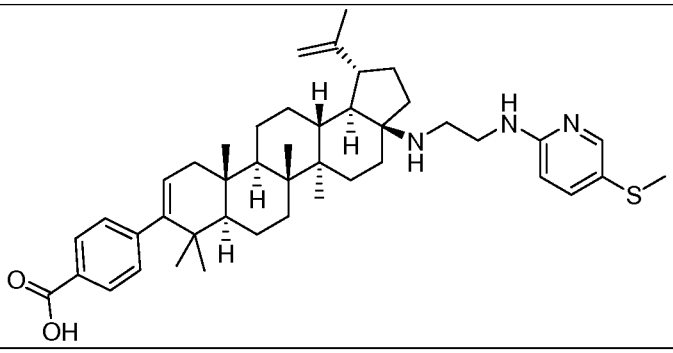
169		A
170		A
171		A
172		A
173		A

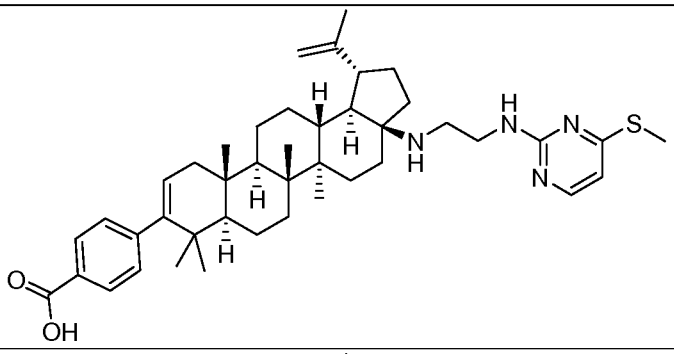
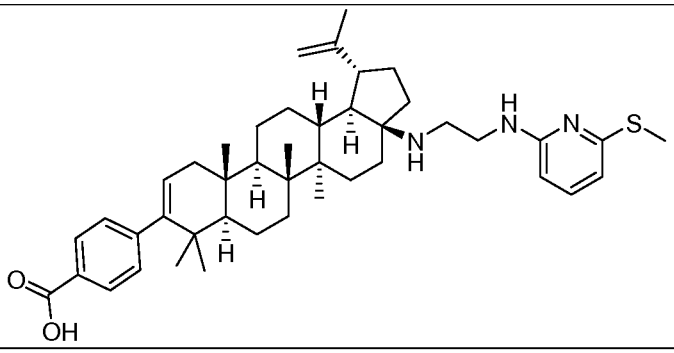
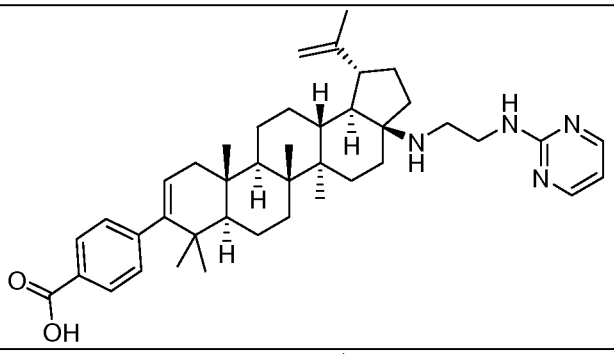
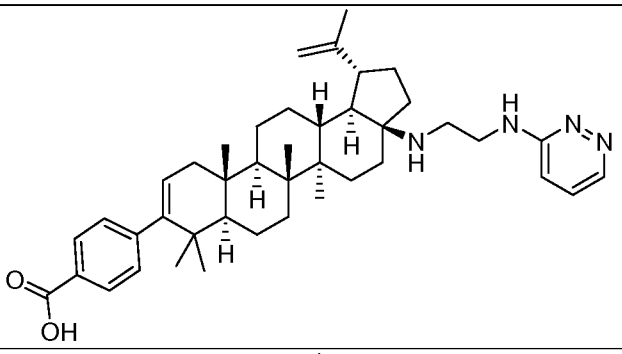
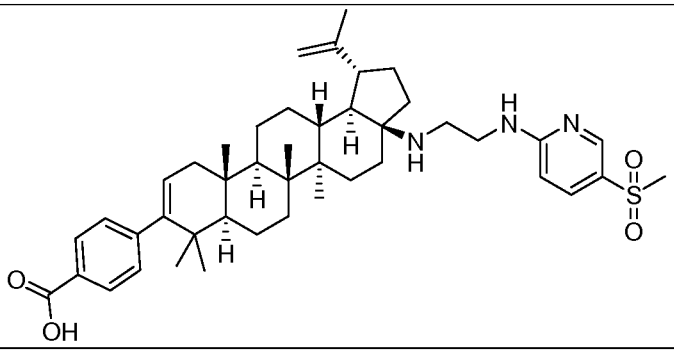
174		0.3
175		0.01
176		A
177		0.009
178		A

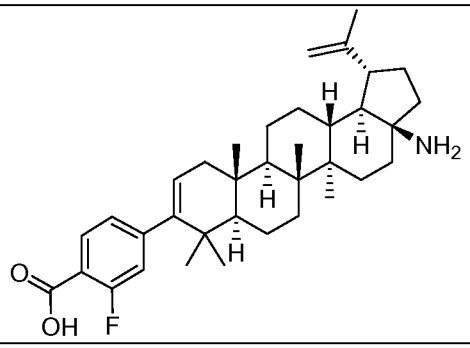
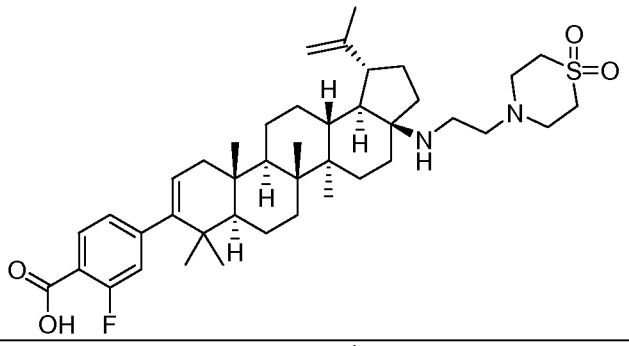
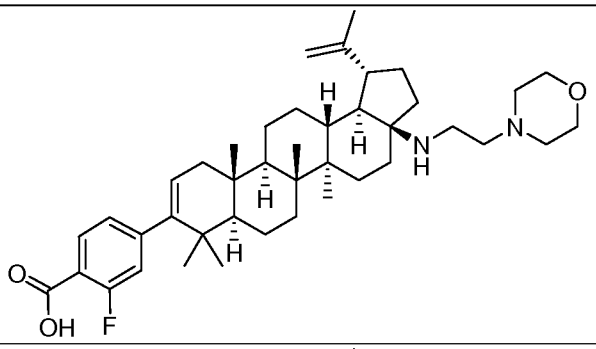
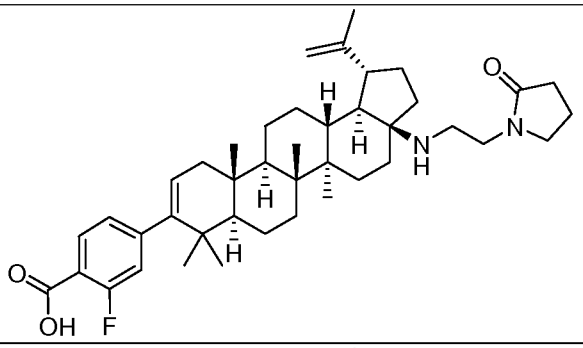
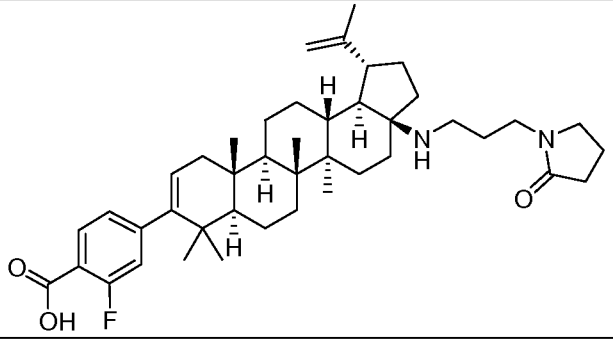
179		A
180		A
181		A
182		B
183		A

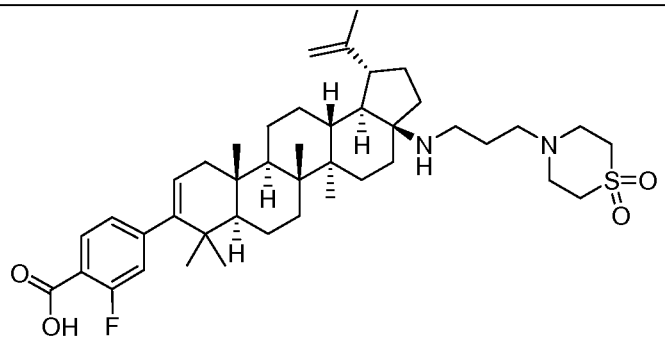
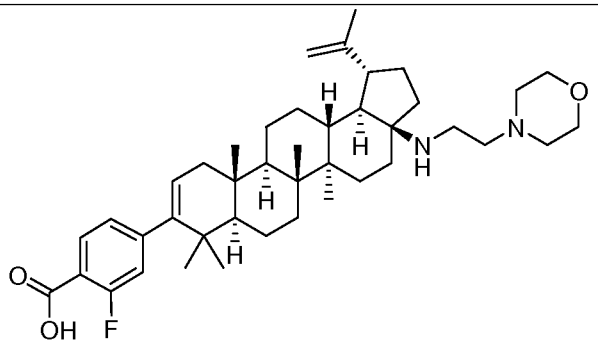
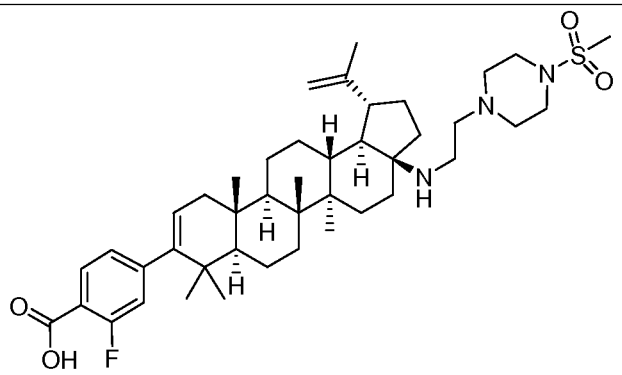
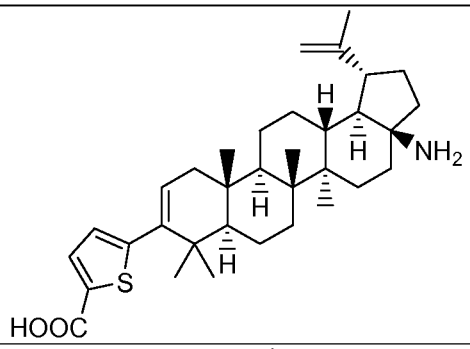
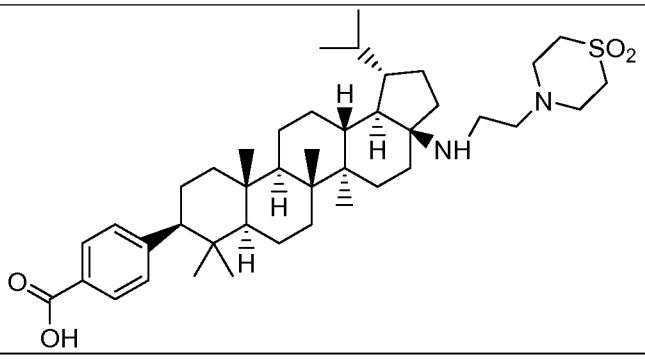
184A		0.39
184B		A
185		B
186		B

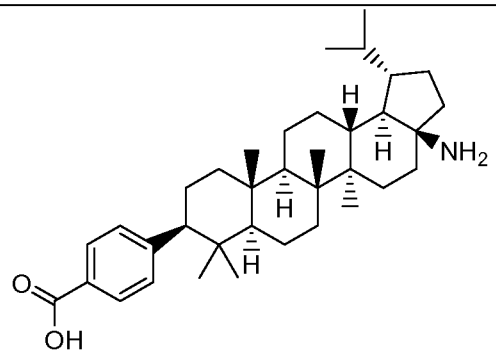
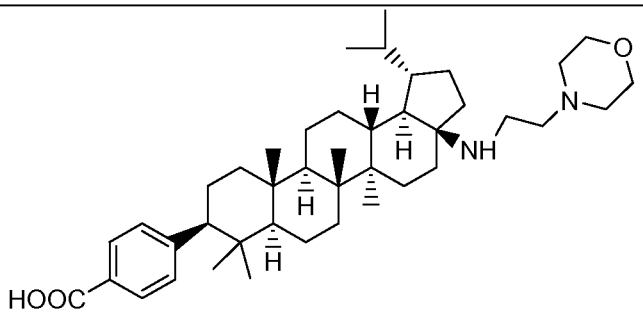
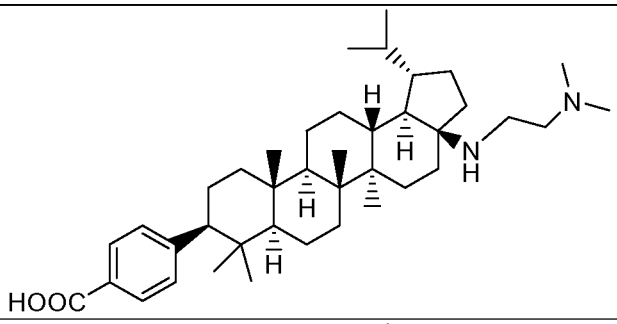
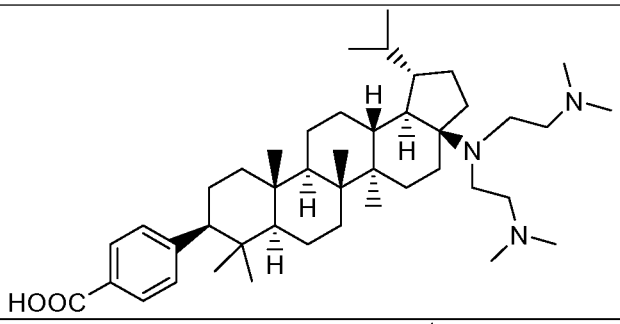
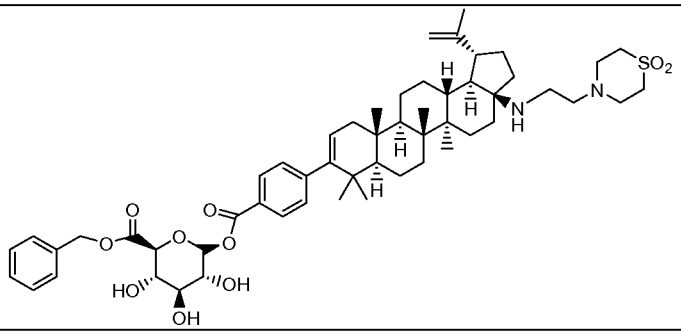
187		A
188		0.001
189		A
190		A
191		A

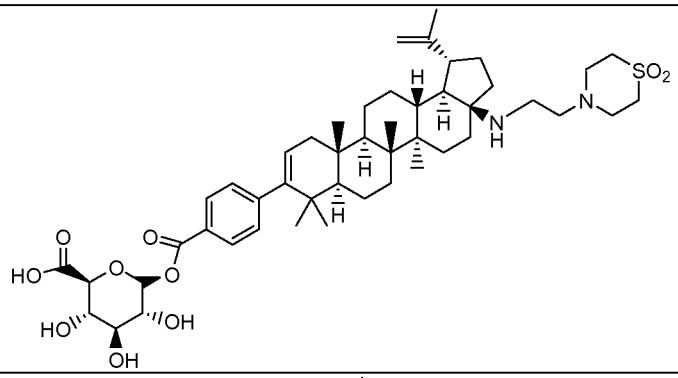
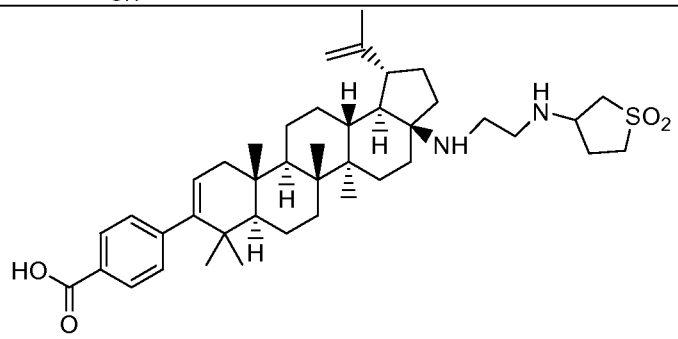
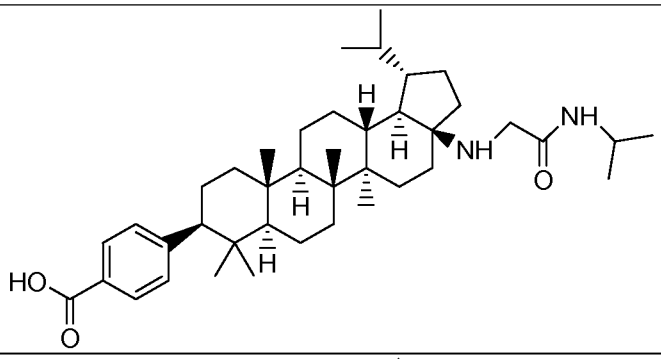
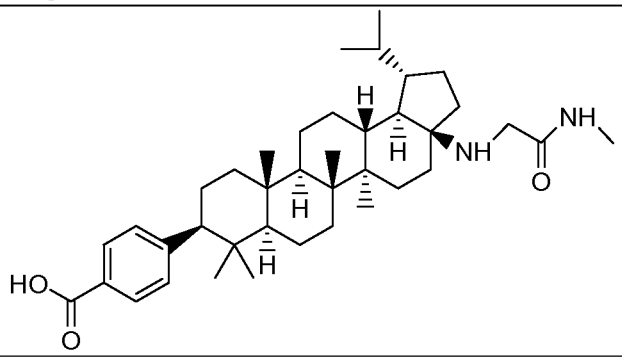
192		A
193		0.02
194		A
195		A
196		A

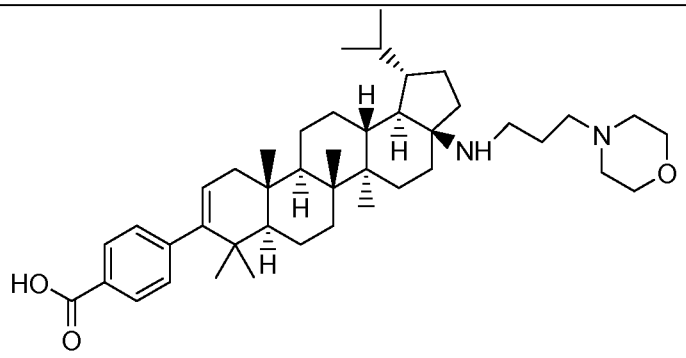
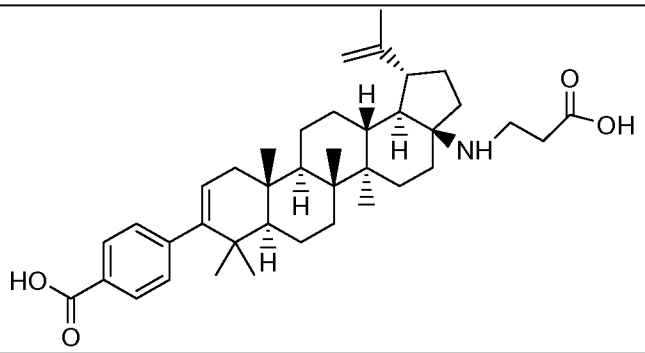
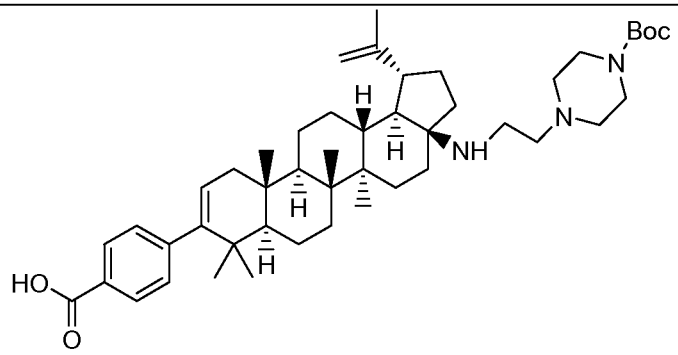
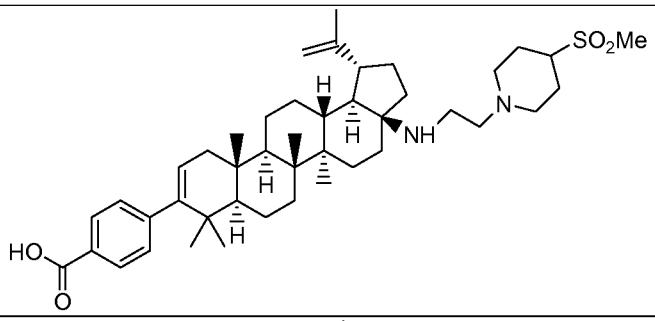
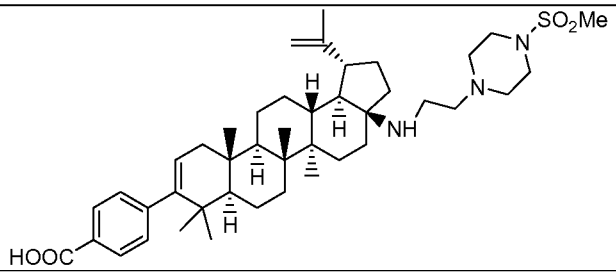
197		A
198		A
199		A
200		A
201		A

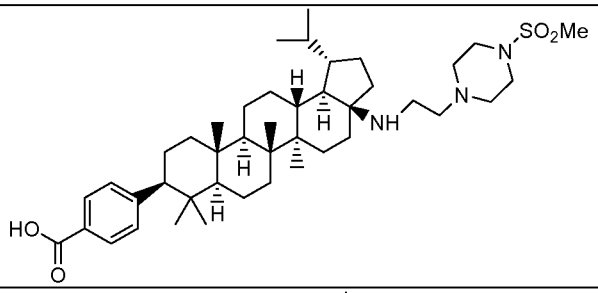
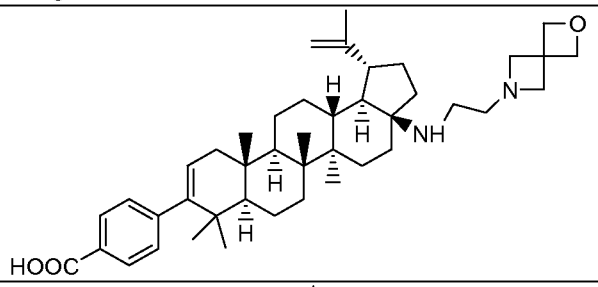
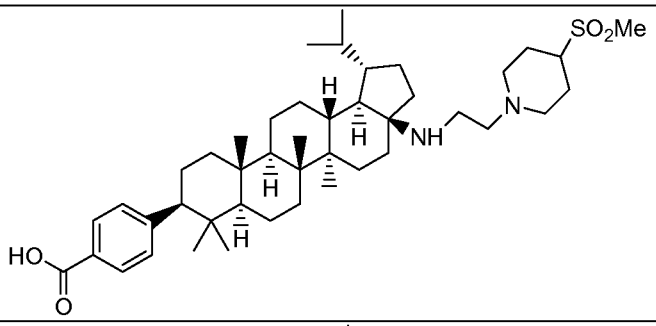
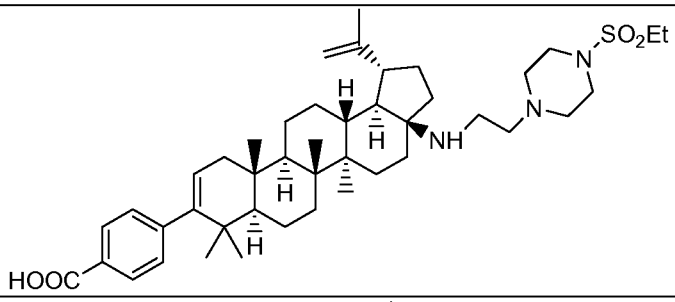
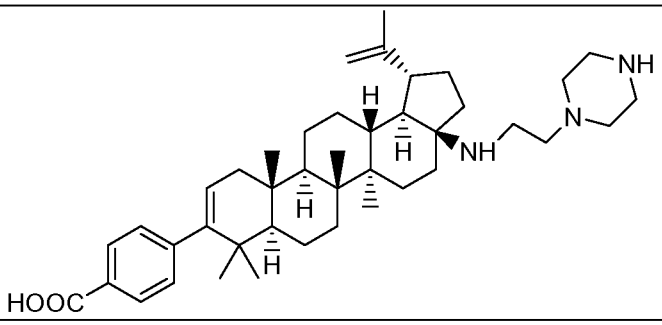
A1		A
A2		A
A3		A
A4		A
A5		A

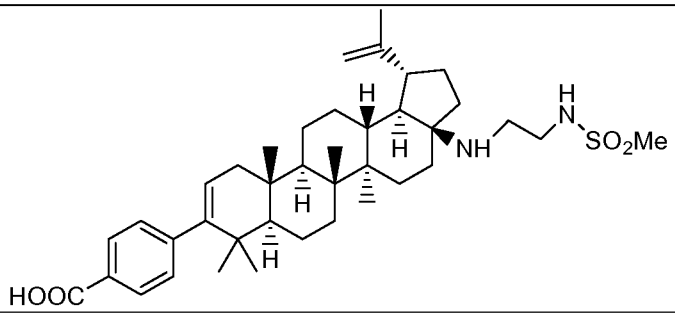
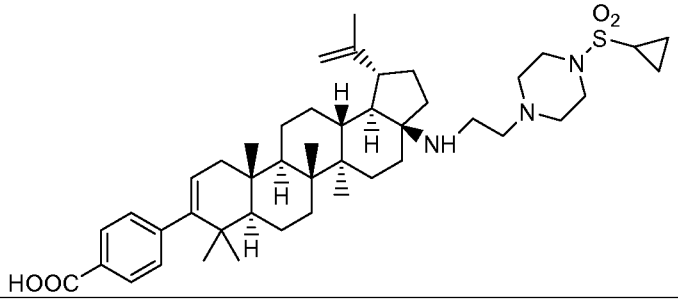
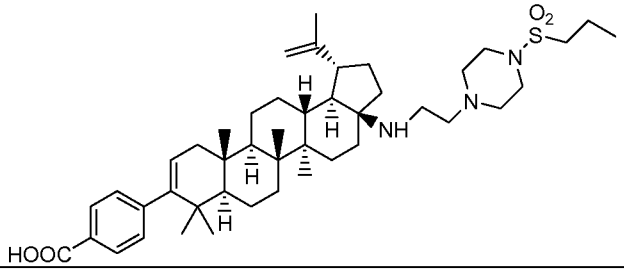
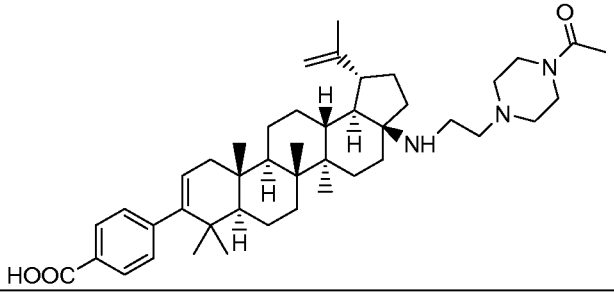
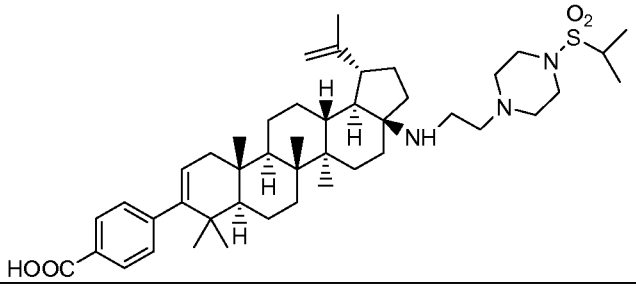
A6		A
A7		A
A8		A
B1		A
B2		A

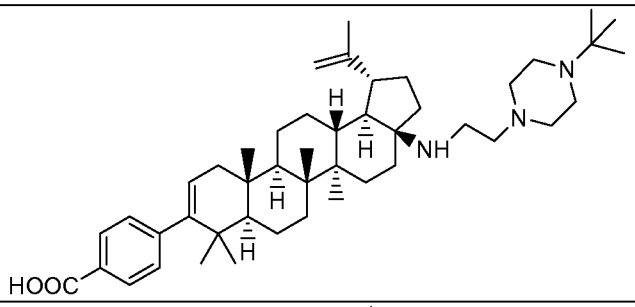
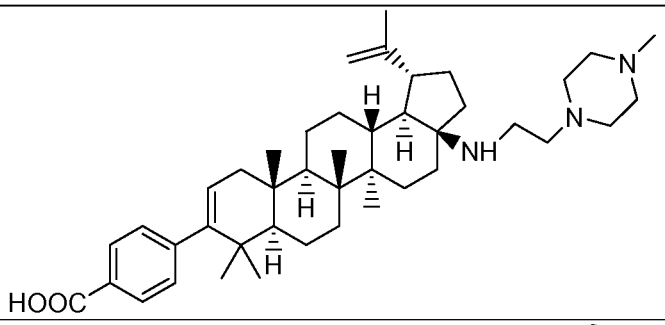
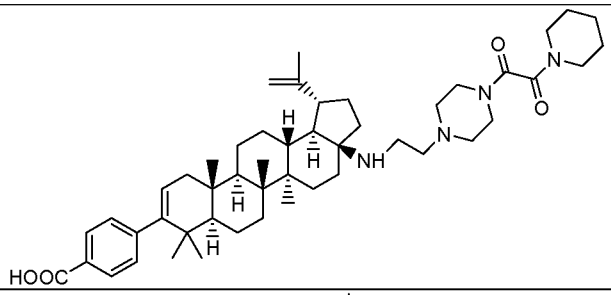
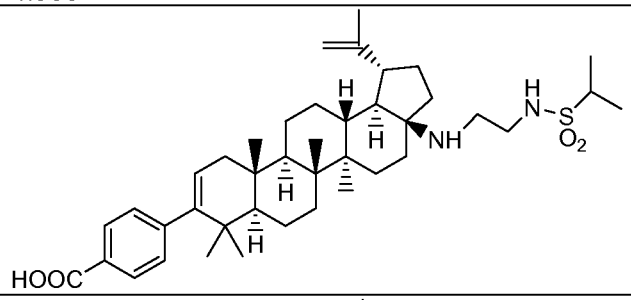
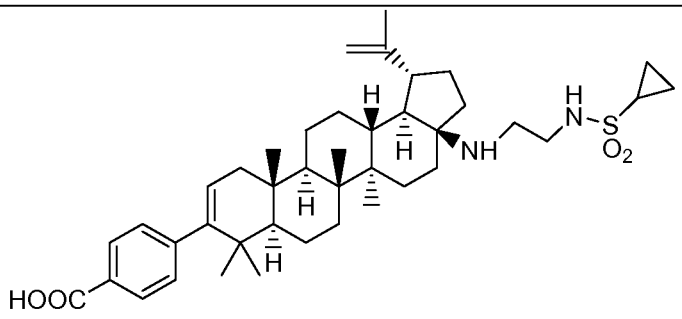
B3		A
B4		A
B5		A
B6		A
B7A		A

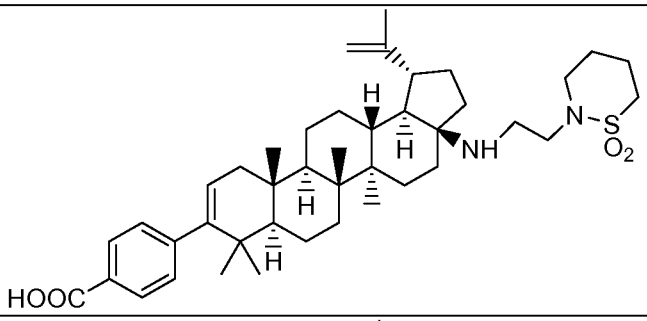
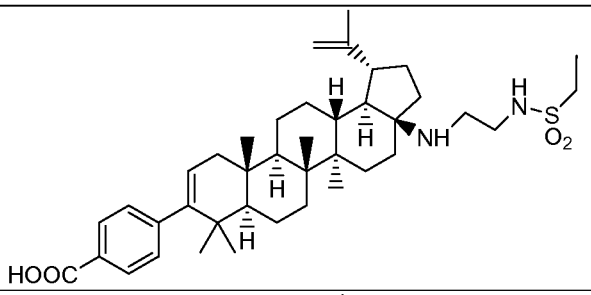
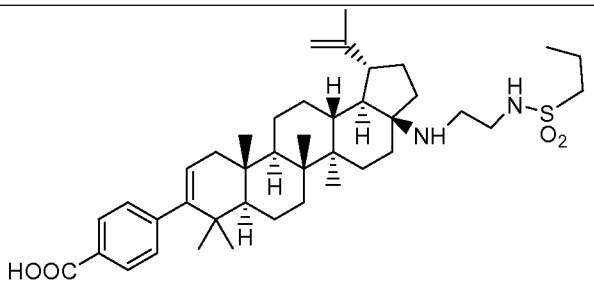
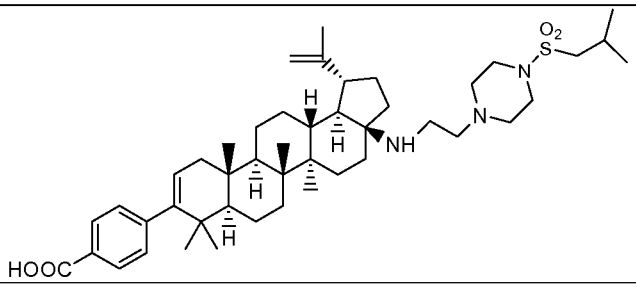
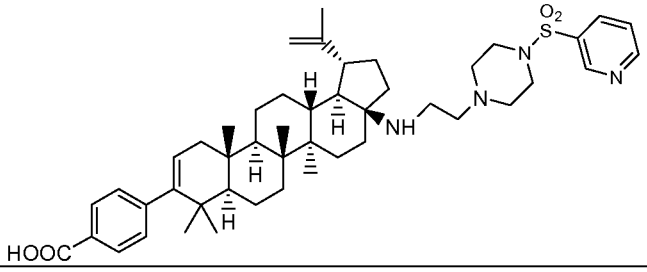
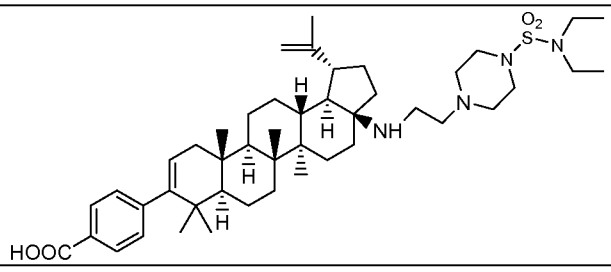
B7B		A
B8		A
B9		0.01
B10		A

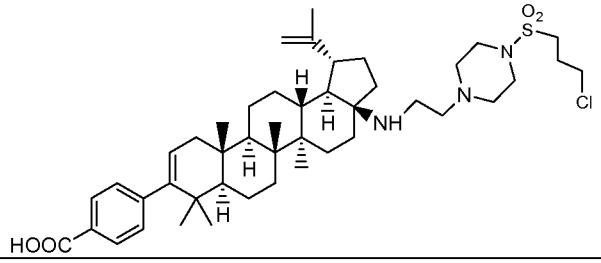
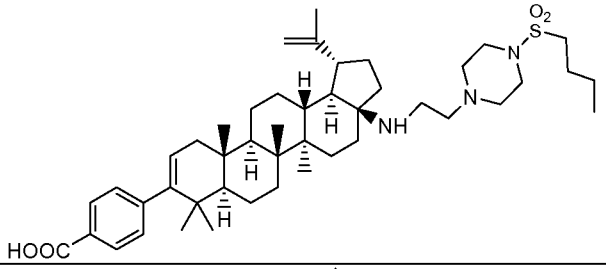
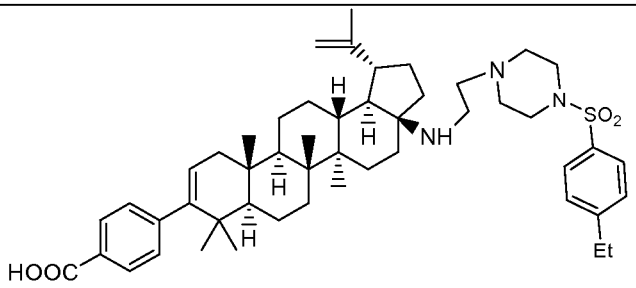
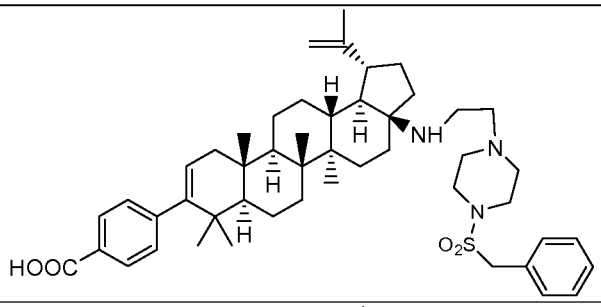
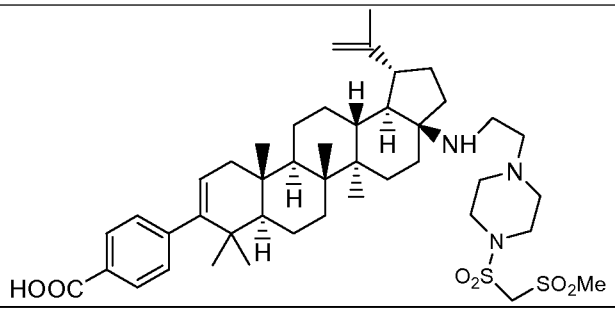
B11		A
B12		A
B13		A
B14		A
B15		A

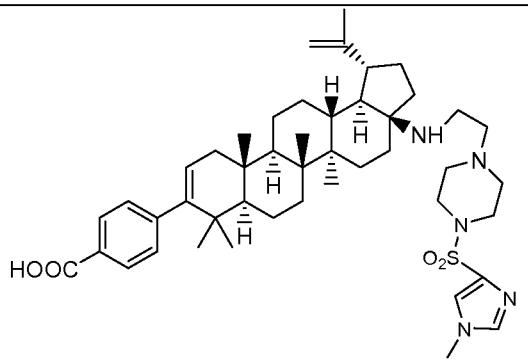
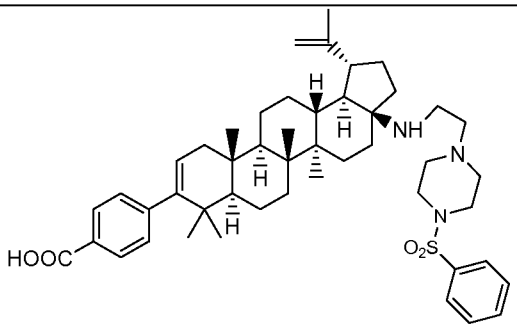
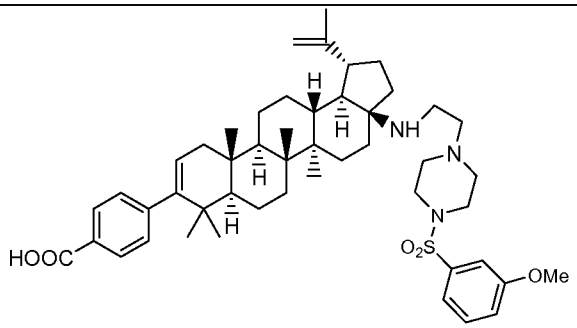
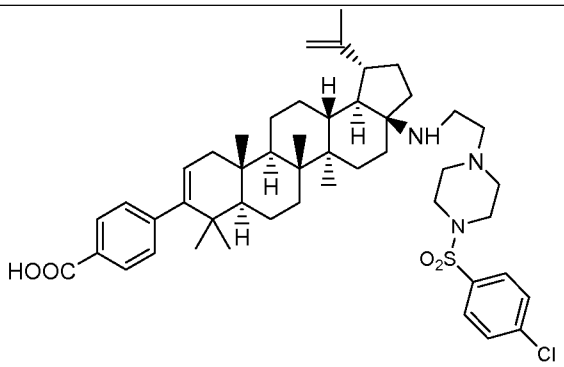
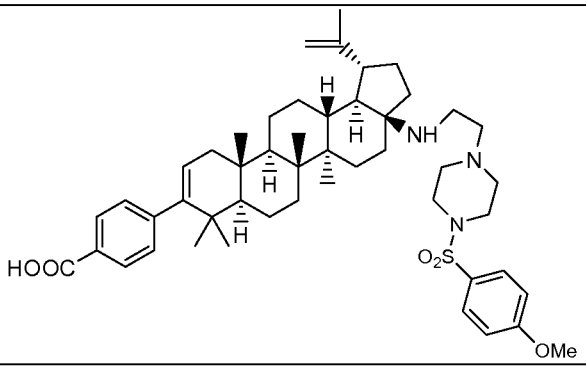
B16		A
B17		A
B18		A
B19		A
B20		A

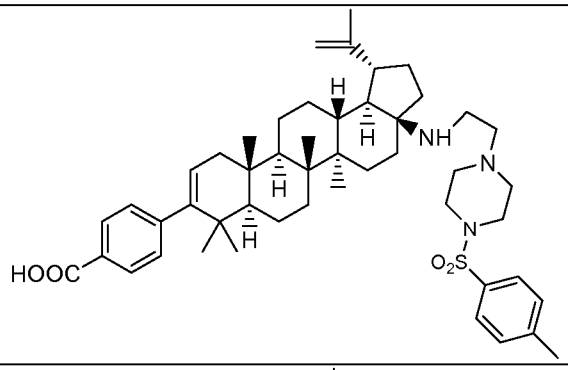
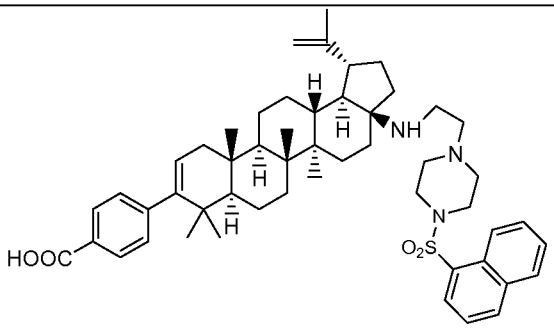
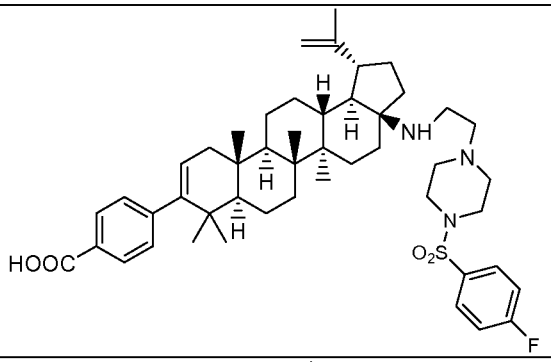
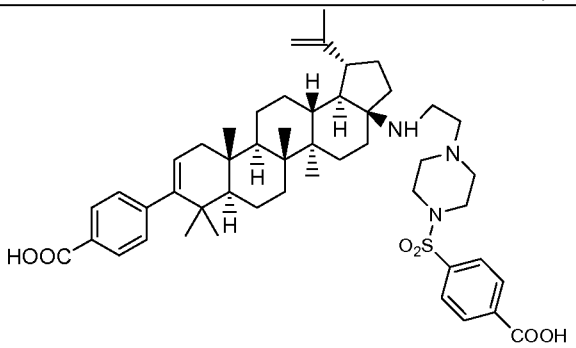
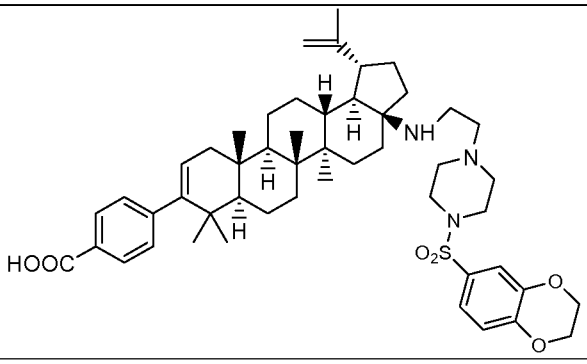
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B26		A

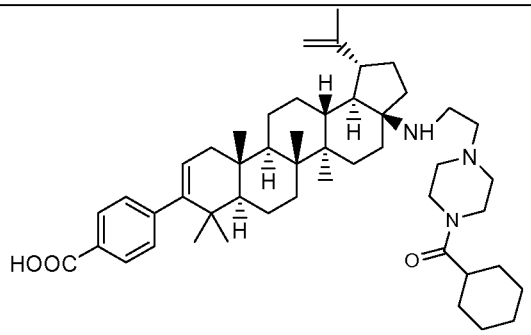
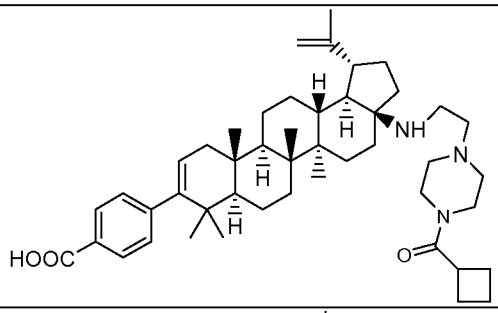
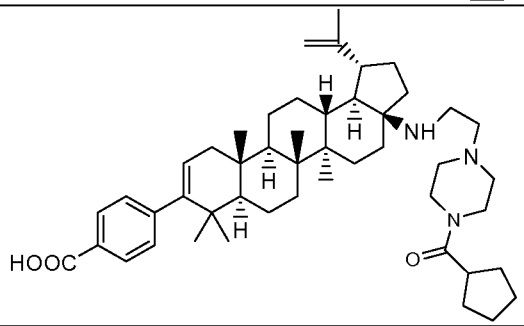
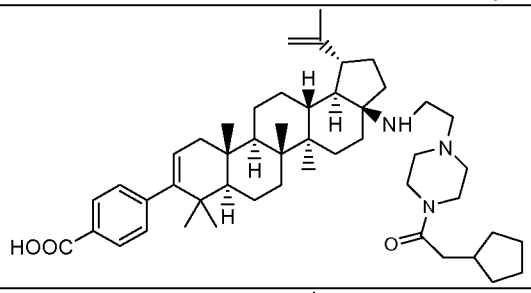
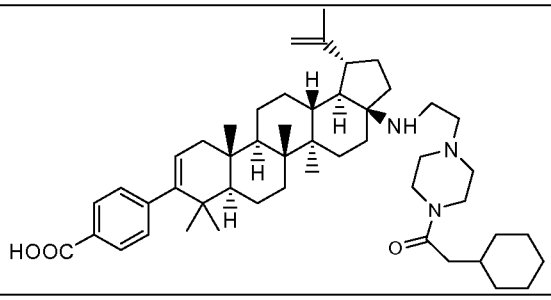
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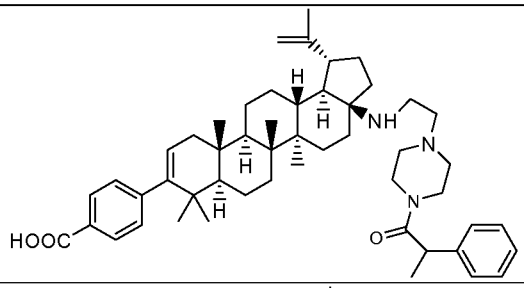
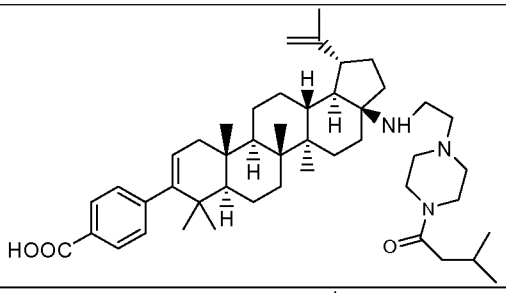
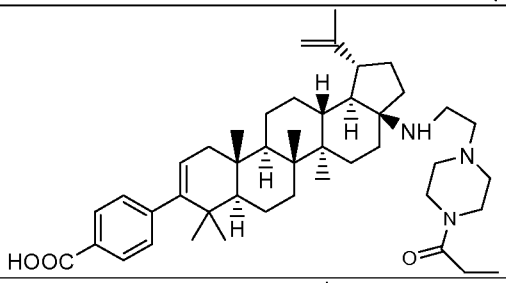
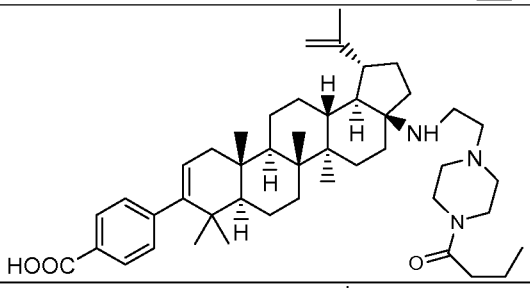
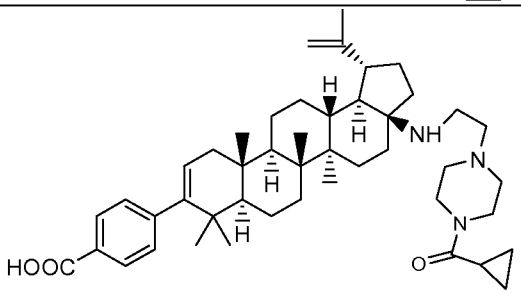
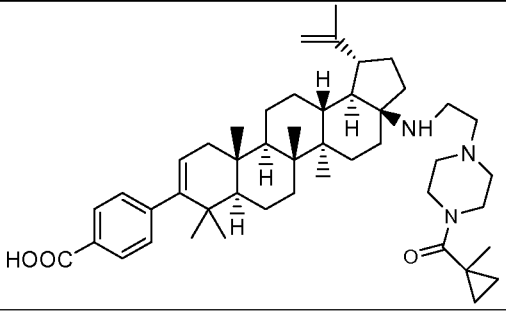
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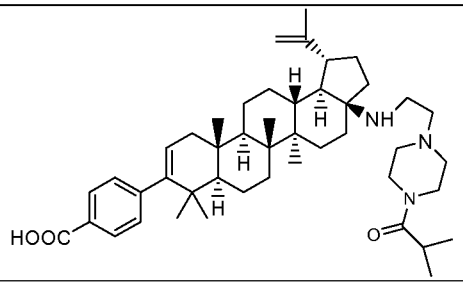
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B55		A
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B64		A 5

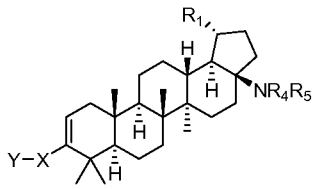
The foregoing description is merely illustrative and should not be understood to limit the scope or underlying principles of the invention in any way. Indeed, various modifications of the invention, in addition to those shown and described herein, will become apparent to those skilled in the art from the following examples and the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

CLAIMS

What is claimed is:

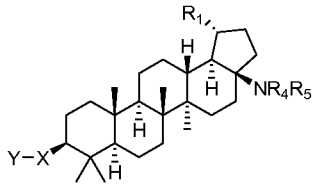
1. A compound, including pharmaceutically acceptable salts thereof, which is selected from the group consisting of:

a compound of formula I



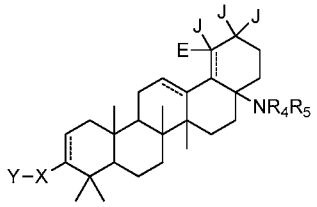
Formula I ;

a compound of formula II



Formula II ; and

a compound of formula III



Formula III ;

wherein R_1 is isopropenyl or isopropyl;

J and E are –H or $–CH_3$, and E is absent when the double bond is present;

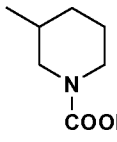
X is a phenyl or heteroaryl ring substituted with A, wherein A is at least one member selected from the group of -H, -halo, -hydroxyl, -C_{1-6} alkyl, -C_{1-6} alkoxy, and -$COOR_2$;

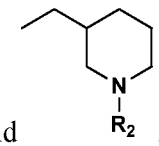
R_2 is -H, -C_{1-6} alkyl, -alkylsubstituted C_{1-6} alkyl or-arylsubstituted C_{1-6} alkyl;

Y is selected from the group of –$COOR_2$, -$C(O)NR_2SO_2R_3$, - $C(O)NHSO_2NR_2R_2$, -$NR_2SO_2R_2$, -$SO_2NR_2R_2$, -C_{3-6} cycloalkyl-$COOR_2$, -C_{2-6} alkenyl-$COOR_2$, -C_{2-6} alkynyl-$COOR_2$, -C_{1-6} alkyl-$COOR_2$, -$NHC(O)(CH_2)_n$-$COOR_2$, -$SO_2NR_2C(O)R_2$, -tetrazole, and –CONHOH,
wherein n=1-6;

R_3 is -C_{1-6} alkyl or -alkylsubstituted C_{1-6} alkyl;

R_4 is selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} alkyl-$C(OR_3)_2$-C_{3-6} cycloalkyl, -C_{1-6} substituted alkyl, -C_{1-6} alkyl-C_{3-6} cycloalkyl, -C_{1-6} alkyl-Q_1, -C_{1-6} alkyl-C_{3-6} cycloalkyl-Q_1, aryl, heteroaryl, substituted heteroaryl, -COR_6, -$COCOR_6$, -SO_2R_7, -$SO_2NR_2R_2$,



, and


;

wherein Q_1 is selected from the group of heteroaryl, substituted heteroaryl, halogen, -CF_3, -OR_2, -$COOR_2$, -NR_8R_9, -$CONR_{10}R_{11}$ and -SO_2R_7;

R_5 is selected from the group of -H, -C_{1-6} alkyl, -C_{3-6} cycloalkyl, -C_{1-6} alkylsubstituted alkyl, -C_{1-6} alkyl-NR_8R_9, -COR_{10}, -COR_6, -$COCOR_6$, -SO_2R_7 and -$SO_2NR_2R_2$;

with the proviso that only one of R_4 or R_5 can be selected from the group of -COR_6, -$COCOR_6$,-SO_2R_7 and -$SO_2NR_2R_2$;
or R_4 and R_5 are taken together with the adjacent N to form



;

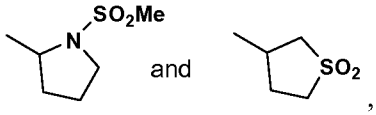
R_6 is selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} alkyl-substitutedalkyl, -C_{3-6} cycloalkyl, -C_{3-6} substitutedcycloalkyl-Q_2, -C_{1-6} alkyl-Q_2, -C_{1-6} alkyl-substitutedalkyl-Q_2,-C_{3-6} cycloalkyl-Q_2, aryl-Q_2, -$NR_{13}R_{14}$, and -OR_{15};

wherein Q_2 is selected from the group of aryl, heteroaryl, substituted heteroaryl, -OR_2, -$COOR_2$, -NR_8R_9, SO_2R_7, -$CONHSO_2R_3$, and -$CONHSO_2NR_2R_2$;

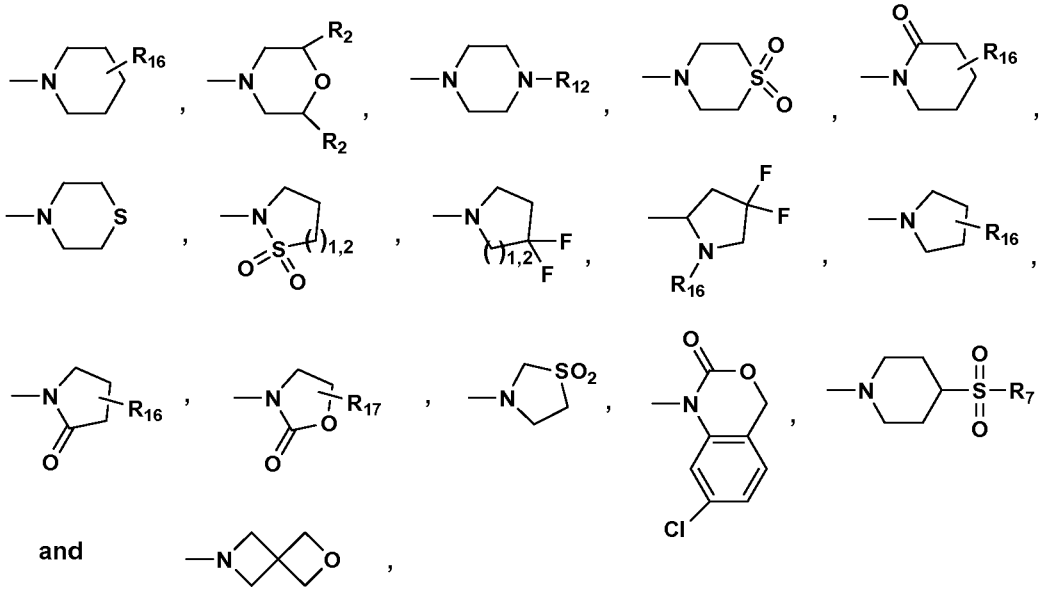
R_7 is selected from the group of -C_{1-6} alkyl, -C_{1-6} substituted alkyl, -C_{3-6} cycloalkyl, aryl, and heteroaryl;

R_8 and R_9 are independently selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} substituted alkyl, aryl, heteroaryl, substituted aryl, substituted heteroaryl, -C_{1-6} alkyl-Q_2, and -$COOR_3$,

and R_8 and R_9 can also be independently selected from the group of



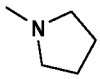
or R_8 and R_9 are taken together with the adjacent N to form a cycle selected from the group of:



with the proviso that only one of R_8 or R_9 can be -$COOR_3$;

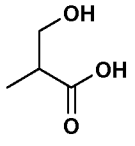
R_{10} and R_{11} are independently selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} substituted alkyl and -C_{3-6} cycloalkyl,

or R_{10} and R_{11} are taken together with the adjacent N to form a cycle such as

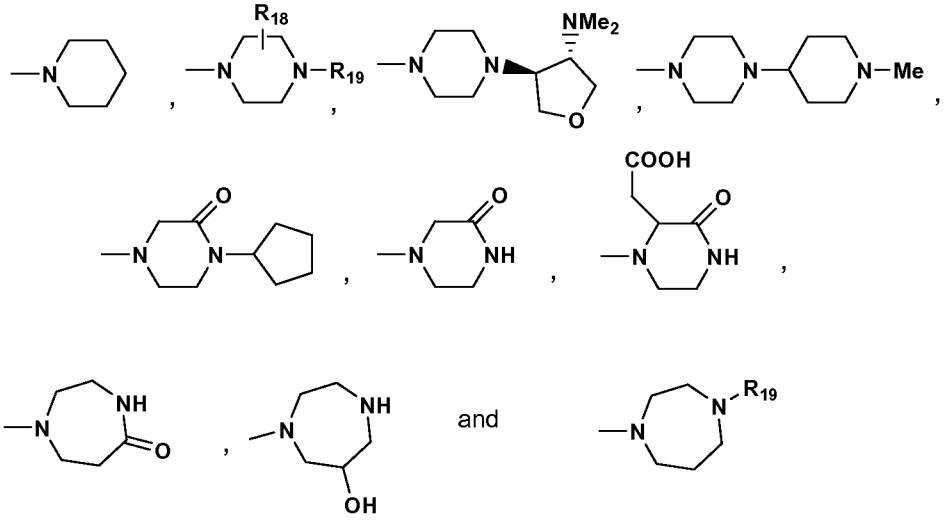

;

R_{12} is selected from the group of -C_{1-6} alkyl, -NR_2R_2, -C_{1-6} alkyl-OH, -C_{1-6} alkyl, -C_{1-6} substituted alkyl,-C_{3-6} cycloalkyl, -COR_7, -$COONR_{22}R_{23}$, -SOR_7, and -$SONR_{24}R_{25}$;

R_{13} and R_{14} are independently selected from the group of -H, -C_{1-6} alkyl, -C_{3-6} cycloalkyl, -C_{1-6} substituted alkyl, -C_{1-6} alkyl-Q_3, -C_{1-6} alkyl-C_{3-6} cycloalkyl-Q_3, C_{1-6} substituted alkyl-Q_3 and


,

or R_{13} and R_{14} are taken together with the adjacent N to form a cycle selected from the group of:


;

Q_3 is selected from the group of heteroaryl, substituted heteroaryl, -$NR_{20}R_{21}$, -$CONR_2R_2$, -$COOR_2$, -OR_2, and -SO_2R_3;

R_{15} is selected from the group of -C_{1-6} alkyl, -C_{3-6} cycloalkyl, -C_{1-6} substituted alkyl, -C_{1-6} alkyl-Q_3, -C_{1-6} alkyl-C_{3-6} cycloalkyl-Q_3 and -C_{1-6} substituted alkyl-Q_3;

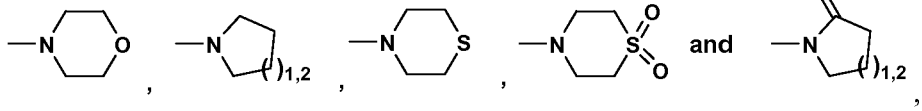
R_{16} is selected from the group of -H, -C_{1-6} alkyl, -NR_2R_2, and -$COOR_3$;

R_{17} is selected from the group of -H, -C_{1-6} alkyl, -$COOR_3$, and aryl;

R_{18} is selected from the group of -$COOR_2$ and -C_{1-6} alkyl-$COOR_2$;

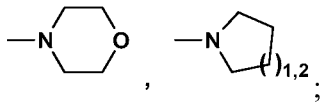
R_{19} is selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} alkyl-Q_4, -COR_3, -$COOR_3$, wherein Q_4 is selected from the group of -NR_2R_2 and -OR_2;

R_{20} and R_{21} are independently selected from the group of -H, -C_{1-6} alkyl, -C_{1-6} substituted alkyl, -C_{1-6} substituted alkyl-OR_2, and -COR_3,
or R_{20} and R_{21} are taken together with the adjacent N to form a cycle selected from the group of



with the proviso that only one of R_{20} or R_{21} can be -COR_3;

R_{22} and R_{23} are independently selected from the group of H, -C_{1-6} alkyl, -C_{1-6} substituted alkyl, and -C_{1-6} cycloalkyl,
or R_{22} and R_{23} are taken together with the adjacent N to form a cycle selected from the group of



;

R_{24} and R_{25} are independently from the group of H, -C_{1-6} alkyl, -C_{1-6} substituted alkyl, -C_{1-6} alkyl-Q_5, -C_{1-6} cycloalkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl,
and Q_5 is selected from the group of halogen and SO_2R_3.

2. The compound as claimed in claim 1, wherein said compound has the Formula I.

3. The compound as claimed in claim 1, wherein said compound has the Formula II.

4. The compound as claimed in claim 1, wherein said compound has the Formula III.

5. The compound as claimed in claim 2, wherein R_1 is isopropenyl.

6. The compound as claimed in claim 5, wherein X is phenyl.

7. The compound as claimed in claim 6, wherein Y is $-COOR_2$.

8. The compound as claimed in claim 7, wherein Y is –COOH.

9. The compound as claimed in claim 6, wherein A is –H.

10. The compound as claimed in claim 6, wherein R_4 is selected from the group of –H, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl-Q_1, and $-COR_6$.

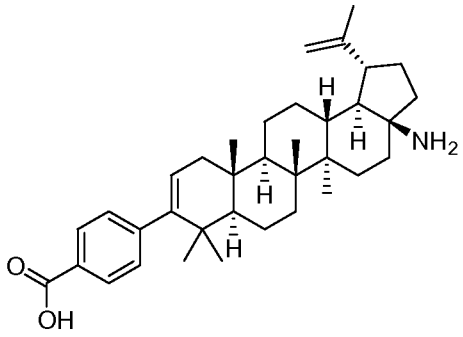
11. The compound as claimed in claim 10, wherein R_5 is –H.

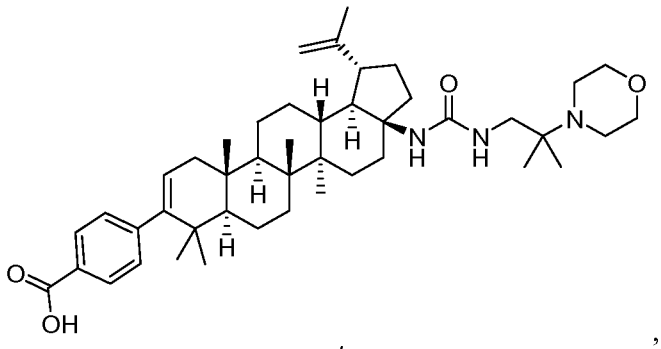
12. The compound as claimed in claim 10, wherein R_4 is $-C_{1-6}$ alkyl-Q_1.

13. The compound as claimed in claim 12, wherein Q_1 is $-NR_8R_9$.

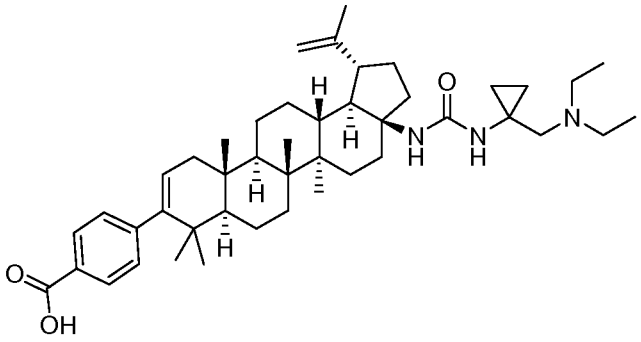
14. The compound as claimed in claim 10, wherein R_4 is $-COR_6$.

15. A compound, including pharmaceutically acceptable salts thereof, which is selected from the group consisting of:

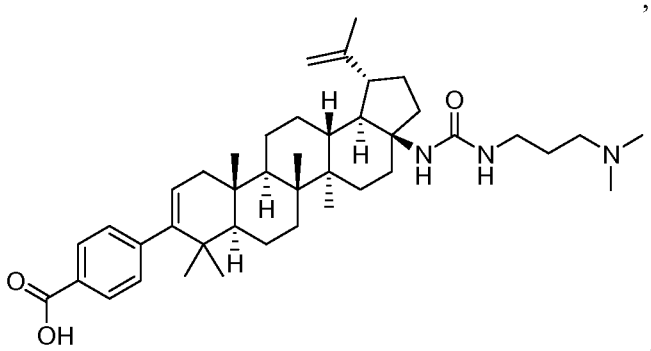




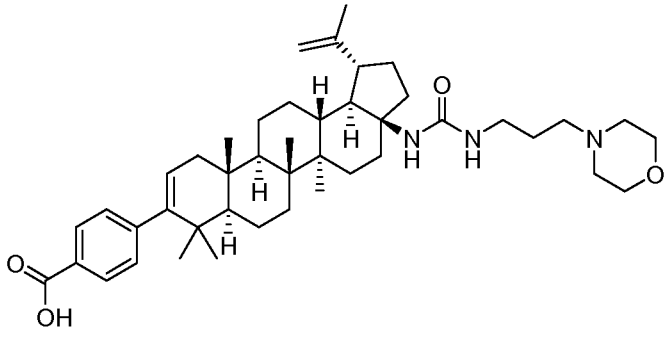
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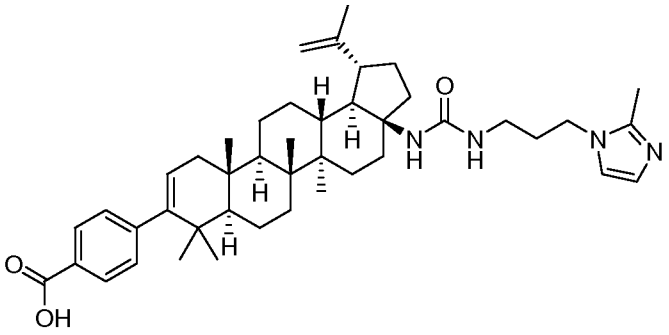
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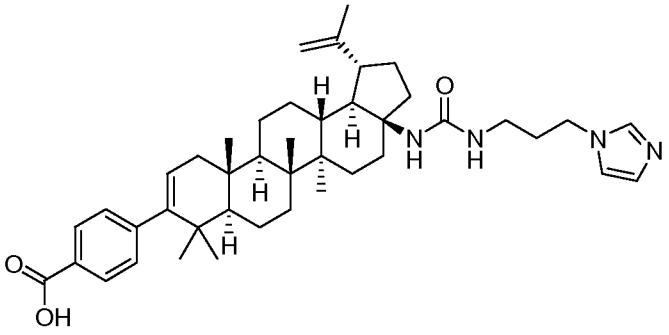


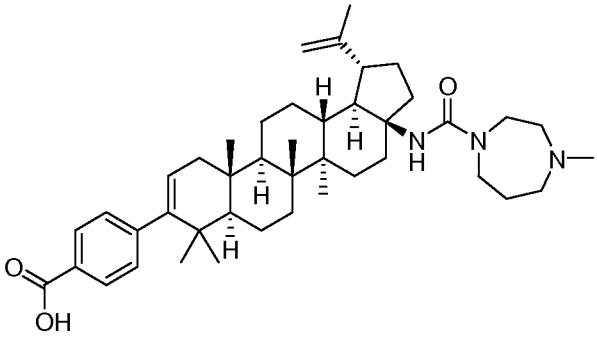
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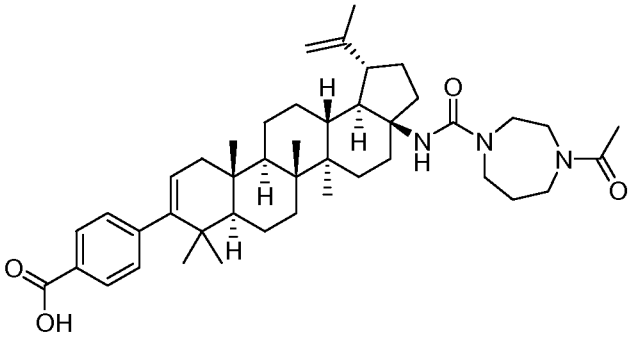


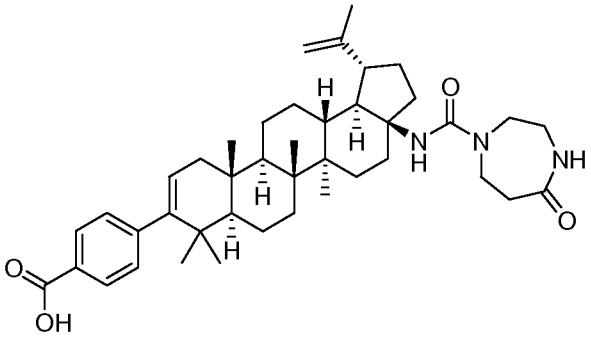
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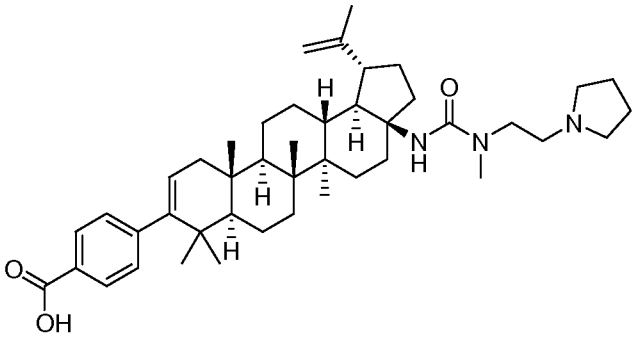

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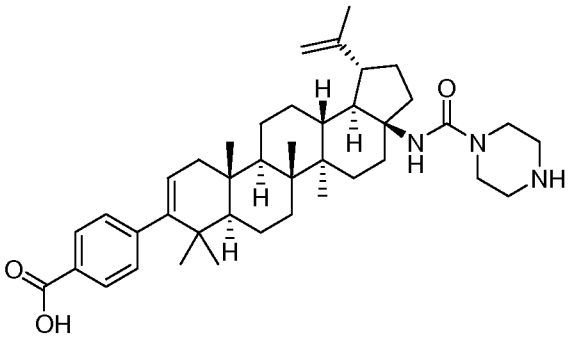

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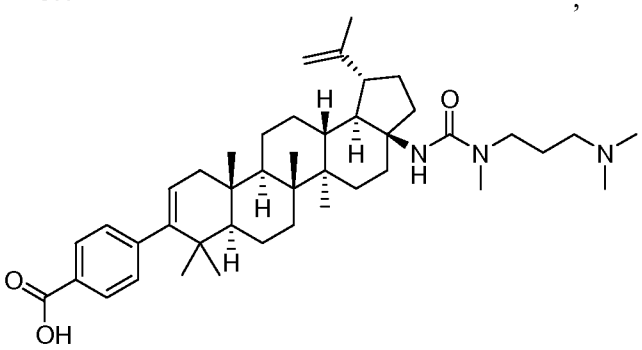

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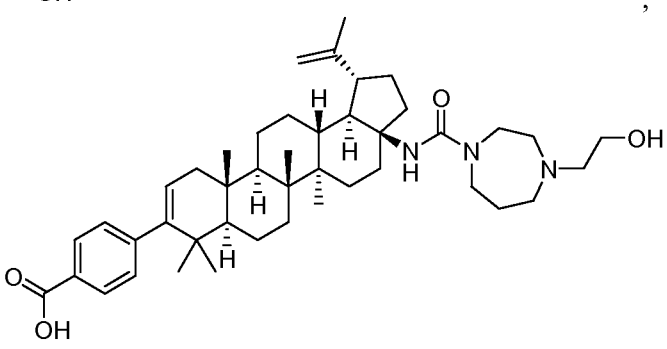
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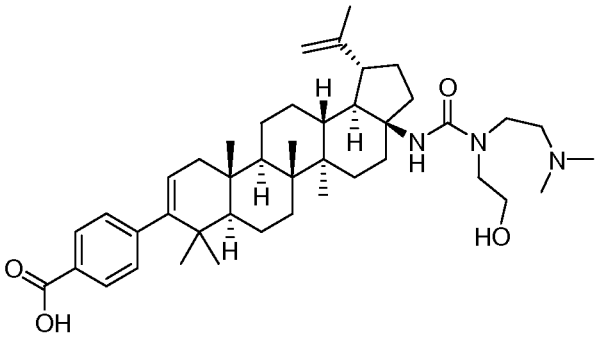
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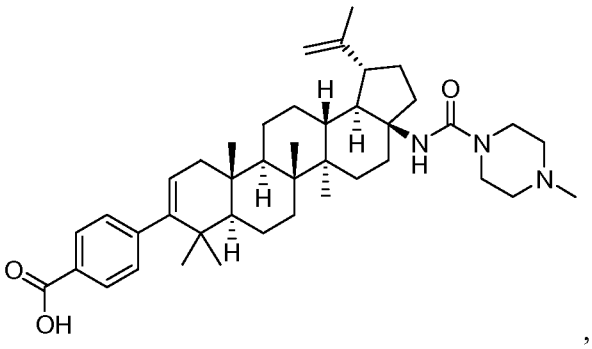


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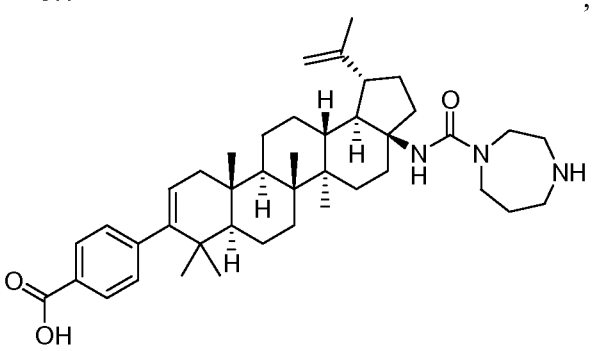


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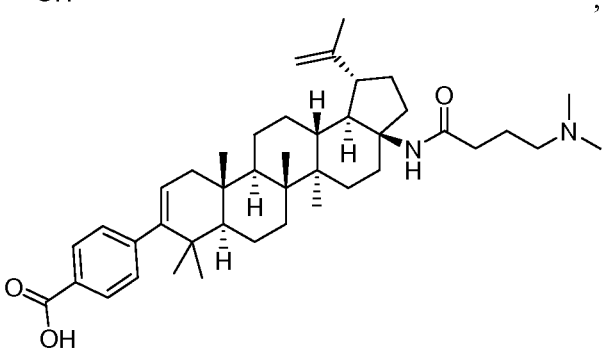




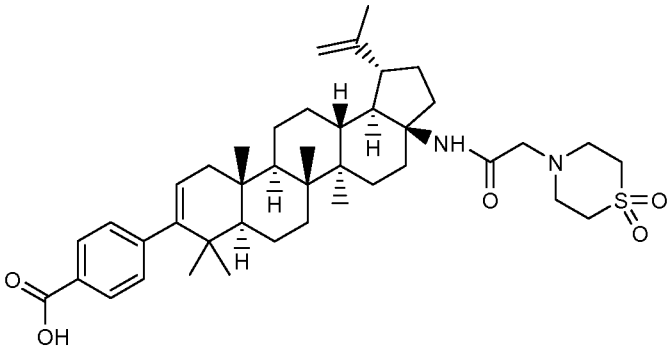
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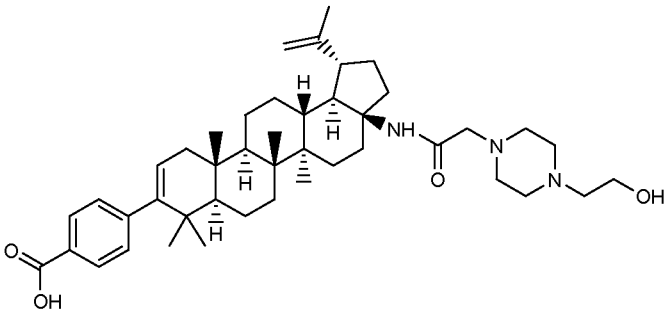


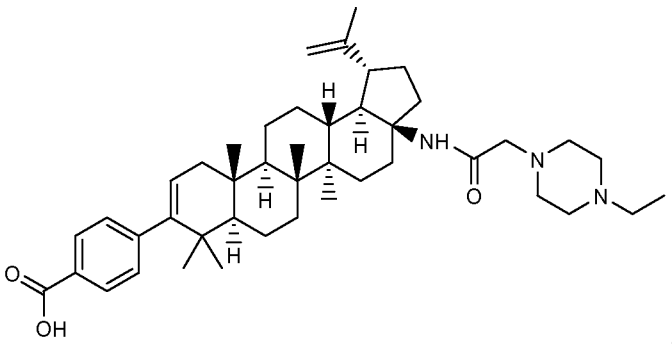
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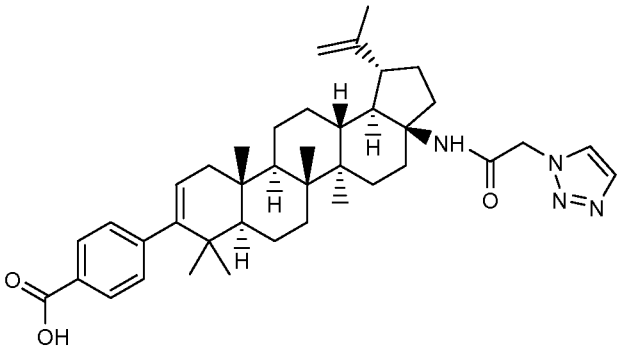


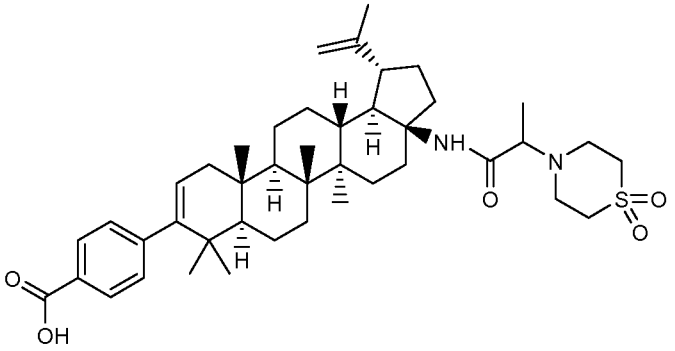




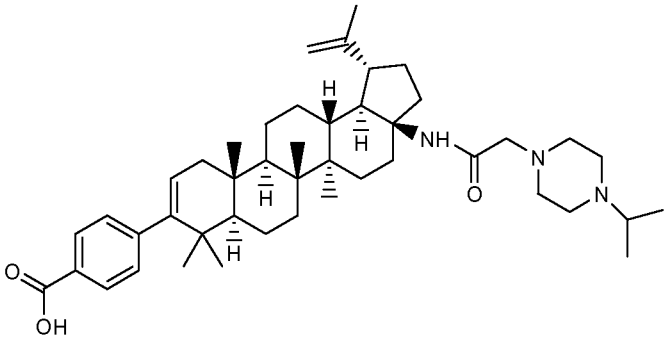
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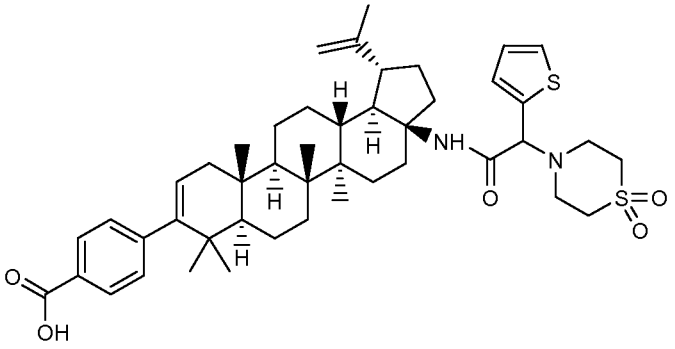
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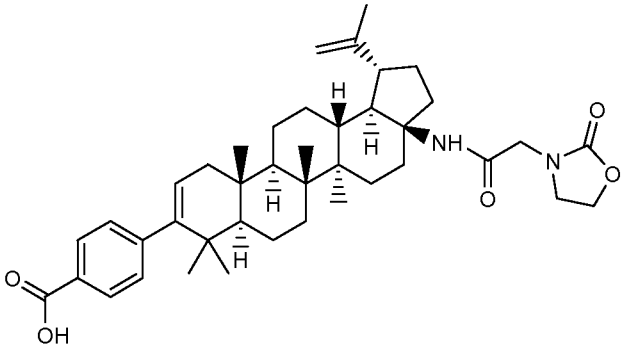




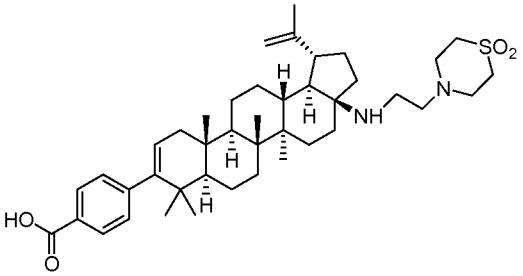
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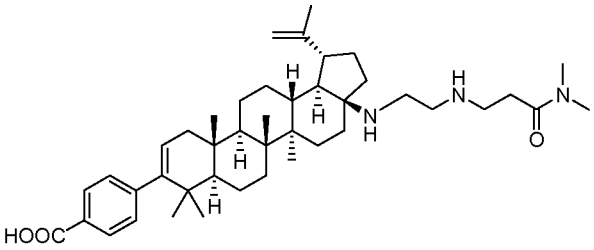


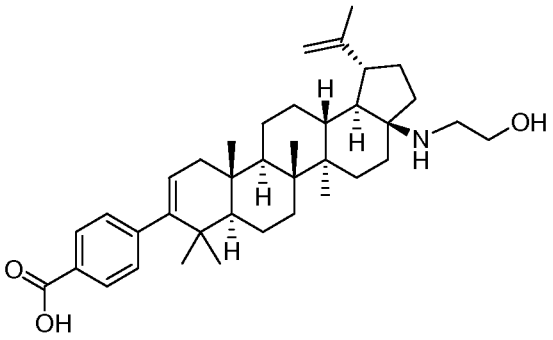


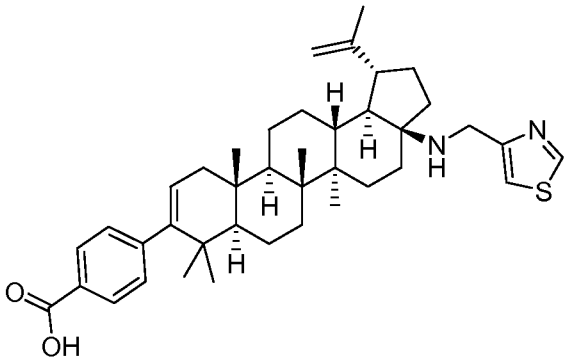


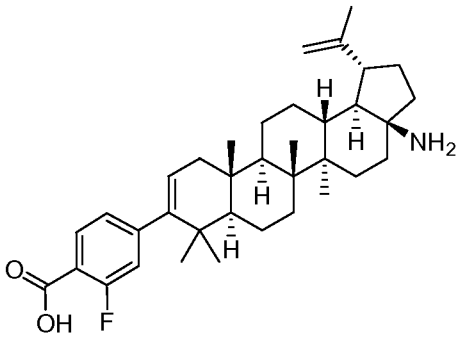
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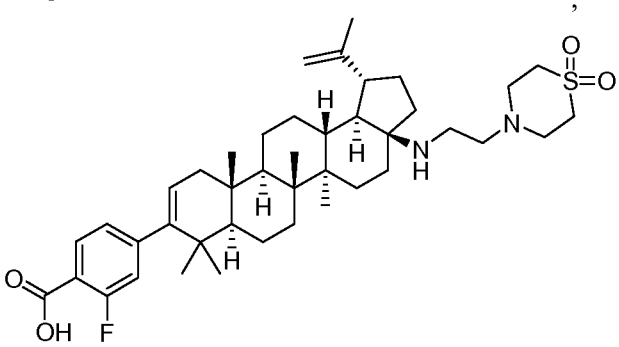




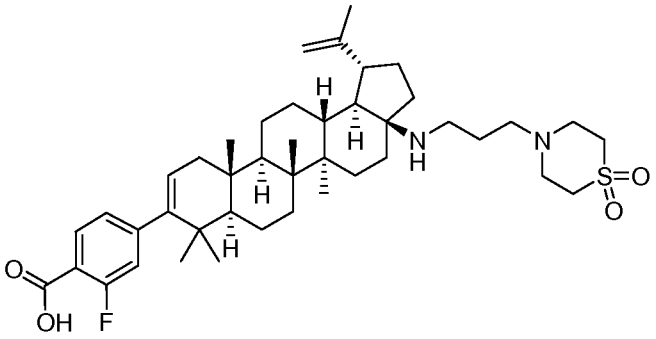




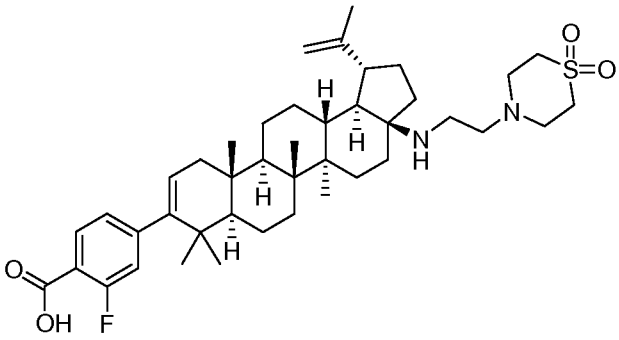
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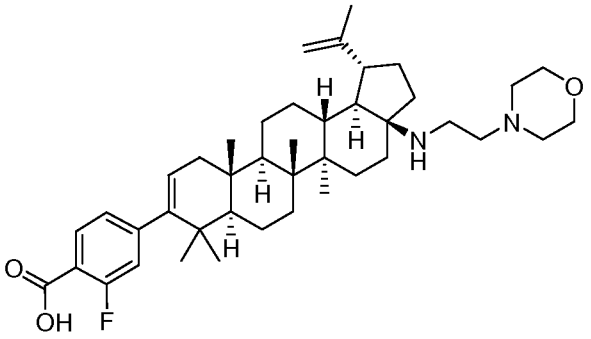
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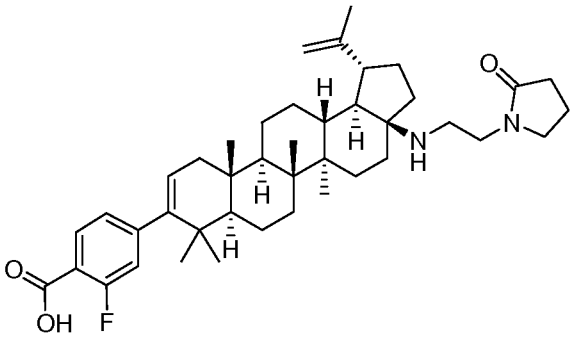
16. A compound, including pharmaceutically acceptable salts thereof, which is selected from the group consisting of:



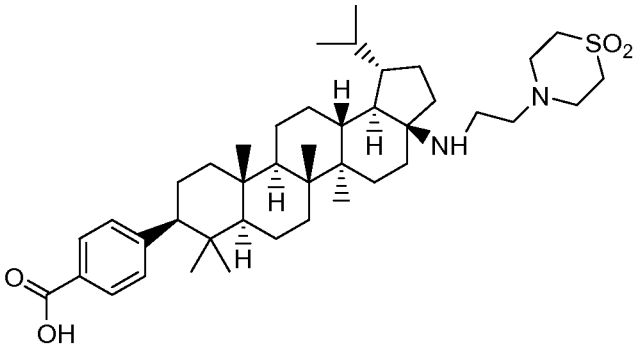
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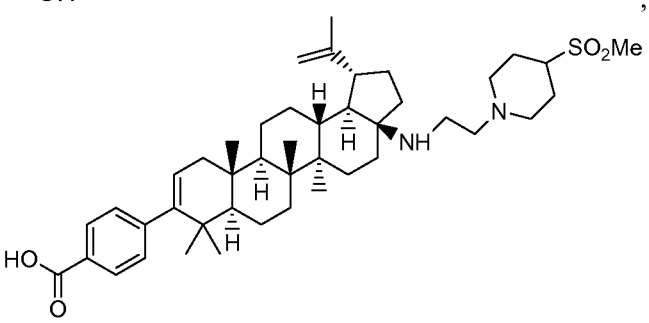
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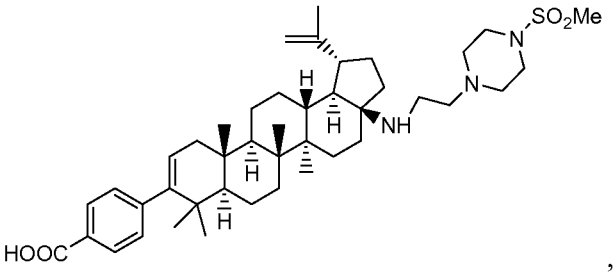
,


SO2
N
H
H
NH
H
O
OH

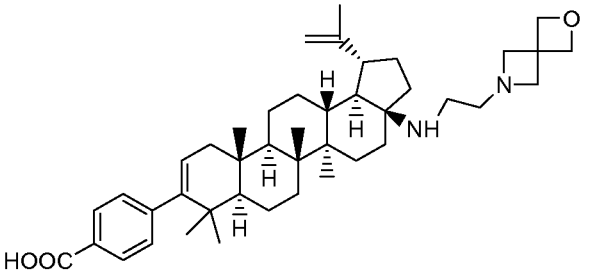
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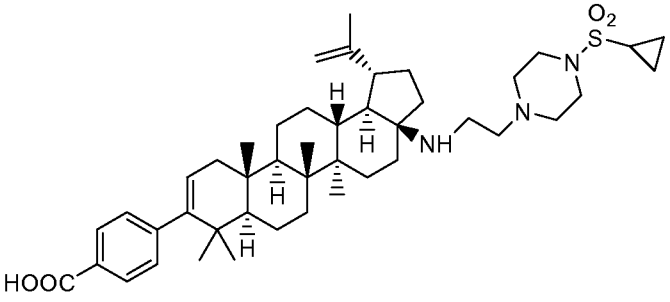

SO2Me
N
H
H
NH
H
HO
O

,

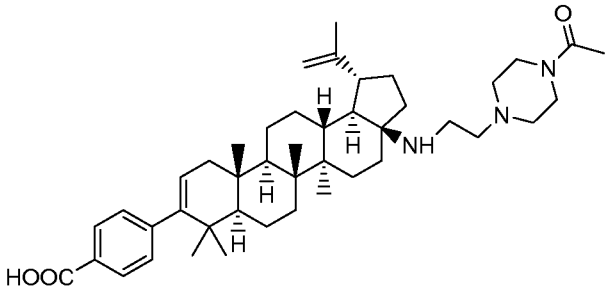

SO2Me
N
N
H
H
NH
H
HOOC

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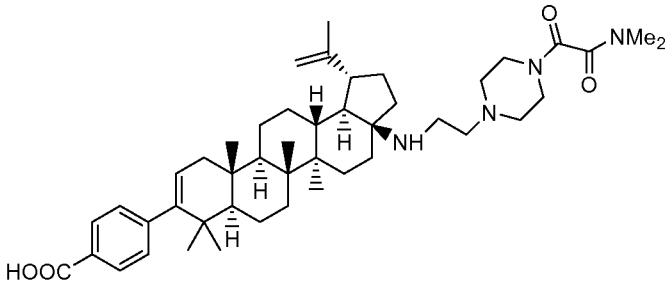

O
N
H
H
NH
H
HOOC


O2
S
N
N
H
H
NH
H
HOOC

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and

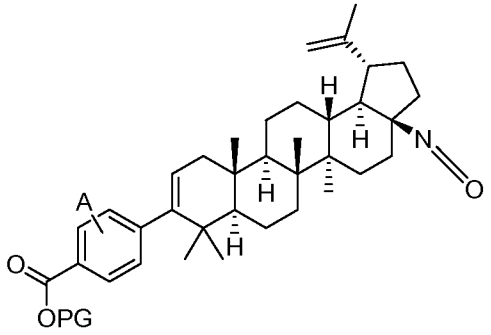


17. A pharmaceutical composition which comprises an antiviral effective amount of one or more of the compounds as claimed in claim 1, together with one or more pharmaceutically acceptable carriers, excipients or diluents.

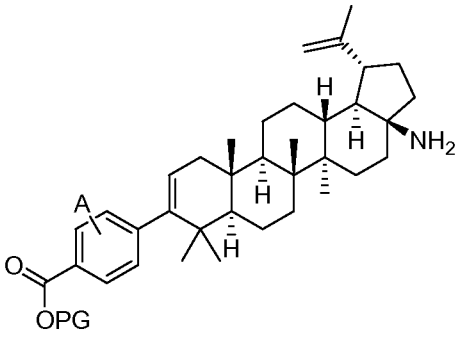
18. The pharmaceutical composition of claim 17, useful for treating infection by HIV, which additionally comprises an antiviral effective amount of an AIDS treatment agent selected from the group consisting of: (a) an AIDS antiviral agent; (b) an anti-infective agent; (c) an immunomodulator; and (d) another HIV entry inhibitor.

19. A method for treating a mammal infected with the HIV virus comprising administering to said mammal an antiviral effective amount of a compound as claimed in claim 1, and one or more pharmaceutically acceptable carriers, excipients or diluents.

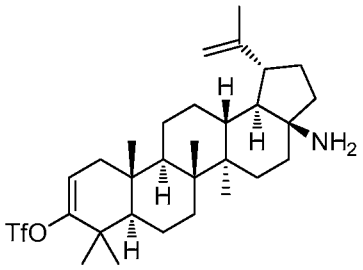
20. An intermediate compound which is selected from the group of



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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/022852

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07J63/00 A61K31/56 A61P31/18
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07J 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 practicable, search terms used)
EPO-Internal, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/100532 A1 (VIROCHEM PHARMA INC [CA]; MOINET CHRISTOPHE [CA]) 20 August 2009 (2009-08-20) the whole document, in particular pages 67-68, compounds 8-1, 9-1; pages 71-73, compounds 11-1, 12-1, 13-1, 13-2 page 99 - page 101; table 6	1-20
Y,P	WO 2011/153315 A1 (SQUIBB BRISTOL MYERS CO [US]; REGUEIRO-REN ALICIA [US]; SWIDORSKI JACO) 8 December 2011 (2011-12-08) the whole document, in particular claims 1,11 and page 1, paragraph 1	1-20
Y,P	WO 2011/153319 A1 (SQUIBB BRISTOL MYERS CO [US]; REGUEIRO-REN ALICIA [US]; LIU ZHENG [US]) 8 December 2011 (2011-12-08) the whole document, in particular claims 1,11 and page 1, paragraph 1	1-20

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 May 2012	18/05/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Watchorn, Peter

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2012/022852

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009100532 A1	20-08-2009	AU 2009214779 A1	20-08-2009
		CA 2714049 A1	20-08-2009
		EP 2257567 A1	08-12-2010
		JP 2011511812 A	14-04-2011
		US 2011077251 A1	31-03-2011
		WO 2009100532 A1	20-08-2009
WO 2011153315 A1	08-12-2011	NONE	
WO 2011153319 A1	08-12-2011	NONE	

TRITERPENOIDES C-17 Y C-3 MODIFICADOS CON ACTIVIDAD INHIBIDORA DE LA MADURACION DEL VIRUS DE INMUNODEFICIENCIA HUMANA

Campo de la Invención

La presente invención se refiere a nuevos compuestos útiles contra el VIH y, más en particular, a compuestos derivados del ácido betulínico y otros compuestos relacionados estructuralmente que son útiles como inhibidores de la maduración del VIH, y a composiciones farmacéuticas que los contienen, así como a métodos para su preparación.

Antecedentes de la Invención

La infección por el VIH-1 (virus de inmunodeficiencia humana 1) sigue siendo un problema médico de grandes magnitudes, y los cálculos indican que hacia fines de 2010 había 45-50 millones de personas infectadas a nivel mundial. La cantidad de casos de VIH y SIDA (síndrome de inmunodeficiencia adquirida) aumentó rápidamente. En 2005, se informaron aproximadamente 5.0 millones de nuevas infecciones y 3.1 millones de personas murieron de SIDA. Los fármacos que se encuentran actualmente disponibles para el tratamiento de VIH incluyen inhibidores de transcriptasa inversa de nucleósido (RT, por sus siglas en inglés) o combinaciones de píldoras únicas aprobadas: zidovudina (o AZT o Retrovir®), didanosina (o Videx®), estavudina (o Zerit®), lamivudina (o

3TC o Epivir®), zalcitabina (o DDC o Hivid®), succinato de abacavir (o Ziagen®), Tenofovir sal de fumarato de disoproxilo (o Viread®), emtricitabina (o FTC-Emtriva®), Combivir® (contiene -3TC más AZT), Trizivir® (contiene abacavir, lamivudina y zidovudina), Epzicom® (contiene abacavir y lamivudina), Truvada® (contiene Viread® y Emtriva®); inhibidores de transcriptasa inversa de no nucleósido: nevirapina (o Viramune®), delavirdina (o Rescriptor®) y efavirenz (o Sustiva®), Atripla® (Truvada® + Sustiva®) y etravirina, inhibidores de proteasa peptidomimética o formulaciones aprobadas: saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, lopinavir, Kaletra®(lopinavir y Ritonavir), darunavir, atazanavir (Reyataz®) y tipranavir (Aptivus®) y cobicistat, inhibidores de integrasa, tales como raltegravir (Isentress®), e inhibidores de entrada, tales como enfuvirtida (T-20) (Fuzeon®) y maraviroc (Selzentry®).

Cada uno de estos fármacos solo puede restringir transitoriamente la replicación viral si se usan solos. Sin embargo, cuando se usan combinados, estos fármacos tienen un gran efecto en el avance de enfermedades y viremia. De hecho, recientemente se documentaron reducciones considerables de las tasas de mortalidad entre pacientes con SIDA como consecuencia de la extensa aplicación de la terapia combinada. Sin embargo, a pesar de estos impresionantes

resultados, las terapias de fármacos combinados pueden finalmente fallar en el 30 al 50% de los pacientes. Una insuficiente potencia de los fármacos, la falta de cumplimiento, una penetración restringida al tejido y limitaciones específicas de los fármacos en ciertos tipos de células (por ejemplo, la mayoría de los análogos de nucleósidos no se pueden fosforilar en las células en reposo) pueden ser la causa de la supresión incompleta de virus sensibles. Además, la alta tasa de replicación y la rápida producción de VIH-1, combinados con la frecuente incorporación de mutaciones, produce la aparición de variantes resistentes a los fármacos y fallas en el tratamiento cuando hay concentraciones subóptimas de fármacos. Por lo tanto, se necesitan nuevos agentes contra el VIH que exhiben diferentes patrones de resistencia y una farmacocinética favorable así como perfiles de seguridad para proveer más opciones de tratamiento. Los inhibidores de la fusión de VIH y los antagonistas de correceptores de la entrada de VIH mejorados son dos ejemplos de nuevas clases de agentes contra el VIH estudiados por varios investigadores.

Los inhibidores de la unión del VIH son otra subclase de compuestos antivirales que se unen a la glicoproteína superficial gp120 del VIH e interfieren con la interacción entre la proteína superficial gp120 y el receptor de la célula hospedero CD4. Por ello, evitan que el VIH se

una a la célula humana CD4 T y bloquean la replicación del VIH en la primera etapa del ciclo de vida del VIH. Las propiedades de los inhibidores de la unión del VIH se mejoraron en un intento por obtener compuestos con máxima utilidad y eficacia como agentes antivirales. En particular, los documentos US 7,354,924 y US 2005/0209246 son ilustrativos de los inhibidores de la unión al VIH.

Otra clase emergente de compuestos para el tratamiento del VIH se denomina inhibidores de la maduración del VIH. La maduración es la última de 10 o más etapas de la replicación del VIH o del ciclo de vida del VIH, en donde el VIH se vuelve infeccioso como consecuencia de varios eventos de clivaje mediados por la proteasa del VIH en la proteína gag que, en última instancia, genera la liberación de la proteína cápsida (CA). Los inhibidores de la maduración evitan que la cápsida del VIH se ensamble y madure de manera adecuada, que forme una cubierta externa protectora o que surja de células humanas. En cambio, se producen virus no infecciosos que evitan ciclos posteriores de la infección por VIH.

Ahora se ha demostrado que ciertos derivados del ácido betulínico exhiben una potente actividad contra el VIH como inhibidores de la maduración del VIH. Por ejemplo, el documento US 7,365,221 describe derivados de dihidrobetulina y betulina monoacilados y su uso como agentes contra el VIH. Como se analiza en la referencia ‘221, la esterificación del

ácido betulínico (1) con ciertos grupos acilo sustituidos, tales como grupos 3',3'-dimetilglutarilo y 3',3'-dimetilsuccinilo produce derivados que tienen mejor actividad (Kashiwada, Y., et al., J. Med. Chem. 39:1016-1017 (1996)). Los derivados del ácido dihidrobetulínico y del ácido betulínico acilados que son potentes agentes contra el VIH también se describen en la patente estadounidense N.° 5,679,828. La esterificación del hidroxilo en el carbono 3 de betulina con ácido succínico también produjo un compuesto capaz de inhibir la actividad del VIH-1 (Pokrovskii, A. G., et al., Gos. Nauchnyi Tsentr Virusol. Biotekhnol. "Vector" 9:485-491 (2001)).

Otras referencias al tratamiento de la infección por VIH con compuestos derivados del ácido betulínico incluyen US 2005/0239748 y US 2008/0207573, así como WO2006/053255, WO2009/100532 y WO2011/007230.

Un compuesto de la maduración del VIH en proceso de desarrollo se identificó como Bevirimat o PA-457, con la fórmula química de $C_{36}H_{56}O_6$ y el nombre IUPAC ácido 3β-(3-carboxi-3-metil-butanoiloxi) lup-20(29)-en-28-oico.

En la presente, también se hace referencia a las solicitudes de Bristol-Myers Squibb tituladas "MODIFIED C-3 BETULINIC ACID DERIVATIVES AS HIV MATURATION INHIBITORS" USSN 13/151,706, presentada el 2 de junio de 2011, y "C-28 AMIDES OF MODIFIED C-3 BETULINIC ACID DERIVATIVES AS HIV MATURATION

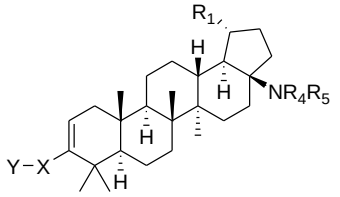
INHIBITORS" USSN 13/151,722, presentada el 2 de junio de 2011. También se hace referencia a la solicitud titulada "C-28 AMINES OF C-3 MODIFIED BETULINIC ACID DERIVATIVES AS HIV MATURATION INHIBITORS" USSN 61/437,870, presentada el 31 de enero de 2011.

En la actualidad se necesitan nuevos compuestos que sean útiles como inhibidores de la maduración del VIH así como nuevas composiciones farmacéuticas que contengan estos compuestos.

Breve Descripción de la Invención

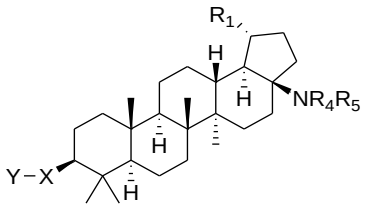
La presente invención provee compuestos de las siguientes Fórmulas I, II y III, que incluyen sus sales farmacéuticamente aceptables, sus formulaciones farmacéuticas y su uso en pacientes que padecen o que son susceptibles de padecer un virus, tal como el VIH. Los compuestos de las Fórmulas I–III son eficaces como agentes antivirales, en particular, como inhibidores del VIH. Son útiles para el tratamiento del VIH y del SIDA.

Una modalidad de la presente invención se refiere a un compuesto, que incluye sus sales farmacéuticamente aceptables, que se selecciona del siguiente grupo: un compuesto de la Fórmula I



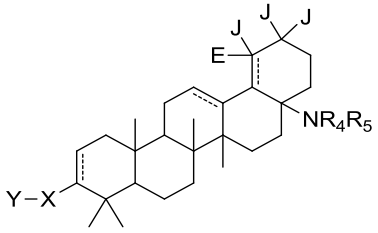
Fórmula I ;

un compuesto de la Fórmula II



Fórmula II ; y

un compuesto de la Fórmula III



Fórmula III ;

en donde R_1 es isopropenilo o isopropilo;

J y E son –H o $-CH_3$, y E está ausente cuando el enlace doble está presente;

X es un anillo de fenilo o heteroarilo sustituido con A, en donde A es, al menos, un elemento seleccionado del grupo que consiste en -H, -halo, -hidroxilo, -alquilo C_{1-6}, -alcoxi C_{1-6} y $-COOR_2$;

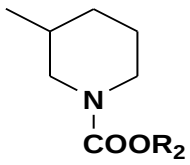
R_2 es -H, -alquilo C_{1-6}, alquilo C_{1-6} sustituido con -alquilo o alquilo C_{1-6} sustituido con -arilo;

Y se selecciona del grupo de $-COOR_2$, $-C(O)NR_2SO_2R_3$, $C(O)NHSO_2NR_2R_2$, $-NR_2SO_2R_2$, $-SO_2NR_2R_2$, -cicloalquilo C_{3-6}-$COOR_2$, -alquenilo C_{2-6}-$COOR_2$, -alquinilo C_{2-6}-$COOR_2$, -alquilo C_{1-6}-$COOR_2$, $-NHC(O)(CH_2)_n$-$COOR_2$, $-SO_2NR_2C(O)R_2$, -tetrazol y –CONHOH,

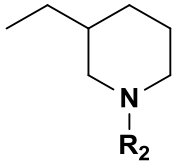
en donde n= 1-6;

R_3 es -alquilo C_{1-6} o alquilo C_{1-6} sustituido con -alquilo;

R_4 se selecciona del grupo de -H, -alquilo C_{1-6}, -alquilo C_{1-6}-$C(OR_3)_2$-cicloalquilo C_{3-6}, -alquilo C_{1-6} sustituido, -alquilo C_{1-6}-cicloalquilo C_{3-6}, -alquilo C_{1-6}-Q_1, -alquilo C_{1-6}-cicloalquilo C_{3-6}-Q_1, arilo, heteroarilo, heteroarilo sustituido, $-COR_6$, $-COCOR_6$, $-SO_2R_7$, $-SO_2NR_2R_2$,



y



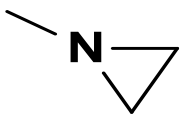
,

en donde Q_1 se selecciona del grupo de heteroarilo, heteroarilo sustituido, halógeno, $-CF_3$, $-OR_2$, $-COOR_2$, $-NR_8R_9$, $-CONR_{10}R_{11}$ y $-SO_2R_7$;

R_5 se selecciona del grupo de -H, -alquilo C_{1-6}, -cicloalquilo C_{3-6}, -alquilo C_{1-6} sustituido con alquilo, -alquilo C_{1-6}-NR_8R_9, $-COR_{10}$, $-COR_6$, $-COCOR_6$, $-SO_2R_7$ y $-SO_2NR_2R_2$;

siempre que solo uno de R_4 o R_5 se pueda seleccionar del grupo de $-COR_6$, $-COCOR_6$,$-SO_2R_7$ y $-SO_2NR_2R_2$;

o R_4 y R_5 se toman en forma conjunta con el N adyacente para formar



;

R_6 se selecciona del grupo de -H, -alquilo C_{1-6}, -alquilo C_{1-6} sustituido con alquilo, -cicloalquilo C_{3-6}, -

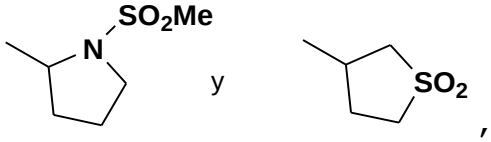
cicloalquilo C_{3-6} sustituido con Q_2, -alquilo C_{1-6}-Q_2, -alquilo C_{1-6} sustituido con alquil-Q_2, -cicloalquilo C_{3-6}-Q_2, aril-Q_2, $-NR_{13}R_{14}$ y $-OR_{15}$;

en donde Q_2 se selecciona del grupo de arilo, heteroarilo, heteroarilo sustituido, $-OR_2$, $-COOR_2$, $-NR_8R_9$, SO_2R_7, $-CONHSO_2R_3$ y $-CONHSO_2NR_2R_2$;

R_7 se selecciona del grupo de -alquilo C_{1-6}, -alquilo C_{1-6} sustituido, -cicloalquilo C_{3-6}, arilo y heteroarilo;

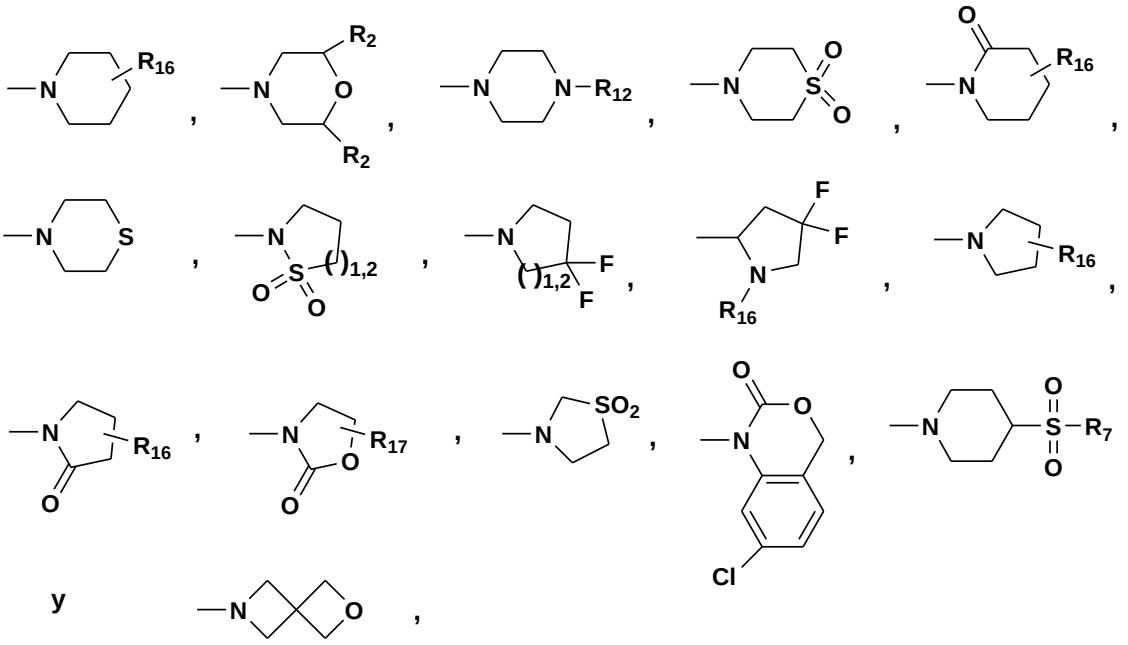
R_8 y R_9 se seleccionan independientemente del grupo de -H, -alquilo C_{1-6}, -alquilo C_{1-6} sustituido, arilo, heteroarilo, arilo sustituido, heteroarilo sustituido, -alquilo C_{1-6}-Q_2 y $-COOR_3$,

y R_8 y R_9 también se pueden seleccionar independientemente del siguiente grupo:



,

o R_8 y R_9 se toman en forma conjunta con el N adyacente para formar un ciclo seleccionado del siguiente grupo:

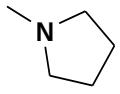


y

siempre que solo uno de R_8 o R_9 pueda ser $-COOR_3$;

R_{10} y R_{11} se seleccionan independientemente del grupo de -H, -alquilo C_{1-6}, -alquilo C_{1-6} sustituido y -cicloalquilo C_3-$_6$,

o R_{10} y R_{11} se toman en forma conjunta con el N adyacente para formar un ciclo, tal como

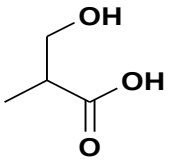


;

R_{12} se selecciona del grupo de -alquilo C_{1-6}, -alquilo C_{1-6}-OH; -alquilo C_{1-6}, -alquilo C_{1-6} sustituido, -cicloalquilo C_3-$_6$, $-COR_7$, $-COONR_{22}R_{23}$, $-SOR_7$ y $-SONR_{24}R_{25}$;

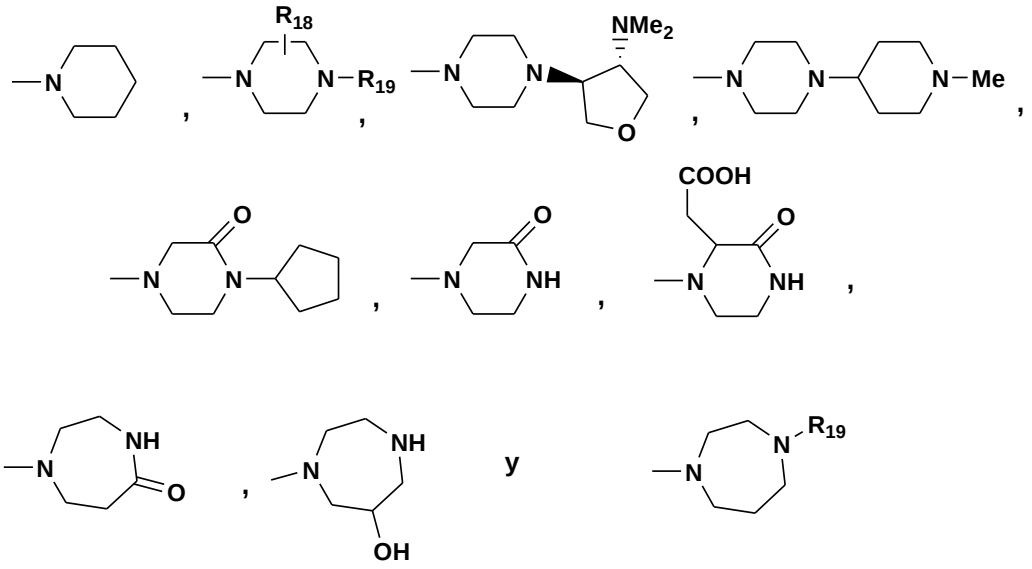
R_{13} y R_{14} se seleccionan independientemente del grupo de -H, -alquilo C_{1-6}, -cicloalquilo C_3-$_6$, -alquilo C_{1-6} sustituido, -alquilo C_{1-6}-Q_3, -alquilo C_{1-6}-cicloalquilo C_3-$_6$-

Q_3, alquilo C_{1-6} sustituido con Q_3 y



,

o R_{13} y R_{14} se toman en forma conjunta con el N adyacente para formar un ciclo seleccionado del siguiente grupo:



;

Q_3 se selecciona del grupo de heteroarilo, heteroarilo sustituido, $-NR_{20}R_{21}$, $-CONR_2R_2$, $-COOR_2$, $-OR_2$ y $-SO_2R_3$;

R_{15} se selecciona del grupo de -alquilo C_{1-6}, -cicloalquilo C_{3-6}, -alquilo C_{1-6} sustituido, -alquilo C_{1-6}-Q_3, -alquilo C_{1-6}-cicloalquilo C_{3-6}-Q_3 y -alquilo C_{1-6} sustituido con Q_3;

R_{16} se selecciona del grupo de -H, -alquilo C_{1-6}, -NR_2R_2 y $-COOR_3$;

R_{17} se selecciona del grupo de -H, -alquilo C_{1-6}, -

$COOR_3$ y arilo;

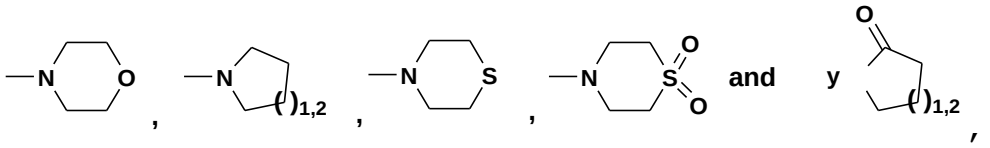
R_{18} se selecciona del grupo de $-COOR_2$ y -alquilo C_{1-6}-$COOR_2$;

R_{19} se selecciona del grupo de -H, -alquilo C_{1-6}, -alquilo C_{1-6}-Q_4, $-COR_3$, $-COOR_3$,

en donde Q_4 se selecciona del grupo de $-NR_2R_2$ y $-OR_2$;

R_{20} y R_{21} se seleccionan independientemente del grupo de -H, -alquilo C_{1-6}, -alquilo C_{1-6} sustituido, -alquilo C_{1-6} sustituido con OR_2 y $-COR_3$,

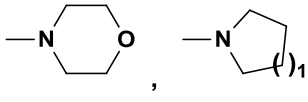
o R_{20} y R_{21} se toman en forma conjunta con el N adyacente para formar un ciclo seleccionado del siguiente grupo:



siempre que solo uno de R_{20} o R_{21} pueda ser $-COR_3$;

R_{22} y R_{23} se seleccionan independientemente del grupo de H, -alquilo C_{1-6}, -alquilo C_{1-6} sustituido y -cicloalquilo C_{1-6},

o R_{22} y R_{23} se toman en forma conjunta con el N adyacente para formar un ciclo seleccionado del siguiente grupo:



;

R_{24} y R_{25} se seleccionan independientemente del grupo

de H, -alquilo C_{1-6}, -alquilo C_{1-6} sustituido, -alquilo C_{1-6}-Q_5, -cicloalquilo C_{1-6}, arilo, arilo sustituido, heteroarilo y heteroarilo sustituido,

y Q_5 se selecciona del grupo de halógeno y SO_2R_3.

En otra modalidad, se provee un método para tratar mamíferos infectados con un virus, en especial cuando tal virus es VIH, que comprende administrarle al mamífero una cantidad eficaz antiviral de un compuesto que se selecciona del grupo de compuestos de las Fórmulas I, II, III anteriores y uno o más portadores, excipientes o diluyentes farmacéuticamente aceptables. Opcionalmente, el compuesto de las Fórmulas I, II y/o III se puede administrar en combinación con una cantidad eficaz antiviral de otro agente para el tratamiento del SIDA seleccionado del grupo que consiste en: (a) un agente antiviral del SIDA; (b) un agente antiinfeccioso; (c) un inmunomodulador; y (d) otros inhibidores de la entrada del VIH.

Otra modalidad de la presente invención es una composición farmacéutica que comprende una cantidad eficaz antiviral de un compuesto que se selecciona del grupo de los compuestos de las Fórmulas I, II y III, y uno o más portadores, excipientes y diluyentes farmacéuticamente aceptables; y, opcionalmente, en combinación con una cantidad eficaz antiviral de otro agente para el tratamiento del SIDA seleccionado del grupo que consiste en: (a) un agente

antiviral del SIDA; (b) un agente antiinfeccioso; (c) un inmunomodulador; y (d) otros inhibidores de la entrada del VIH.

En otra modalidad de la invención se proporcionan uno o más métodos para obtener los compuestos de las Fórmulas I, II y III de la presente.

En la presente, también se proporcionan compuestos intermediarios útiles para obtener los compuestos de las Fórmulas I, II y III de la presente.

La presente invención se refiere a ellos así como a otros extremos importantes, que se describen a continuación.

Descripción Detallada de la Invención

Debido a que los compuestos de la presente invención pueden tener centros asimétricos y, por ello, producirse como mezclas de diastereómeros y enantiómeros, la presente descripción incluye las formas diastereoisoméricas y enantioméricas individuales de los compuestos de las Fórmulas I, II y III además de sus mezclas.

Definiciones

A menos que se indique específicamente de otro modo en la solicitud, se pueden usar uno o más de los siguientes términos en la presente y tendrán los siguientes significados:

"H" se refiere a hidrógeno, incluso sus isótopos, tales como deuterio.

Como se usa en la presente y en las reivindicaciones (a menos que se especifique de otro modo), el término "alquilo C_{1-6}" significa grupos alquilo de cadena lineal o ramificada, tales como metilo, etilo, propilo, isopropilo, butilo, isobutilo, t-butilo, amilo, hexilo y similares.

"fluoroalquilo C_1–C_4" se refiere a alquilo C_1–C_4sustituido con F, en donde al menos un átomo H se sustituye con el átomo F y cada átomo H se puede sustituir independientemente con el átomo F;

"Halógeno" se refiere a cloro, bromo, yodo o flúor.

Un grupo "arilo" o "Ar" se refiere a grupos de carbono monocíclicos o policíclicos de anillo fusionado (es decir, anillos que comparten pares adyacentes de átomos de carbono) que tienen un sistema de electrones pi completamente conjugados. Los ejemplos, sin limitación, de grupos arilo son fenilo, naptalenilo y antracenilo. El grupo arilo puede ser sustituido o no sustituido. Cuando se sustituyen, los grupos sustituidos son, preferentemente, uno o más seleccionados de alquilo, cicloalquilo, arilo, heteroarilo, heteroaliciclilo, hidroxi, alcoxi, ariloxi, heteroariloxi, heteroalicicloxi, tiohidroxi, tioariloxi, tioheteroariloxi, tioheteroalicicloxi, ciano, halógeno, nitro, carbonilo, O-carbamilo, N-carbamilo, C-amido, N-amido, C-carboxi, O-carboxi, sulfinilo, sulfonilo, sulfonamido, trihalometilo,

ureido, amino y $-NR^xR^y$, en donde R^x y R^y se seleccionan, independientemente, del grupo que consiste en hidrógeno, alquilo, cicloalquilo, arilo, carbonilo, C-carboxi, sulfonilo, trihalometilo y un anillo heterocíclico de 5 o 6 miembros combinado.

Como se usa en la presente, un grupo "heteroarilo" se refiere a un grupo de anillos monocíclicos o fusionados (es decir, anillos que comparten un par adyacente de átomos) que tiene, en los anillos, uno o más átomos seleccionados del grupo que consiste nitrógeno, oxígeno y azufre, y que tiene, además, un sistema de electrones pi completamente conjugado. A menos que se indique de otro modo, el grupo heteroarilo se puede unir a un átomo de carbono o de nitrógeno dentro del grupo heteroarilo. Se debe tener en cuenta que el término "heteroarilo" pretende abarcar un N-óxido del heteroarilo de origen si tal N-óxido es químicamente viable como se conoce en el arte. Los ejemplos de grupos heteroarilo son, sin limitación, furilo, tienilo, benzotienilo, tiazolilo, imidazolilo, oxazolilo, oxadiazolilo, tiadiazolilo, benzotiazolilo, triazolilo, tetrazolilo, isoxazolilo, isotiazolilo, pirrolilo, piranilo, tetrahidropiranilo, pirazolilo, piridilo, pirimidinilo, quinolinilo, isoquinolinilo, purinilo, carbazolilo, benzoxazolilo, benzimidazolilo, indolilo, isoindolilo, pirazinilo, diazinilo, pirazina, triazinilo, tetrazinilo y tetrazolilo.

Cuando se sustituyen, los grupos sustituidos son, preferentemente, uno o más seleccionados de alquilo, cicloalquilo, arilo, heteroarilo, heteroaliciclilo, hidroxi, alcoxi, ariloxi, heteroariloxi, heteroalicicloxi, tioalcoxi, tiohidroxi, tioariloxi, tioheteroariloxi, tioheteroalicicloxi, ciano, halógeno, nitro, carbonilo, O-carbamilo, N-carbamilo, C-amido, N-amido, C-carboxi, O-carboxi, sulfinilo, sulfonilo, sulfonamido, trihalometilo, ureido, amino y $-NR^xR^y$, en donde R^x y R^y son como se definieron anteriormente.

Como se usa en la presente, un grupo "heterocíclico" se refiere a un grupo de anillos monocíclicos o fusionados que tienen, en los anillos, uno o más átomos seleccionados del grupo que consiste en nitrógeno, oxígeno y azufre. Los anillos se seleccionan de aquellos que proporcionan disposiciones de uniones estables y no pretenden abarcar sistemas que no existen. Los anillos también pueden tener uno o más enlaces dobles. Sin embargo, los anillos no tienen un sistema de electrones pi completamente conjugados. Los ejemplos de grupos heteroalicíclicos son, sin limitación, azetidinilo, piperidilo, piperazinilo, imidazolinilo, tiazolidinilo, 3-pirrolidin-1-ilo, morfolinilo, tiomorfolinilo y tetrahidropiranilo. Cuando se sustituyen, los grupos sustituidos son, preferentemente, uno o más seleccionados de alquilo, cicloalquilo, arilo, heteroarilo,

heteroaliciclilo, hidroxi, alcoxi, ariloxi, heteroariloxi, heteroalicicloxi, tiohidroxi, tioalkoxi, tioariloxi, tioheteroariloxi, tioheteroalicicloxi, ciano, halógeno, nitro, carbonilo, tiocarbonilo, O-carbamilo, N-carbamilo, O-tiocarbamilo, N-tiocarbamilo, C-amido, C-tioamido, N-amido, C-carboxi, O-carboxi, sulfinilo, sulfonilo, sulfonamido, trihalometansulfonamido, trihalometansulfonilo, sililo, guanilo, guanidino, ureido, fosfonilo, amino y $-NR^xR^y$, en donde R^x y R^y son como se definieron anteriormente.

Un grupo "alquilo" se refiere a un hidrocarburo alifático saturado que incluye grupos de cadena lineal y ramificada. Preferentemente, el grupo alquilo tiene de 1 a 20 átomos de carbono (siempre que en la presente se indique un intervalo numérico, por ejemplo, "1-20", significa que el grupo, en este caso el grupo alquilo, puede contener 1 átomo de carbono, 2 átomos de carbono, 3 átomos de carbono, etc. hasta 20 átomos de carbono inclusive). Con mayor preferencia, es un alquilo de tamaño medio que tiene de 1 a 10 átomos de carbono. Con máxima preferencia, es un alquilo inferior que tiene de 1 a 4 átomos de carbono. El grupo alquilo puede ser sustituido o no sustituido. Cuando se sustituyen, los grupos sustituidos son, preferentemente, uno o más seleccionados individualmente de trihaloalquilo, cicloalquilo, arilo, heteroarilo, heteroaliciclilo, hidroxi, alcoxi, ariloxi, heteroariloxi, heteroalicicloxi, tiohidroxi, tioalkoxi,

tioariloxi, tioheteroariloxi, tioheteroalicicloxi, ciano, halo, nitro, carbonilo, tiocarbonilo, O-carbamilo, N-carbamilo, O-tiocarbamilo, N-tiocarbamilo, C-amido, C-tioamido, N-amido, C-carboxi, O-carboxi, sulfinilo, sulfonilo, sulfonamido, trihalometansulfonamido, trihalometansulfonilo y un anillo heterocíclico de 5 o 6 miembros combinado.

Un grupo "cicloalquilo" se refiere a un grupo de anillos de carbono monocíclico o fusionado (es decir, anillos que comparten un par adyacente de átomos de carbono), en donde uno o más anillos no tiene un sistema de electrones pi completamente conjugado. Los ejemplos de grupos cicloalquilo son, sin limitación, ciclopropano, ciclobutano, ciclopentano, ciclopenteno, ciclohexano, ciclohexeno, cicloheptano, cicloheptano y adamantano. Un grupo cicloalquilo puede ser sustituido o no sustituido. Cuando se sustituyen, los grupos sustituidos son, preferentemente, uno o más seleccionados individualmente de alquilo, arilo, heteroarilo, heteroaliciclilo, hidroxi, alcoxi, ariloxi, heteroariloxi, heteroalicicloxi, tiohidroxi, tioalkoxi, tioariloxi, tioheteroariloxi, tioheteroalicicloxi, ciano, halo, nitro, carbonilo, tiocarbonilo, O-carbamilo, N-carbamilo, O-tiocarbamilo, N-tiocarbamilo, C-amido, C-tioamido, N-amido, C-carboxi, O-carboxi, sulfinilo, sulfonilo, sulfonamido, trihalometansulfonamido, trihalometansulfonilo, sililo,

amidino, guanidino, ureido, fosfonilo, amino y $-NR^xR^y$, en donde R^x y R^y son como se definieron anteriormente.

Un grupo "alquenilo" se refiere a un grupo alquilo, como se define en la presente, que tiene al menos dos átomos de carbono y al menos un enlace doble de carbono-carbono.

Un grupo "alquinilo" se refiere a un grupo alquilo, como se define en la presente, que tiene al menos dos átomos de carbono y al menos un enlace triple de carbono-carbono.

Un grupo "hidroxi" se refiere a un grupo –OH.

Un grupo "alcoxi" se refiere tanto a un grupo –O-alquilo como a un grupo –O-cicloalquilo, como se definen en la presente.

Un grupo "ariloxi" se refiere tanto a un grupo –O-arilo como a un grupo –O-heteroarilo, como se definen en la presente.

Un grupo "heteroariloxi" se refiere a un grupo heteroaril-O- con heteroarilo como se define en la presente.

Un grupo "heteroalicicloxi" se refiere a un grupo heteroaliciclil-O- con heteroaliciclilo como se define en la presente.

Un grupo "tiohidroxi" se refiere a un grupo –SH.

Un grupo "tioalcoxi" se refiere tanto a un grupo S-alquilo como a un grupo S-cicloalquilo, como se definen en la presente.

Un grupo "tioariloxi" se refiere tanto a un grupo -

S-arilo como a un grupo -S-heteroarilo, como se definen en la presente.

Un grupo "tioheteroariloxi" se refiere a un grupo heteroaril-S- con heteroarilo como se define en la presente.

Un grupo "tioheteroalicicloxi" se refiere a un grupo heteroaliciclil-S- con heteroaliciclilo como se define en la presente.

Un grupo "carbonilo" se refiere a un grupo –C(=O)-R", en donde R" se selecciona del grupo que consiste en hidrógeno, alquilo, alquenilo, alquinilo, cicloalquilo, arilo, heteroarilo (unido por un carbono del anillo) y heteroaliciclilo (unido por un carbono del anillo), como se define cada uno en la presente.

Un grupo "aldehído" se refiere a un grupo carbonilo, en donde R" es hidrógeno.

Un grupo "tiocarbonilo" se refiere a un grupo -C(=S)-R'' con R'' como se define en la presente.

Un grupo "ceto" se refiere a un grupo –CC(=O)C-, en donde el carbono en uno o ambos lados de C=O puede ser alquilo, cicloalquilo, arilo o un carbono de un grupo heteroarilo o heteroaliciclilo.

Un grupo "trihalometancarbonilo" se refiere a un grupo $Z_3CC(=O)$-, en donde tal Z es un halógeno.

Un grupo "C-carboxi" se refiere a un grupo -C(=O)O-R'' con R'' como se define en la presente.

Un grupo "O-carboxi" se refiere a un grupo R"C(=O)O-, en donde R" es como se define en la presente.

Un grupo de "ácido carboxílico" se refiere a un grupo C-carboxi, en donde R" es hidrógeno.

Un grupo "trihalometilo" se refiere a un grupo $-CZ_3$, en donde Z es un grupo halógeno como se define en la presente.

Un grupo "trihalometansulfonilo" se refiere a un grupo $Z_3CS(=O)_2-$, en donde Z es como se define en la presente.

Un grupo "trihalometansulfonamido" se refiere a un grupo $Z_3CS(=O)_2NR^X-$, en donde Z es como se definió anteriormente y R^X es H o alquilo (C_{1-6}).

Un grupo "sulfinilo" se refiere a un grupo –S(=O)-R", en donde R" es alquilo (C_{1-6}).

Un grupo "sulfonilo" se refiere a un grupo $-S(=O)_2R"$, en donde R" es alquilo (C_{1-6}).

Un grupo "S-sulfonamido" se refiere a $-S(=O)_2NR^XR^Y$, en donde R^X y R^Y son, independientemente, H o alquilo (C_{1-6}).

Un grupo "N-sulfonamido" se refiere a un grupo $R"S(=O)_2NR_X-$, en donde R_x es H o alquilo (C_{1-6}).

Un grupo "O-carbamilo" se refiere a un grupo $-OC(=O)NR^xR^y$, en donde R^X y R^Y son, independientemente, H o alquilo (C_{1-6}).

Un grupo "N-carbamilo" se refiere a un grupo $R^xOC(=O)NR^y$, en donde R^x y R^y son, independientemente, H o

alquilo (C_{1-6}).

Un grupo "O-tiocarbamilo" se refiere a un grupo –$OC(=S)NR^XR^Y$, en donde R^X y R^Y son, independientemente, H o alquilo (C_{1-6}).

Un grupo "N-tiocarbamilo" se refiere a un grupo $R^XOC(=S)NR^Y$, en donde R^x y R^y son, independientemente, H o alquilo (C_{1-6}).

Un grupo "amino" se refiere a un grupo $–NH_2$.

Un grupo "C-amido" se refiere a un grupo –$C(=O)NR^XR^Y$, en donde R^X y R^Y son, independientemente, H o alquilo (C_{1-6}).

Un grupo "C-tioamido" se refiere a un grupo –$C(=S)NR^XR^Y$, en donde R^X y R^Y son, independientemente, H o alquilo (C_{1-6}).

Un grupo "N-amido" se refiere a un grupo $R^XC(=O)NR^Y$, en donde R^x y R^y son, independientemente, son H o alquilo (C_{1-6}).

Un grupo "ureido" se refiere a un grupo –$NR^XC(=O)NR^YR^{y2}$, en donde R^x, R^y y R^{y2} son, independientemente, H o alquilo (C_{1-6}).

Un grupo "guanidino" se refiere a un grupo –$R^XNC(=N)NR^YR^{y2}$, en donde R^x, R^y y R^{y2} son, independientemente, H o alquilo (C_{1-6}).

Un grupo "amidino" se refiere a un grupo $R^XR^YNC(=N)-$, en donde R^x y R^y son, independientemente, H o

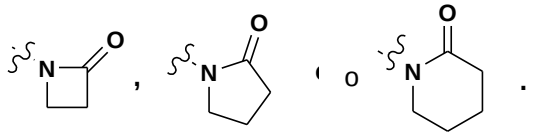
alquilo (C_{1-6}).

Un grupo "ciano" se refiere a un grupo –CN.

Un grupo "sililo" se refiere a $-Si(R'')_3$, en donde R" es alquilo (C_{1-6}) o fenilo.

Un grupo "fosfonilo" se refiere a $P(=O)(OR^x)_2$, en donde R^x es alquilo (C_{1-6}).

Un grupo "hidrazino" se refiere a un grupo $-NR^xNR^yR^{y2}$, en donde R^x, R^y y R^{y2} son, independientemente, H o alquilo (C_{1-6}).

Un grupo "N-lactama cíclica del anillo de 4, 5 o 6 miembros" se refiere a  .

Dos grupos R adyacentes se pueden combinar para formar un anillo de arilo, cicloalquilo, heteroarilo o heterocíclico adicional fusionado al anillo que inicialmente tiene esos grupos R.

Se sabe en el arte que los átomos de nitrógeno en los sistemas de heteroarilo pueden "participar en enlace doble del anillo de heteroarilo", y esto se refiere a la forma de los enlaces dobles en las dos estructuras tautoméricas que comprenden grupos heteroarilo de 5 miembros.

Esto indica si los nitrógenos se pueden sustituir, como lo comprenden los químicos en el arte. La descripción y las reivindicaciones de la presente descripción se basan en

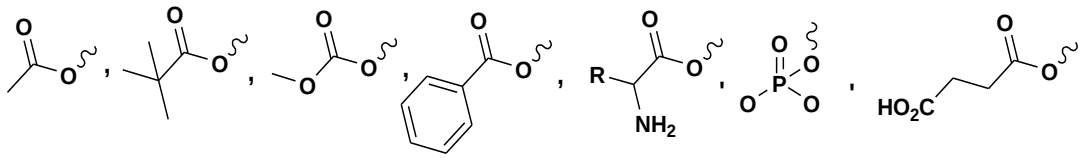
los principios generales conocidos de la unión química. Se entiende que las reivindicaciones no abarcan estructuras que se sabe son inestables y que no pueden existir sobre la base de la literatura.

Los profármacos y las sales farmacéuticamente aceptables de los compuestos descritos en la presente se encuentran dentro del alcance de la invención. Como se usa en la presente y en las reivindicaciones, el término "sal farmacéuticamente aceptable" pretende incluir sales de adición básica no tóxicas. Las sales adecuadas incluyen aquellas que derivan de ácidos orgánicos e inorgánicos, tales como, sin limitación, ácido clorhídrico, ácido bromhídrico, ácido fosfórico, ácido sulfúrico, ácido metansulfónico, ácido acético, ácido tartárico, ácido láctico, ácido sulfínico, ácido cítrico, ácido maleico, ácido fumárico, ácido aconítico, ácido salicílico, ácido ftálico y similares. El térmico "sal farmacéuticamente aceptable" como se usa en la presente también pretende incluir sales de los grupos ácidos, tales como, carboxilato, con contraiones, tales como sales de amonio, sales de metal alcalino, en particular, sodio o potasio, sales de metal alcalino térreo, en particular, calcio o magnesio y sales con bases orgánicas adecuadas, tales como alquilaminas inferiores (metilamina, etilamina, ciclohexilamina, y similares) o con alquilaminas inferiores sustituidas (por ejemplo, alquilaminas sustituidas con

hidroxilo, tales como, dietanolamina, trietanolamina o tris(hidroximetil)- aminometano), o con bases, tales como, piperidina o morfolina.

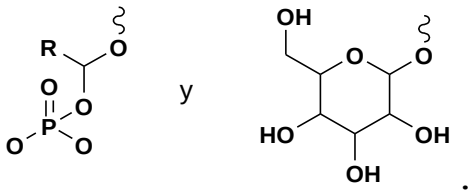
Como se indicó anteriormente, los compuestos de la invención también incluyen "profármacos". Como se usa en la presente, el término "profármaco" abarca tanto el término "ésteres de profármacos" como el término "éteres de profármacos". Como se usa en la presente, el término "ésteres de profármacos" incluye ésteres y carbonatos que se forman mediante la reacción de uno o más hidroxililos de los compuestos de la Fórmula I con agentes de fosforilación o agentes de acilación sustituidos con alquilo, alcoxi o arilo, mediante el uso de procedimientos conocidos por los expertos en el arte para generar acetatos, pivalatos, metilcarbonatos, benzoatos, ésteres de aminoácidos, fosfatos, ésteres medio ácidos, tales como malonatos, succinatos o glutaratos y similares. En ciertas modalidades, se pueden preferir especialmente los ésteres de aminoácidos.

Los ejemplos de tales ésteres de profármacos incluyen:



El término "éteres de profármacos" incluye acetales de fosfato y O-glucósidos. Los ejemplos representativos de

tales éteres de profármacos incluyen:

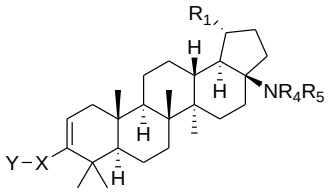


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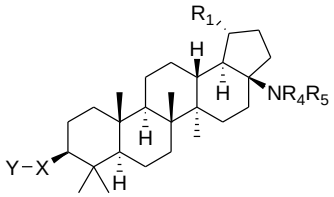
Como se indicó anteriormente, la invención se refiere a un compuesto, que incluye sus sales farmacéuticamente aceptables, que se selecciona del siguiente grupo:

un compuesto de la Fórmula I



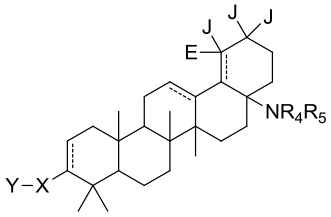
Fórmula I ;

un compuesto de la Fórmula II



Fórmula II ; y

un compuesto de la Fórmula III



Fórmula III ;

en donde R_1 es isopropenilo o isopropilo;

J y E son –H o $-CH_3$, y E está ausente cuando el enlace doble está presente;

X es un anillo de fenilo o heteroarilo sustituido con A, en donde A es, al menos, un elemento seleccionado del grupo de -H, -halo, -hidroxilo, -alquilo C_{1-6}, -alcoxi C_{1-6} y $COOR_2$;

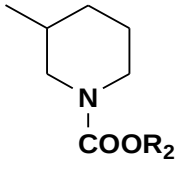
R_2 es -H, -alquilo C_{1-6}, alquilo C_{1-6} sustituido con -alquilo o alquilo C_{1-6} sustituido con -arilo;

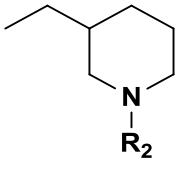
Y se selecciona del grupo de $-COOR_2$, $-C(O)NR_2SO_2R_3$, $-C(O)NHSO_2NR_2R_2$, $-NR_2SO_2R_2$, $-SO_2NR_2R_2$, -cicloalquilo C_{3-6}-$COOR_2$, -alquenilo C_{2-6}-$COOR_2$, -alquinilo C_{2-6}-$COOR_2$, -alquilo C_{1-6}-$COOR_2$, $-NHC(O)(CH_2)_n$-$COOR_2$, $-SO_2NR_2C(O)R_2$, -tetrazol y –CONHOH,

en donde n=1-6;

R_3 es -alquilo C_{1-6} o alquilo C_{1-6} sustituido con -alquilo;

R_4 se selecciona del grupo de -H, -alquilo C_{1-6}, -alquilo C_{1-6}-$C(OR_3)_2$-cicloalquilo C_{3-6}, -alquilo C_{1-6} sustituido, -alquilo C_{1-6}-cicloalquilo C_{3-6}, -alquilo C_{1-6}-Q_1, -alquilo C_{1-6}-cicloalquilo C_{3-6}-Q_1, arilo, heteroarilo, heteroarilo sustituido, $-COR_6$, $-COCOR_6$, $-SO_2R_7$, $-SO_2NR_2R_2$,



, y


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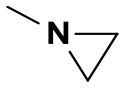
en donde Q_1 se selecciona del grupo de heteroarilo,

heteroarilo sustituido, halógeno, $-CF_3$, $-OR_2$, $COOR_2$, $-NR_8R_9$, $-CONR_{10}R_{11}$ y $-SO_2R_7$;

R_5 se selecciona del grupo de -H, -alquilo C_{1-6}, -cicloalquilo C_3-$_6$, -alquilo C_{1-6} sustituido con alquilo, -alquilo C_{1-6}-NR_8R_9, $-COR_{10}$, $-COR_6$, $-COCOR_6$, $-SO_2R_7$ y $-SO_2NR_2R_2$;

siempre que solo uno de R_4 o R_5 se pueda seleccionar del grupo de $-COR_6$, $COCOR_6$, $-SO_2R_7$ y $-SO_2NR_2R_2$;

o R_4 y R_5 se toman en forma conjunta con el N adyacente para formar



;

R_6 se selecciona del grupo de -H, -alquilo C_{1-6}, -alquilo C_{1-6} sustituido con alquilo, -cicloalquilo C_3-$_6$, -cicloalquilo C_3-$_6$ sustituido con Q_2, -alquilo C_{1-6}-Q_2, -alquilo C_{1-6} sustituido con alquil-Q_2, -cicloalquilo C_3-$_6$-Q_2, aril-Q_2, $-NR_{13}R_{14}$ y $-OR_{15}$;

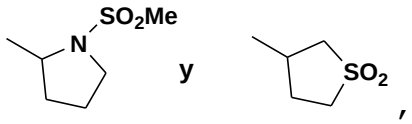
en donde Q_2 se selecciona del grupo de arilo, heteroarilo, heteroarilo sustituido, $-OR_2$, $-COOR_2$, $-NR_8R_9$, SO_2R_7, $-CONHSO_2R_3$ y $-CONHSO_2NR_2R_2$;

R_7 se selecciona del grupo de -alquilo C_{1-6}, -alquilo C_{1-6} sustituido, -cicloalquilo C_3-$_6$, arilo y heteroarilo;

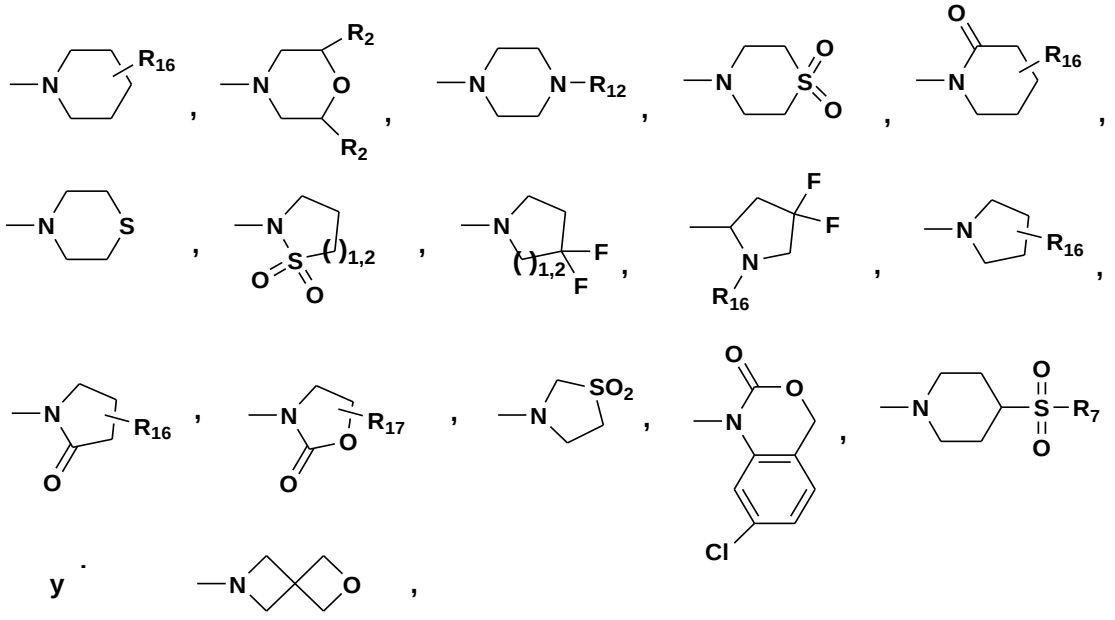
R_8 y R_9 se seleccionan independientemente del grupo de -H, -alquilo C_{1-6}, -alquilo C_{1-6} sustituido, arilo, heteroarilo, arilo sustituido, heteroarilo sustituido, -

alquilo C_{1-6}-Q_2 y -$COOR_3$,

y R_8 y R_9 también se pueden seleccionar independientemente del siguiente grupo:



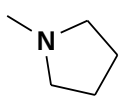
o R_8 y R_9 se toman en forma conjunta con el N adyacente para formar un ciclo seleccionado del siguiente grupo:



siempre que solo uno de R_8 o R_9 pueda ser -$COOR_3$;

R_{10} y R_{11} se seleccionan independientemente del grupo de -H, -alquilo C_{1-6}, -alquilo C_{1-6} sustituido y -cicloalquilo C_{3-6},

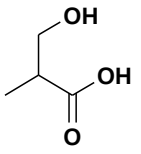
o R_{10} y R_{11} se toman en forma conjunta con el N adyacente para formar un ciclo, tal como



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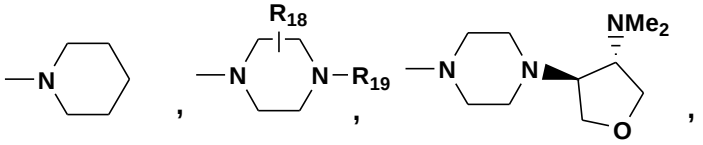
R_{12} se selecciona del grupo de -alquilo C_{1-6}, -alquilo C_{1-6}-OH, -alquilo C_{1-6}, -alquilo C_{1-6} sustituido, -cicloalquilo C_{3-6}, $-COR_7$, $-COONR_{22}R_{23}$, $-SOR_7$ y $-SONR_{24}R_{25}$;

R_{13} y R_{14} se seleccionan independientemente del grupo de -H, -alquilo C_{1-6}, -cicloalquilo C_{3-6}, -alquilo C_{1-6} sustituido, -alquilo C_{1-6}-Q_3, -alquilo C_{1-6}-cicloalquilo C_{3-6}-Q_3, alquilo C_{1-6} sustituido con Q_3 y

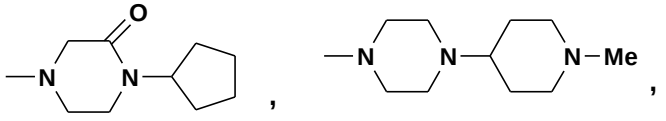


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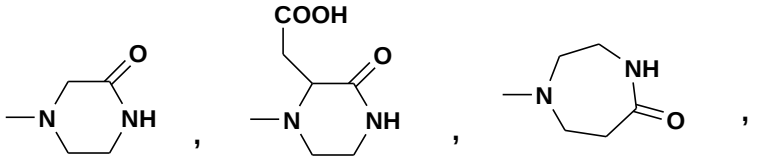
o R_{13} y R_{14} se toman en forma conjunta con el N adyacente para formar un ciclo seleccionado del siguiente grupo:



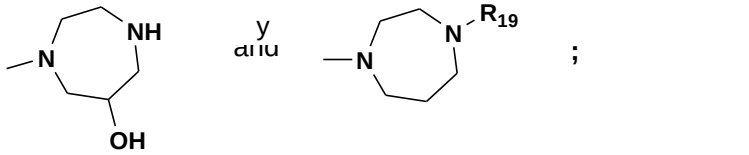
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y

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Q_3 se selecciona del grupo de heteroarilo,

heteroarilo sustituido, $-NR_{20}R_{21}$, $-CONR_2R_2$, $-COOR_2$, $-OR_2$ y $-SO_2R_3$;

R_{15} se selecciona del grupo de -alquilo C_{1-6}, -cicloalquilo C_{3-6}, -alquilo C_{1-6} sustituido, -alquilo C_{1-6}-Q_3, -alquilo C_{1-6}-cicloalquilo C_{3-6}-Q_3 y -alquilo C_{1-6} sustituido con Q_3;

R_{16} se selecciona del grupo de -H, -alquilo C_{1-6}, $-NR_2R_2$ y $-COOR_3$;

R_{17} se selecciona del grupo de -H, -alquilo C_{1-6}, $-COOR_3$ y arilo;

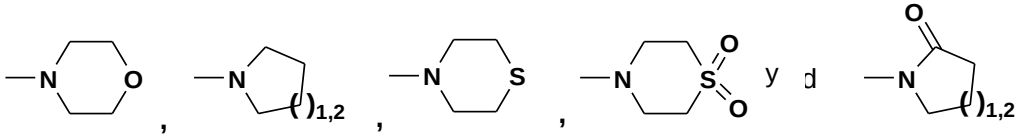
R_{18} se selecciona del grupo de $-COOR_2$ y -alquilo C_{1-6}-$COOR_2$;

R_{19} se selecciona del grupo de -H, -alquilo C_{1-6}, -alquilo C_{1-6}-Q_4, $-COR_3$, $-COOR_3$,

en donde Q_4 se selecciona del grupo de $-NR_2R_2$ y $-OR_2$;

R_{20} y R_{21} se seleccionan independientemente del grupo de -H, -alquilo C_{1-6}, -alquilo C_{1-6} sustituido, -alquilo C_{1-6} sustituido con OR_2 y $-COR_3$,

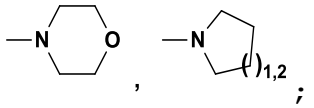
o R_{20} y R_{21} se toman en forma conjunta con el N adyacente para formar un ciclo seleccionado del siguiente grupo:



siempre que solo uno de R_{20} o R_{21} pueda ser $-COR_3$;

R_{22} y R_{23} se seleccionan independientemente del grupo de H, -alquilo C_{1-6}, -alquilo C_{1-6} sustituido y -cicloalquilo C_{1-6},

o R_{22} y R_{23} se toman en forma conjunta con el N adyacente para formar un ciclo seleccionado del siguiente grupo:



R_{24} y R_{25} se seleccionan independientemente del grupo de H, -alquilo C_{1-6}, -alquilo C_{1-6} sustituido, -alquilo C_{1-6}-Q_5, -cicloalquilo C_{1-6}, arilo, arilo sustituido, heteroarilo y heteroarilo sustituido,

y Q_5 se selecciona del grupo de halógeno y SO_2R_3.

Los compuestos aun más preferidos incluyen aquellos en los que R_1 es isopropenilo.

Los compuestos más preferidos incluyen los que abarca la Fórmula I. De estos, son de mayor preferencia aquellos en los que X es un anillo de fenilo. Son aún de mayor preferencia los compuestos de la Fórmula I, en donde X es un anillo de fenilo e Y se encuentra en la posición para.

También se prefieren los compuestos de la Fórmula I, en donde A es al menos un elemento seleccionado del grupo de –H, -OH, -halo, -alquilo C_{1-3} y -alcoxi C_{1-3}, en donde –halo se selecciona del grupo de –Cl, -F y –Br; –F el de mayor

preferencia. Es aun de mayor preferencia que A sea –H.

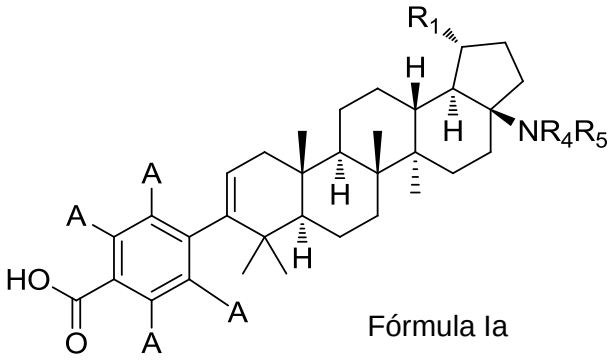
También se prefieren los compuestos de la Fórmula, en donde Y es $-COOR_2$, y con mayor preferencia, –COOH.

También se prefieren los compuestos en donde R_4 se selecciona del grupo de –H, -alquilo C_{1-6}, -alquilo C_{1-6}-Q_1 y $-COR_6$. Se prefieren en especial los compuestos en donde R_4 es -alquilo C_{1-6}-Q_1 o $-COR_6$.

También se prefiere que R_5 sea –H.

Además, se prefiere que Q_1 sea $-NR_8R_9$.

En otra modalidad preferida se provee un compuesto de la siguiente Fórmula Ia, en donde X es un anillo de fenilo e Y es –COOH en la posición para:



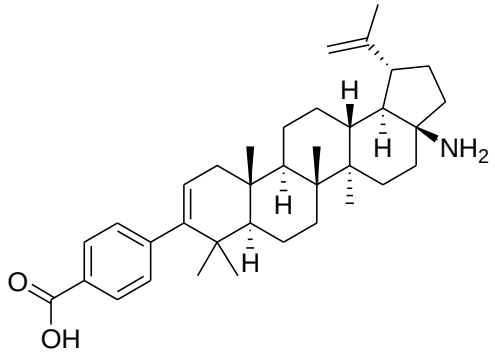
Fórmula Ia .

En esta modalidad, también se prefiere que A sea al menos un elemento seleccionado del grupo de –H, -halo, –OH, -alquilo C_{1-3} y -alcoxi C_{1-3}. En particular, se prefiere que A sea, al menos, un elemento seleccionado del grupo de –H, -flouro, -cloro, –OH, -metilo y -metoxi; –H aun más preferido.

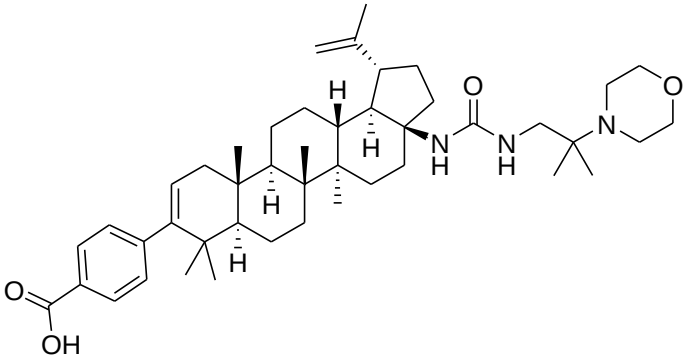
Además, en otra modalidad de la invención, se prefieren los compuestos de la Fórmula II, al igual que los

compuestos de la Fórmula III.

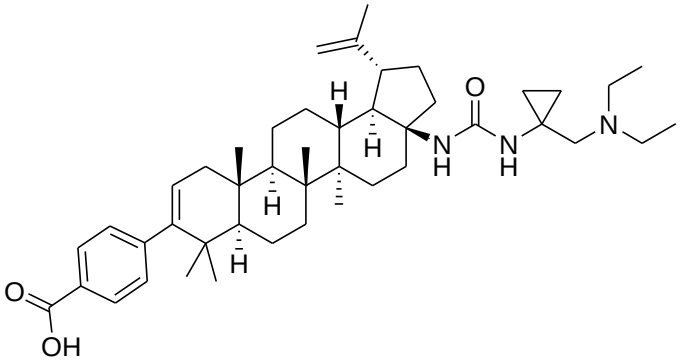
Otros compuestos, incluso, las sales de estos aceptables desde el punto de vista farmacéutico, que se prefieren como parte de la invención incluyen los siguientes:



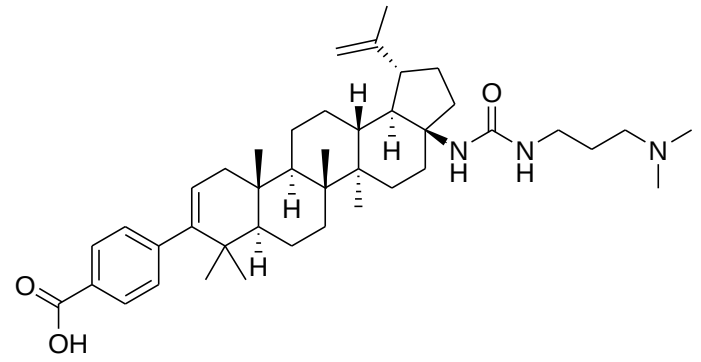
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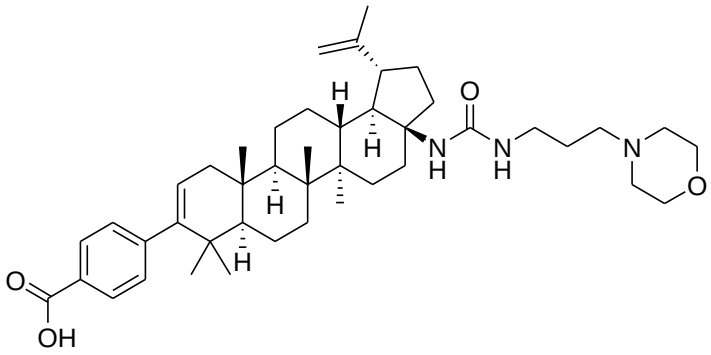
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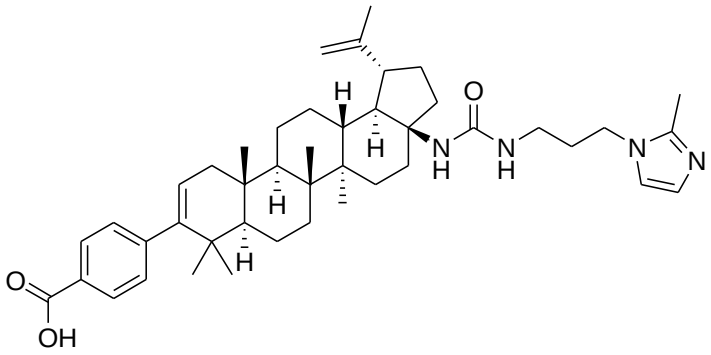
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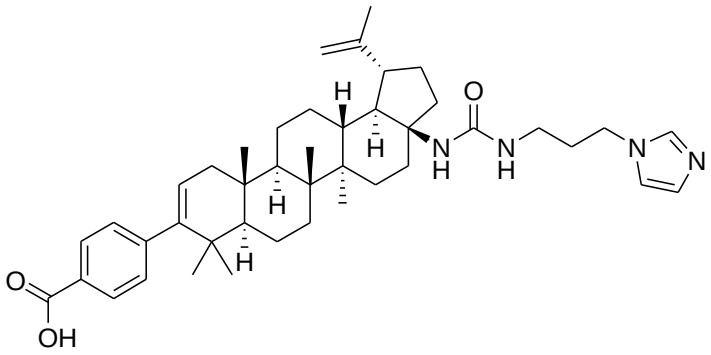
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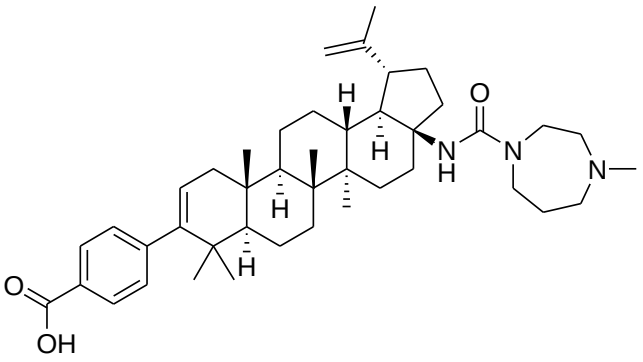
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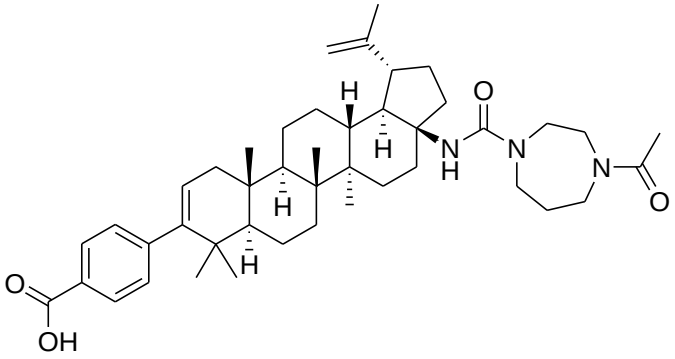
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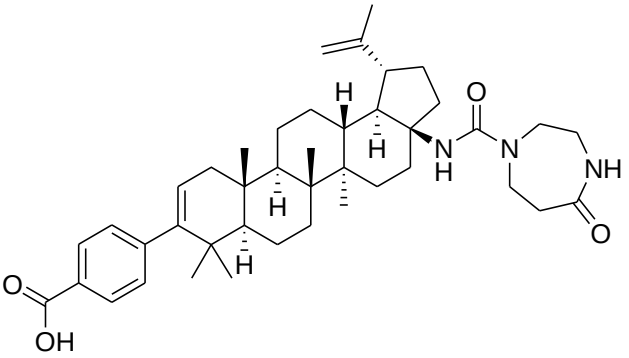
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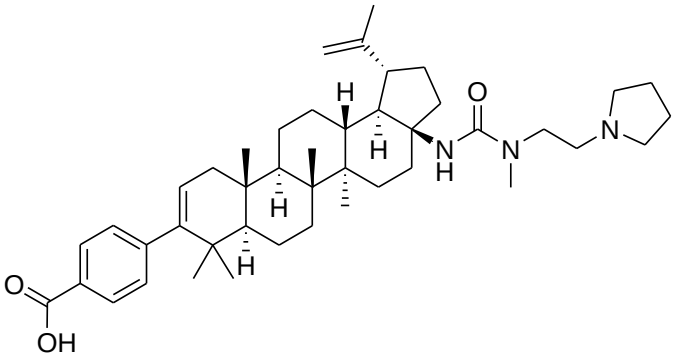
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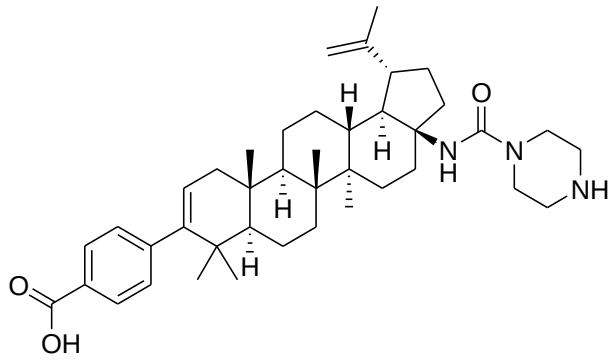
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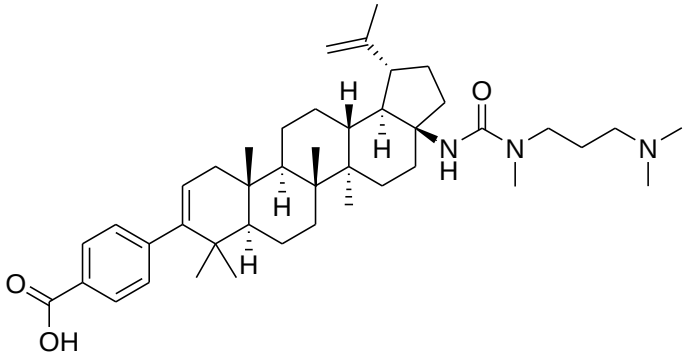
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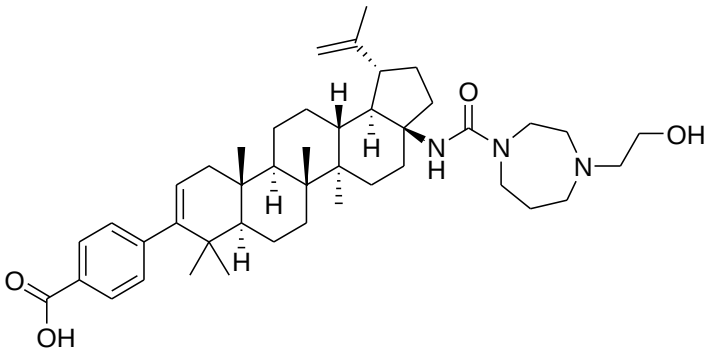
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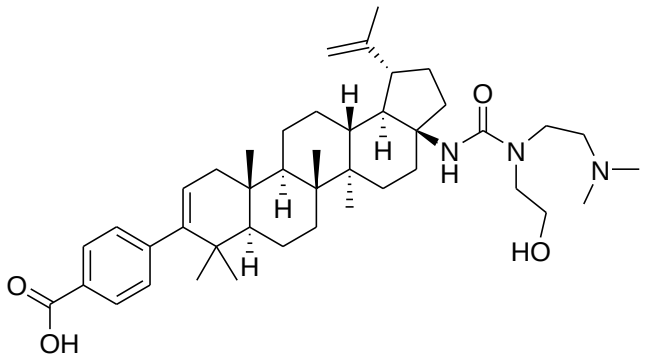
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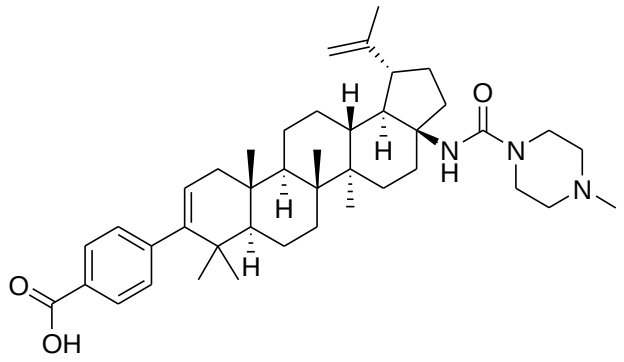
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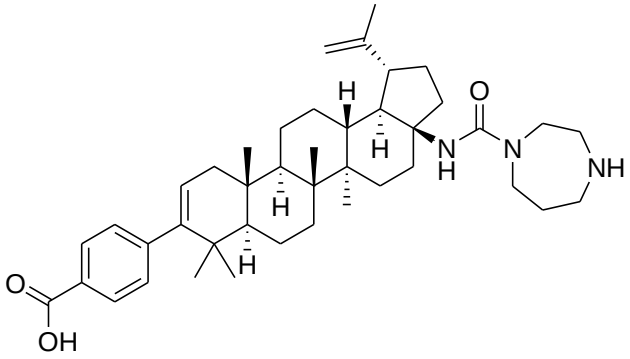
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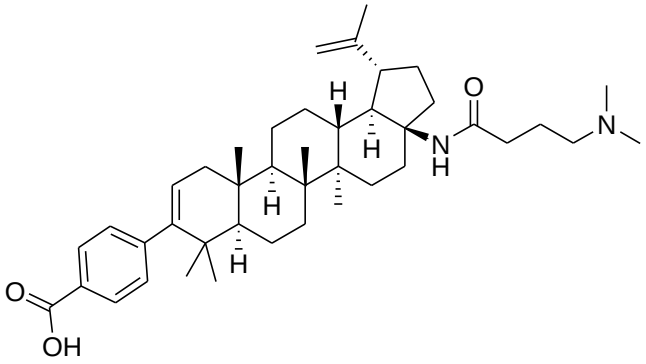
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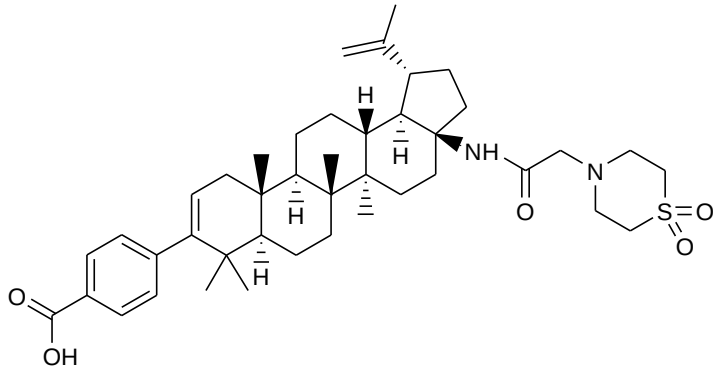
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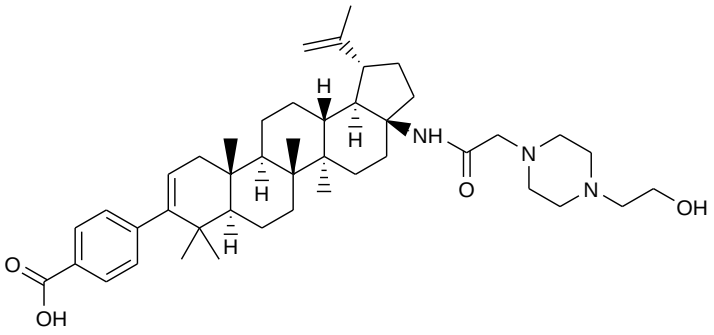
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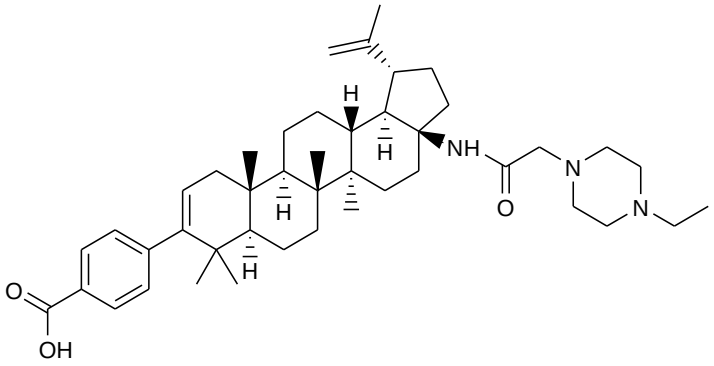
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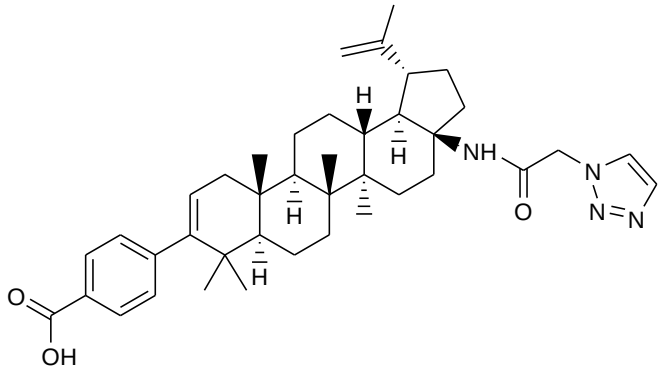
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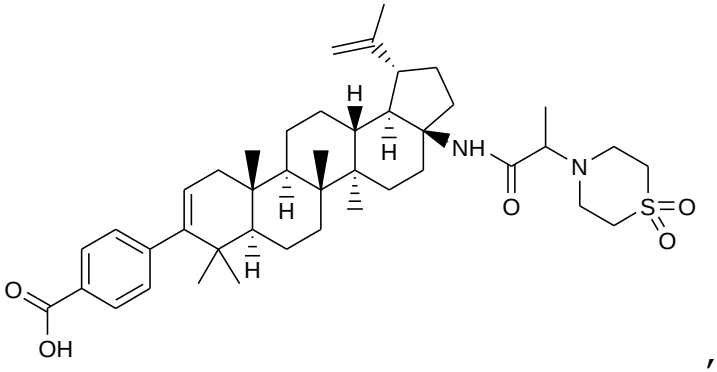
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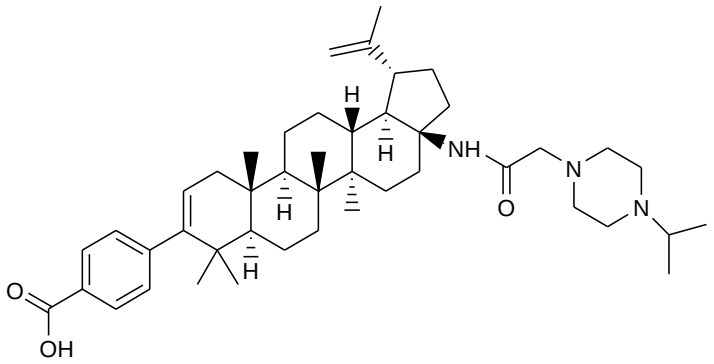
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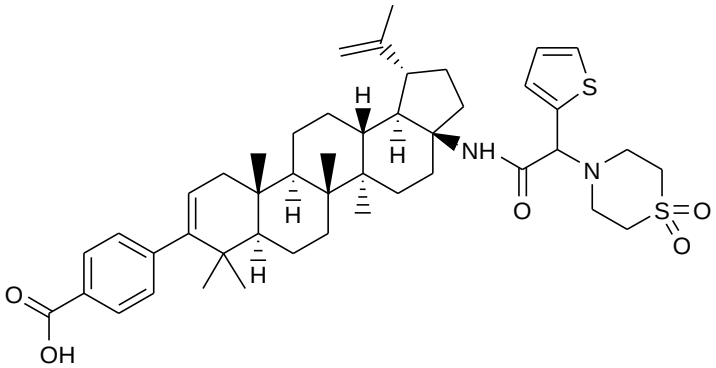
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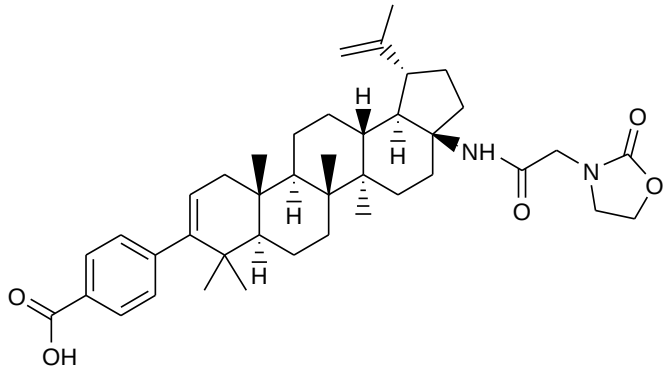
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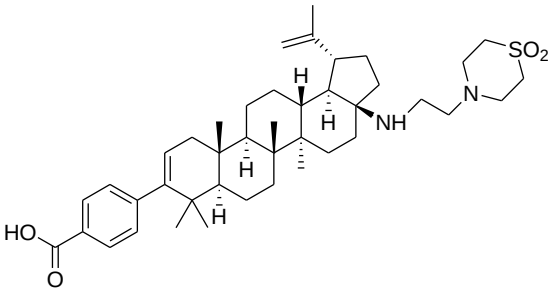
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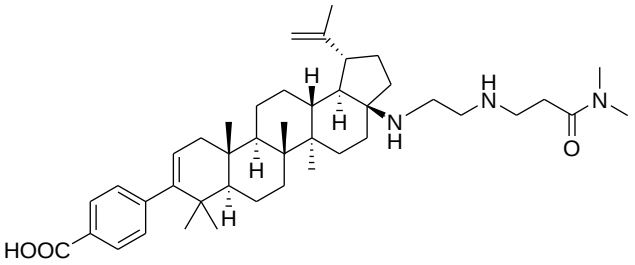
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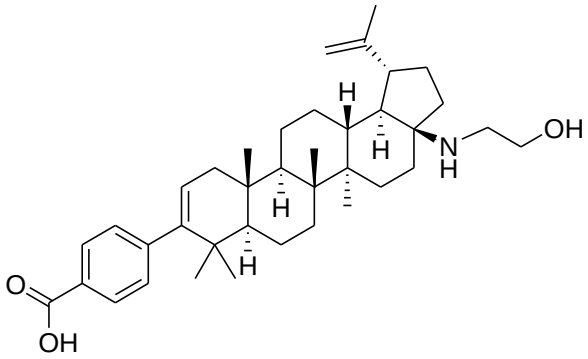
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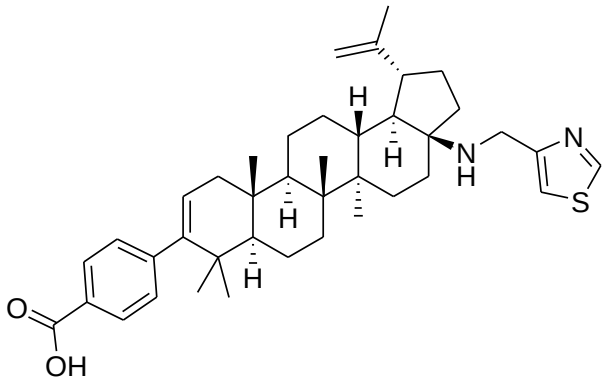
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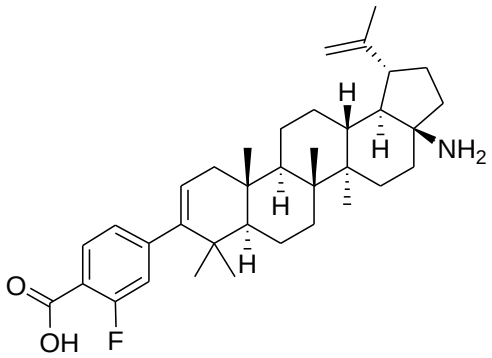
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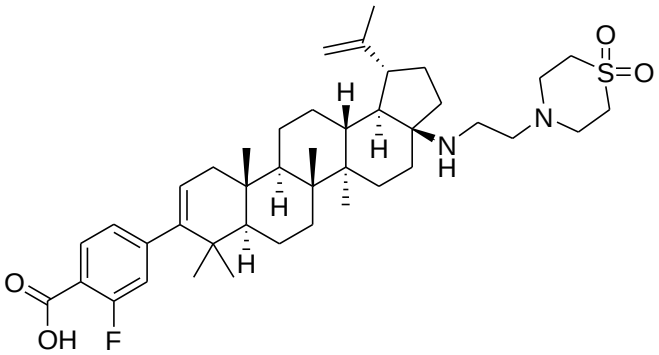
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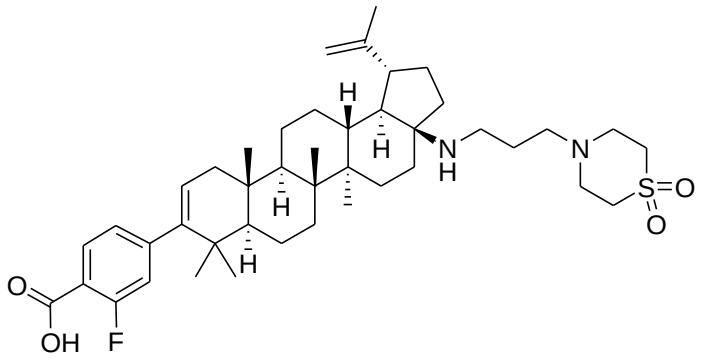
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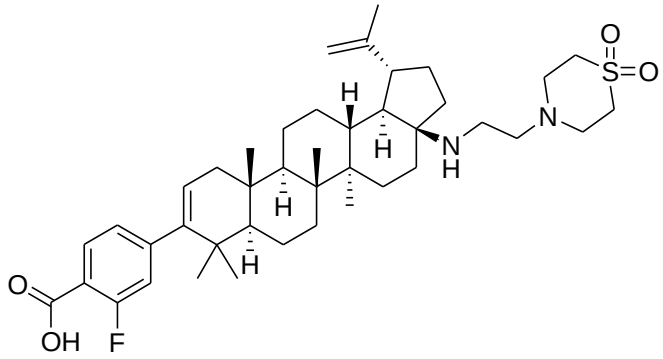


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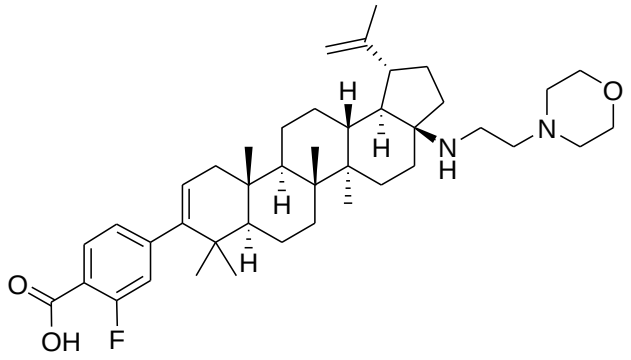


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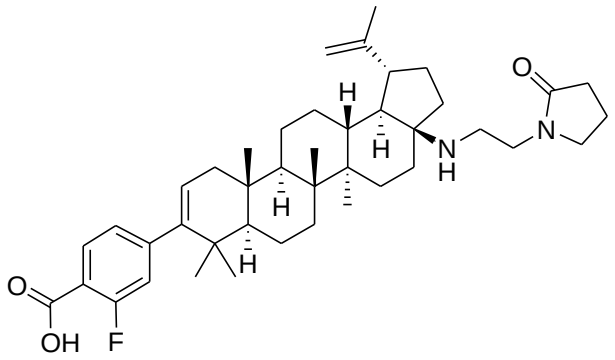
También se prefieren los siguientes compuestos, incluso, las sales de estos aceptables desde el punto de vista farmacéutico:



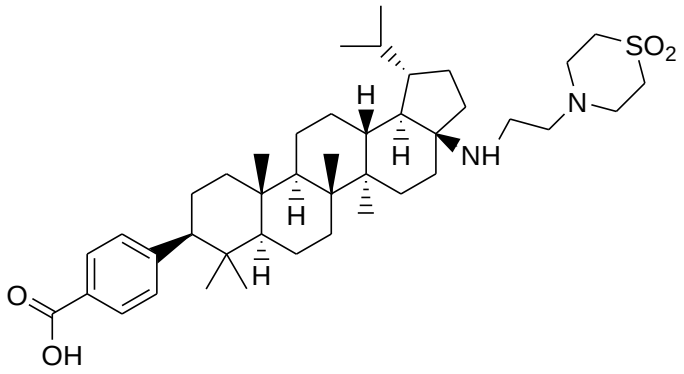
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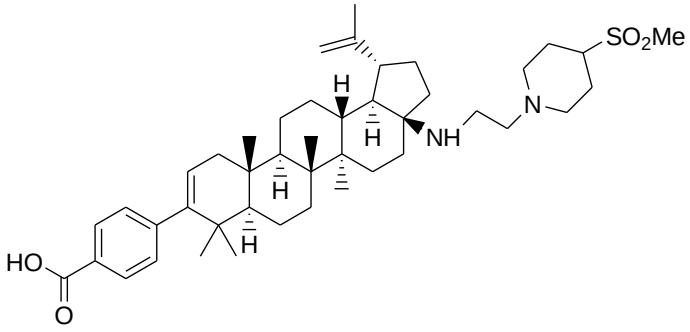
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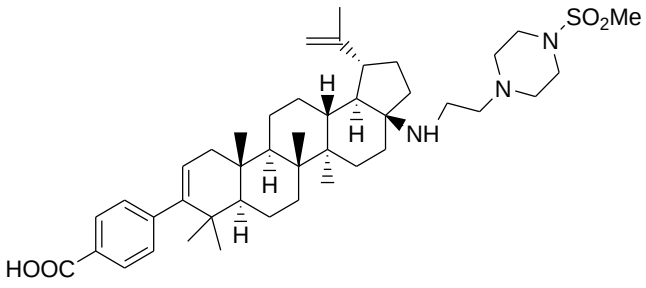
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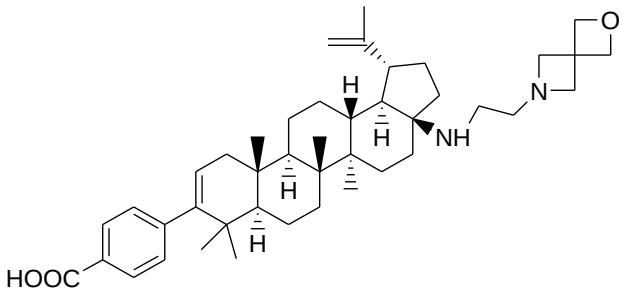
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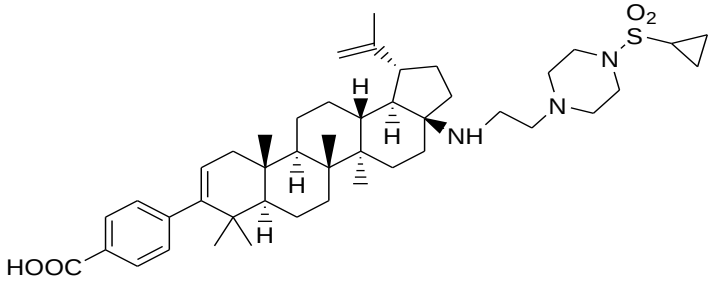


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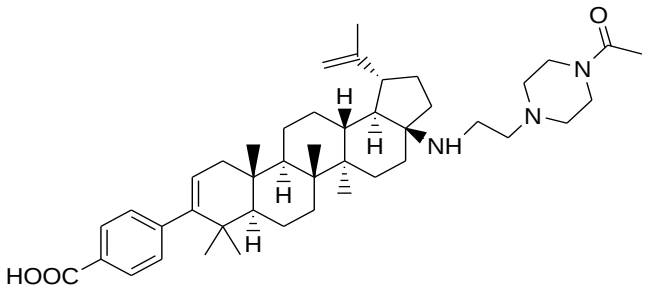


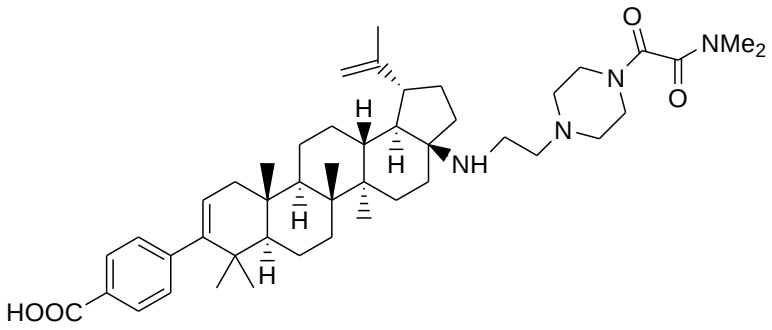
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De acuerdo con las varias modalidades antes descritas, los compuestos de la presente invención se pueden administrar por vía oral, parenteral (incluso inyecciones subcutáneas, intravenosas, intramusculares, intrasternales o técnicas de infusión), atomización para

inhalar o por vía rectal, y por otros medios, en formulaciones unitarias de dosificación que contienen portadores, excipientes y diluyentes farmacéuticamente aceptables no tóxicos disponibles para el experto en el arte. También se pueden incluir uno o más adyuvantes.

Por ello, de acuerdo con la presente invención, también se proporciona un método de tratamiento y una composición farmacéutica para tratar infecciones virales, tales como infección por VIH y SIDA. El tratamiento incluye administrarle a un paciente que necesita tal tratamiento una composición farmacéutica que contiene una cantidad eficaz antiviral de uno o más de los compuestos de las Fórmulas I, II y/o III, junto con uno o más portadores, excipientes o diluyentes farmacéuticamente aceptables. Como se usa en la presente, el término “cantidad eficaz antiviral” significa la cantidad total de cada componente activo de la composición y método que es suficiente para generar un beneficio considerable para el paciente, es decir, inhibir, mejorar o curar las afecciones agudas caracterizadas por la inhibición de la infección por VIH. Cuando se aplica a un ingrediente activo individual, administrado solo, el término se refiere a ese ingrediente solo. Cuando se aplica a una combinación, el término se refiere a cantidades

combinadas de los ingredientes activos que producen el efecto terapéutico, ya sea que se administren de manera combinada, serial o simultánea. Como se usan en la presente y en las reivindicaciones, los términos "tratar, que trata, tratamiento" significan prevenir, mejorar o curar enfermedades asociadas con la infección por VIH.

Las composiciones farmacéuticas de la invención pueden estar en forma de suspensiones o comprimidos de administración oral, así como pulverizadores nasales, preparaciones estériles inyectables, por ejemplo, como supositorios o suspensiones oleaginosas o acuosas estériles inyectables. Los portadores, excipientes o diluyentes farmacéuticamente aceptables se pueden usar en las composiciones farmacéuticas y son los que se usan en el arte de las preparaciones farmacéuticas.

Cuando se administran de forma oral, como una suspensión, estas composiciones se preparan de acuerdo con técnicas típicamente conocidas en el arte de las formulaciones farmacéuticas y pueden contener celulosa microcristalina para generar un mayor volumen, ácido algínico o alginato de sodio como un agente de suspensión, metilcelulosa como un mejorador de la viscosidad y agentes savorizantes/endulzantes conocidos en el arte. Como comprimidos de liberación inmediata,

estas composiciones pueden contener celulosa microcristalina, fosfato dicálcico, almidón, estearato de magnesio y lactosa y/u otros excipientes, aglutinantes, extensores, desintegrantes, diluyentes y lubricantes conocidos en el arte.

Las soluciones o suspensiones inyectables se pueden formular de acuerdo con el arte conocido, mediante el uso de diluyentes o solventes parenteralmente aceptables no tóxicos, tales como manitol, 1,3-butandiol, agua, solución de Ringer o solución isotónica de cloruro de sodio, o agentes de dispersión, humectación o suspensión adecuados, tales como aceites estériles, blandos, fijos, que incluyen mono- o diglicéridos sintéticos, y ácidos grasos, que incluyen ácido oleico.

Los compuestos indicados en la presente se pueden administrar oralmente a humanos, en un intervalo de alrededor de 1 a 100 mg/kg de peso corporal en dosis divididas, usualmente durante un período extendido de tiempo, por ejemplo, durante, días, semanas, meses o incluso años. Un intervalo de dosificación preferido es de alrededor de 1 a 10 mg/kg de peso corporal por vía oral en dosis divididas. Otro intervalo de dosificación preferido es de alrededor de 1 a 20 mg/kg de peso corporal en dosis divididas. Sin embargo, se comprenderá

que el nivel de dosis específico y la frecuencia de dosificación para cualquier paciente en particular pueden variar y dependerán de varios factores, que incluyen la actividad del compuesto específico empleado, la estabilidad metabólica y la duración de la acción de ese compuesto, la edad, el peso corporal, el estado de salud general, el sexo, la alimentación, la forma y el tiempo de administración, la velocidad de excreción, la combinación de fármacos, la gravedad de la afección particular y el hospedero que se somete a terapia.

En la presente también se contemplan combinaciones de los compuestos de las Fórmulas I, II y/o III indicadas en la presente, junto con uno o más de otros agentes útiles para el tratamiento del SIDA. Por ejemplo, los compuestos de la presente descripción se pueden administrar de manera eficaz, ya sea en períodos de preexposición y/o posexposición, en combinación con cantidades eficaces de los antivirales, inmunomoduladores, antiinfecciosos o vacunas contra el SIDA, tales como los que se indican de manera no limitativa en la siguiente tabla:

ANTIVIRALES

Nombre del Fármaco	*Fabricante*	*Indicación*
097	Hoechst/Bayer	Infección del VIH, SIDA, ARC (inhibidor no nucleósido de la transcriptasa inversa (RT))
Amprenavir 141 W94 GW 141	Glaxo Wellcome	Infección del VIH, SIDA, ARC (inhibidor de proteasa)
Abacavir (1592U89) GW 1592	Glaxo Wellcome	Infección del VIH, SIDA, ARC (inhibidor de RT)
Acemanano	Carrington Labs (Irving, TX)	ARC
Aciclovir	Burroughs Wellcome	Infección del VIH, SIDA, ARC
AD-439	Tanox Biosystems	Infección del VIH, SIDA, ARC
AD-519	Tanox Biosystems	Infección del VIH, SIDA, ARC
Adefovir dipivoxil AL-721	Gilead Sciences Ethigen (Los Ángeles, CA)	Infección del VIH, ARC, PGL, VIH positivo, SIDA
Interferón alfa	Glaxo Wellcome	Sarcoma Kaposi, VIH en combinación con/Retroviral

Ansamicina LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC
Anticuerpo el cual neutraliza el pH lábil alfa aberrante de interferón	Advanced Biotherapy Concepts (Rockville, MD)	SIDA, ARC
AR177	Aronex Pharm	Infección del VIH, SIDA, ARC
Beta-fluoro-ddA	Nat'l Cancer Institute	Enfermedades asociadas con SIDA
BMS-234475 (CGP-61755)	Bristol-Myers Squibb/Novartis	Infección del VIH, SIDA, ARC (inhibidor de proteasa)
CI-1012	Warner-Lambert	infección del VIH-1
Cidofovir	Gilead Science	retinitis del CMV
Sulfato de curdlan	AJI Pharma USA	Infección del VIH
globina inmune de citomegalovirus	MedImmune	retinitis del CMV
Citoveno	Syntex	Amenaza ligera
Ganciclovir		CMV CMV periférico retinitis
Darunavir	Tibotec- J & J	Infección del VIH, SIDA, ARC (inhibidor de proteasa)

Delaviridina	Pharmacia-Upjohn	Infección del VIH, SIDA, ARC (inhibidor de RT)
Sulfato de dextrano	Ueno Fine Chem. Ind. Ltd. (Osaka, Japón)	SIDA, ARC, VIH positivo asintomático
ddC didesoxicitidina	Hoffmann-La Roche	Infección del VIH, SIDA, ARC,
ddI didesoxiinosina	Bristol-Myers Squibb	Infección del VIH, SIDA, ARC; combinación con AZT/d4T
DMP-450	AVID (Camden, NJ)	Infección del VIH, SIDA, ARC (inhibidor de proteasa)
Efavirenz (DMP 266, Sustiva®) (-)6-Cloro-4-(S)-ciclopropiletinil-4(S)-trifluoro-metil-1,4-dihidro-2H-3,1-benzoxazin-2-ona, ESTOCRINO	Bristol Myers Squibb	Infección del VIH, SIDA, ARC, (inhibidor de RT no nucleósido)
EL10	Elan Corp, PLC (Gainesville, GA)	Infección del VIH
Etravirina	Tibotec/J & J	Infección del VIH, SIDA, ARC (inhibidor de la transcriptasa inversa no nucleósido)

Famciclovir	Smith Kline	herpes zoster, herpes simple
GS 840	Gilead	Infección del VIH, SIDA, ARC (inhibidor de transcriptasa inversa)
HBY097	Hoechst Marion Roussel	Infección del VIH, SIDA, ARC (inhibidor no nucleósido de transcriptasa inversa)
Hipericina	VIMRx Pharm.	Infección del VIH, SIDA, ARC
Interferón beta humano recombinante	Triton Biosciences (Almeda, CA)	SIDA, sarcoma Kaposi, ARC
Interferón alfa-n3	Interferon Sciences	ARC, SIDA
Indinavir	Merck	Infección del VIH, SIDA, ARC, VIH positivo asintomático, también en combinación con AZT/ddI/ddC
ISIS 2922	ISIS Pharmaceuticals	retinitis del CMV
KNI-272	Nat'l Cancer Institute	enfermedades asociadas con VIH
Lamivudina, 3TC	Glaxo Wellcome	Infección del VIH, SIDA, ARC (inhibidor de transcriptasa inversa); también con AZT

Lobucavir	Bristol-Myers Squibb	Infecciones del CMV
Nelfinavir	Agouron Pharmaceuticals	Infección del VIH, SIDA, ARC (inhibidor de proteasa
Nevirapina	Boeheringer Ingelheim	Infección del VIH, SIDA, ARC (inhibidor de proteasa
Novapren	Novaferon Labs, Inc. (Akron, OH)	Inhibidor del VIH
Secuencia de octapéptido del péptido T	Peninsula Labs (Belmont, CA)	SIDA
Fosfonoformiato trisódico	Astra Pharm Products, Inc.	Retinitis de CMV, infección del VIH, otras infecciones del CMV
PNU-140690	Pharmacia Upjohn	Infección del VIH, SIDA, ARC (inhibidor de proteasa)
Probucol	Vyrex	Infección del VIH, SIDA
RBC-CD4	Sheffield Med. Tech (Houston, Tx)	Infección del VIH, SIDA, ARC
Ritonavir	Abbott	Infección del VIH, SIDA, ARC (inhibidor de proteasa)
Saquinavir	Hoffmann-LaRoche	Infección del VIH, SIDA, ARC (inhibidor de proteasa)
Estavudina; d4T dideshidrodesoxi-timidina	Bristol-Myers Squibb	Infección del VIH, SIDA, ARC
Tipranavir	Boehringer Ingelheim	Infección del VIH, SIDA, ARC (inhibidor de proteasa

Valaciclovir	Glaxo Wellcome	Infecciones genitales del HSV y CMV,
Virazol Ribavirina	Viratec/ICN (Costa Mesa, CA)	VIH positivo asintomático, LAS, ARC
VX-478	Vertex	Infección del VIH, SIDA, ARC
Zalcitabina	Hoffmann-LaRoche	Infección del VIH, SIDA, ARC con AZT
Zidovudina; AZT	Glaxo Wellcome	Infección del VIH, SIDA, ARC, sarcoma Kaposi, en combinación con otras terapias
Sal de fumarato de Tenofovir disoproxil, (Viread®)	Gilead	Infección del VIH, SIDA, (inhibidor de transcriptasa inversa)
Emtriva® (Emtricitabina)(FTC)	Gilead	Infección del VIH, SIDA, (inhibidor de transcriptasa inv.)
Combivir®	GSK	Infección del VIH, SIDA, (inhibidor de transcriptasa inv.)
Succinato de abacavir (o Ziagen®)	GSK	Infección del VIH, SIDA, (inhibidor de transcriptasa inv.)
Reyataz® (o atazanavir)	Bristol-Myers Squibb	Infección del VIH SIDA, inhibidor de proteasa
Fuzeon® (Enfuvirtido o T-20)	Roche/Trimeris	Infección del VIH, SIDA, inhibidor de Fusión viral
Lexiva® (o Fosamprenavir de calcio)	GSK/Vertex	Infección del VIH, SIDA, inhibidor de proteasa viral

Selzentry Maraviroc; (UK 427857)	Pfizer	Infección de VIH, SIDA, antagonista de CCR5, en desarrollo)
Trizivir®	GSK	Infección del VIH SIDA; (combinación de tres fármacos)
Sch-417690 (vicriviroc)	Schering-Plough	Infección del VIH SIDA, (antagonista del CCR5, en desarrollo)
TAK-652	Takeda	Infección del VIH SIDA, (antagonista del CCR5, en desarrollo)
GSK 873140 (ONO-4128)	GSK/ONO	Infección del VIH SIDA, (antagonista del CCR, en desarrollo)
Raltegravir MK-0518 Inhibidor de Integrasa	Merk	Infección del VIH SIDA
Truvada®	Gilead	Combinación de sal de disoproxil fumarato de Tenofovir (Veread®) y Emtriva® (Emtricitabina)
Elvitegravir GS917/JTK-303 Inhibidor de Integrasa	Gilead/Japan Tobacco	Infección del VIH SIDA en desarrollo
Triple combinación de fármaco Atripla®	Gilead/Bristol-Myers Squibb	Combinación de sal de disoproxil fumarato de Tenofovir (Veread®), Emtriva®(Emtricitabina) y Sustiva® (Efavirenz)
Festinavir® 4'-etinil-d4T	Oncolys Biopharma BMS	Infección del VIH SIDA en desarrollo
CMX-157 Conjugado lípido de nucleótido tenofovir	Chimerix	Infección del VIH SIDA

Inhibidor de integrasa de GSK 1349575	GSK	Infección del VIH SIDA
INMUNOMODULADORES		
Nombre del Fármaco	*Fabricante*	*Indicación*
AS-101	Wyeth-Ayerst	SIDA
Bropirimina	Pharmacia Upjohn	SIDA avanzado
Acemannan	Carrington Labs, Inc. (Irving, TX)	SIDA, ARC
CL246,738	Wyeth Lederle Labs	SIDA, Sarcoma Kaposi
FP-21399	Fuki ImmunoPharm	Bloques de fusión de VIH con células CD4+
Gamma Interferón	Genentech	ARC, en combinación con/TNF (factor necrosis del tumor)
Factor de estimulación de la colonia de macrófagos del granulocito	Genetics Institute Sandoz	SIDA
Factor de estimulación de la colonia de macrófagos del granulocito	Hoechst-Roussel Immunex	SIDA
Factor de estimulación de la colonia de macrófagos del granulocito	Schering-Plough	SIDA, combinación con/AZT
Partícula Nuclear del VIH Inmunoestimulante	Rorer	VIH seropositivo

Interleucina-2 IL-2	Cetus	SIDA, en combinación con/AZT,
Interleucina-2 IL-2	Hoffman-LaRoche Immunex	SIDA, ARC, VIH, en combinación con/AZT
Interleucina-2 IL-2 (aldeslukin)	Chiron	SIDA, incremento en conteo de células DC4+
Globulina Inmune Intravenosa (humana)	Cutter Biological (Berkeley, CA)	SIDA pediátrico, en combinación con/AZT
IMREG-1	Imreg (New Orleans, LA)	SIDA, sarcoma Kaposi, ARC, PGL
IMREG-2	Imreg (New Orelans, LA)	SIDA, sarcoma Kaposi, ARC, PGL
Ditio carbamato de imutiol dietílico	Merieux Institute	SIDA, ARC
Interferón alfa-2	Schering Ploug	Sarcoma kaposi con/AZT, SIDA
Metionina-Encefalina	TNI Pharmaceutical (Chicago, IL)	SIDA, ARC
Muramil-Tripéptido MTP-PE	Ciba-Giegy Corp.	sarcoma Kaposi
Factor de estimulación de la colonia del granulocito	Amgen	SIDA, en combinación con/AZT
Remune	Immune Response Corp.	Inmunoterapéutico
CD4 humana soluble recombinante rCD4	Genentech	SIDA, ARC

híbridos de rCD-IgG		SIDA, ARC
CD4 Humano soluble recombinante	Biogen	SIDA, ARC
Alfa 2a Interferón	Hoffman-La Roche	Sarcoma Kaposi, SIDA, ARC, en combinación con/AZT
SK&F106528 T4 soluble	Smith Kline	Infección del VIH
Timopentina	Immunobiology Research Institute (Annandale, NJ)	Infección del VIH
Factor Necrosis del Tumor; TNF	Genentech	ARC, en combinación con/gama interferón
ANTI-INFECTIVOS		
Nombre del Fármaco	*Fabricante*	*Indicaciones*
Clindamicina con primaquina	Pharmacia Upjohn	PCP
Fluconazol	Pfizer	Meningitis criptococal, candidiasis
Pasilla de Nystatina en Pastilla	Squibb Corp.	Prevención de candidiasis oral
Ornidil Eflornitina	Merrell Dow	PCP
Isetionato de pentamidina (IM&IV)	LyphoMed (Rosemont, IL)	Tratamiento de PCP
Trimetoprim		Antibacteriano
Trimetoprim/sulfa		Antibacteriano

Piritrexim	Burroughs Wellcome	tratamiento de PCP
Isetionato de pentamidina para inhalación	Fisons Corporation	Profilaxis de PCP
Espiramicina	Rhone-Poulenc diarrhea	Critosporidial
Intraconazol-R51211	Jansen-Pharm.	Histoplasmosis; meningitis criptococal
Trimetrexato	Warner-Lambert	PCP
Daunorubicina	NeXstar, Sequus	Sarcoma Kaposi
Eritropoyetina humana recombinante	Ortho Pharm.Corp	Anemia severa asociada con terapia de AZT
Hormona de crecimiento humano recombinante	Serono	Desgaste relacionado con SIDA, caquexia
Acetato de gemestrol	Bristol-Myers Squibb	Tratamiento de anorexia asociada con SIDA
Testosterona	Alza, Smith Kline	Desgaste relacionado con SIDA
Nutrición entérica total	Norwich Eaton Pharmaceuticals	diarrea y mala absorción relacionada con SIDA

Además, los compuestos de la descripción indicados se pueden usar en combinación con inhibidores de la entrada

de VIH. Los ejemplos de tales inhibidores de la entrada del VIH se analizan en DRUGS OF THE FUTURE 1999, 24(12), pp. 1355-1362; CELL, Vol. 9, pp. 243-246, 29 de octubre de 1999; y DRUG DISCOVERY TODAY, Vol. 5, No. 5, mayo de 2000, pp. 183-194 e *Inhibitors of the entry of HIV into host cells*. Meanwell, Nicholas A.; Kadow, John F. Current Opinion in Drug Discovery & Development (2003), 6(4), 451-461. En especial, los compuestos se pueden utilizar en combinación con inhibidores de la unión, inhibidores de la fusión y antagonistas del receptor de quimiocina dirigidos hacia el correceptor CCR5 o CXCR4. Los inhibidores de unión a VIH también se describen en los documentos US 7,354,924 y US 2005/0209246.

Cabe destacar que el alcance de las combinaciones de los compuestos de esta aplicación con antivirales para el tratamiento del SIDA, inmunomoduladores, fármacos antiinfecciosos, inhibidores de la entrada del VIH o vacunas no se limita a la lista de la Tabla anterior, sino que incluye, en principio, cualquier combinación con una composición farmacéutica útil para el tratamiento del SIDA.

Las combinaciones preferidas son tratamientos simultáneos o alternativos con un compuesto de la presente descripción y un inhibidor de la proteasa del VIH y/o un inhibidor no nucleósido de la transcriptasa inversa del VIH.

Un cuarto componente opcional en la combinación es

un inhibidor nucleósido de la transcriptasa inversa del VIH, tales como AZT, 3TC, ddC o ddI. Un inhibidor preferido de la proteasa del VIH es Reyataz® (ingrediente activo atazanavir). Por lo general, una dosis de 300 a 600 mg se administra una vez al día. Esto se puede coadministrar con una dosis baja de ritonavir (50 a 500 mg). Otro inhibidor preferido de la proteasa del VIH es Kaletra®. Otro inhibidor útil de la proteasa del VIH es indinavir, que es la sal de sulfato de etanolato de N-(2(R)-hidroxi-1-(S)-indanil)-2(R)-fenilmetil-4-(S)-hidroxi-5-(1-(4-(3-piridil-metil)-2(S)-N'-(t-butilcarboxamido)-piperazinil))-pentanamida, y se sintetiza de acuerdo con el documento U.S. 5,413,999. Por lo general, indinavir se administra en una dosis de 800 mg tres veces por día. Otros inhibidores de proteasa preferidos son nelfinavir y ritonavir. Otro inhibidor preferido de la proteasa de VIH es saquinavir, que se administra en una dosis de 600 o 1200 mg tid. Los inhibidores no nucleósidos preferidos de la transcriptasa inversa del VIH incluyen efavirenz. Estas combinaciones pueden tener efectos no previstos en cuanto a que limitan la expansión y el grado de infección del VIH. Las combinaciones preferidas incluyen las siguientes (1) indinavir con efavirenz y, opcionalmente, AZT y/o 3TC y/o ddI y/o ddC; (2) indinavir y cualquiera de AZT y/o ddI y/o ddC y/o 3TC, en particular, indinavir y AZT y 3TC; (3) estavudina y 3TC y/o zidovudina; (4) sal de tenofovir disoproxil

fumarato y emtricitabina.

En esas combinaciones, el compuesto de la presente invención y otros agentes activos se pueden administrar de manera separada o conjunta. Además, la administración de un elemento se puede realizar antes, durante o después de la administración de otros agentes.

QUÍMICA GENERAL (MÉTODOS DE SÍNTESIS)

La presente invención comprende compuestos de las Fórmulas I, II y III, sus formulaciones farmacéuticas y su uso en pacientes que padecen o que son susceptibles de padecer la infección por VIH. Los compuestos de las Fórmulas I, II y III también incluyen sus sales farmacéuticamente aceptables. Los procedimientos generales para la construcción de los compuestos de las Fórmulas I, II y III e intermediarios útiles para su síntesis, se describen en los siguientes Esquemas de reacción (luego de las Abreviaturas).

Abreviaturas:

Una o más de las siguientes abreviaturas, la mayoría de las cuales son abreviaturas habituales conocidas por los expertos en el arte, se pueden usar a lo largo de la descripción y de los ejemplos:

Bz_2O = anhídrido benzoico

TBTU = tetrafluoroborato de O-(benzotriazol-1-il)-*N*,*N*,*N*',*N*'-tetrametiluronio

HATU = 2-(1H-7-azabenzotriazol-1-il)-1,1,3,3-

tetrametiluronio hexafluorofosfato metanaminio

DCE = dicloroetano

DCM = diclorometano

CDI = carbonildiimidazol

HPLC prep. = cromatografía líquida preparativa de alto rendimiento

ta = temperatura ambiente

DIPEA = diisopropiletilamina

DMAP = 4-dimetilaminopiridina

DMSO = dimetilsulfóxido

THF = tetrahidrofurano

KHMDS = potasio bis(trimetilsilil)amida

min = minuto(s)

h = hora(s)

sat. = saturado

TEA = trietilamina

EtOAc = acetato de etilo

TFA = ácido trifluoroacético

PCC = clorocromato de piridinio

TLC = cromatografía de capa delgada

Tf_2NPh = (trifluorometilsulfonil)metansulfonamida

dioxano = 1,4-dioxano

PG = grupo protector

atm = atmósfera(s)

mol = mol(es)

mmol = milimol

mg = miligramo(s)

µg = microgramo(s)

µl = microlitro(s)

µm= micrómetro(s)

mm= milímetro(s)

HOAc = ácido acético

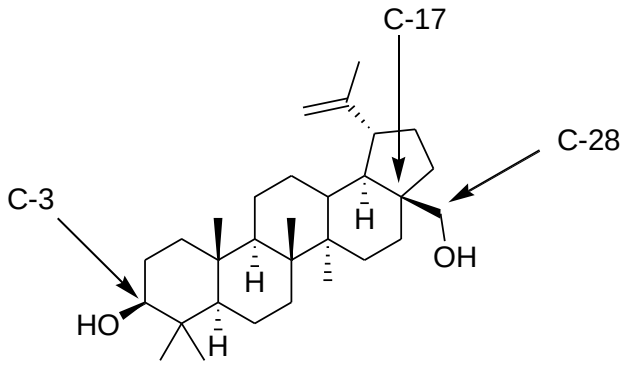
MeOH= metanol

DMF = *N*,*N*-dimetilformamida

TBAF = fluoruro de tetrabutilamonio

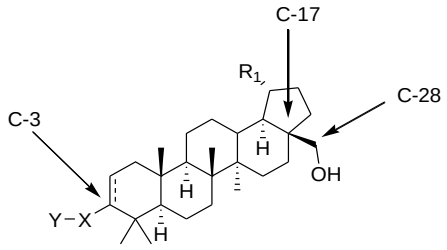
TBDMSCl= cloruro de *terc-butil*dimetilsililo

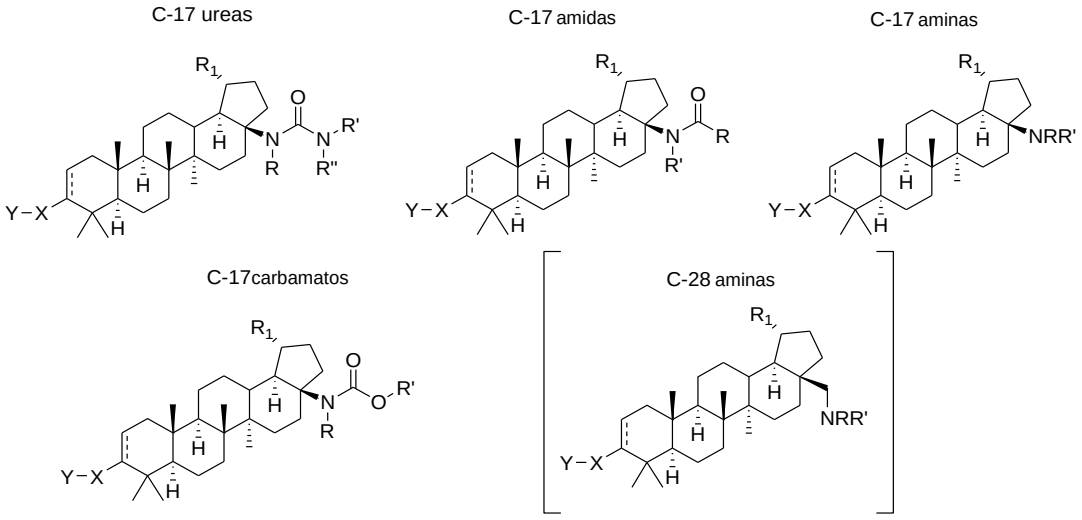
Los términos "C-3" y "C-28" se refieren a ciertas posiciones de un núcleo de triterpeno enumerado de acuerdo con las normas IUPAC (las posiciones se representan a continuación con respecto a un triterpeno ilustrativo: betulina):



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La misma numeración se mantiene con referencia a las series de compuestos en los esquemas de reacción y descripciones generales de los métodos.





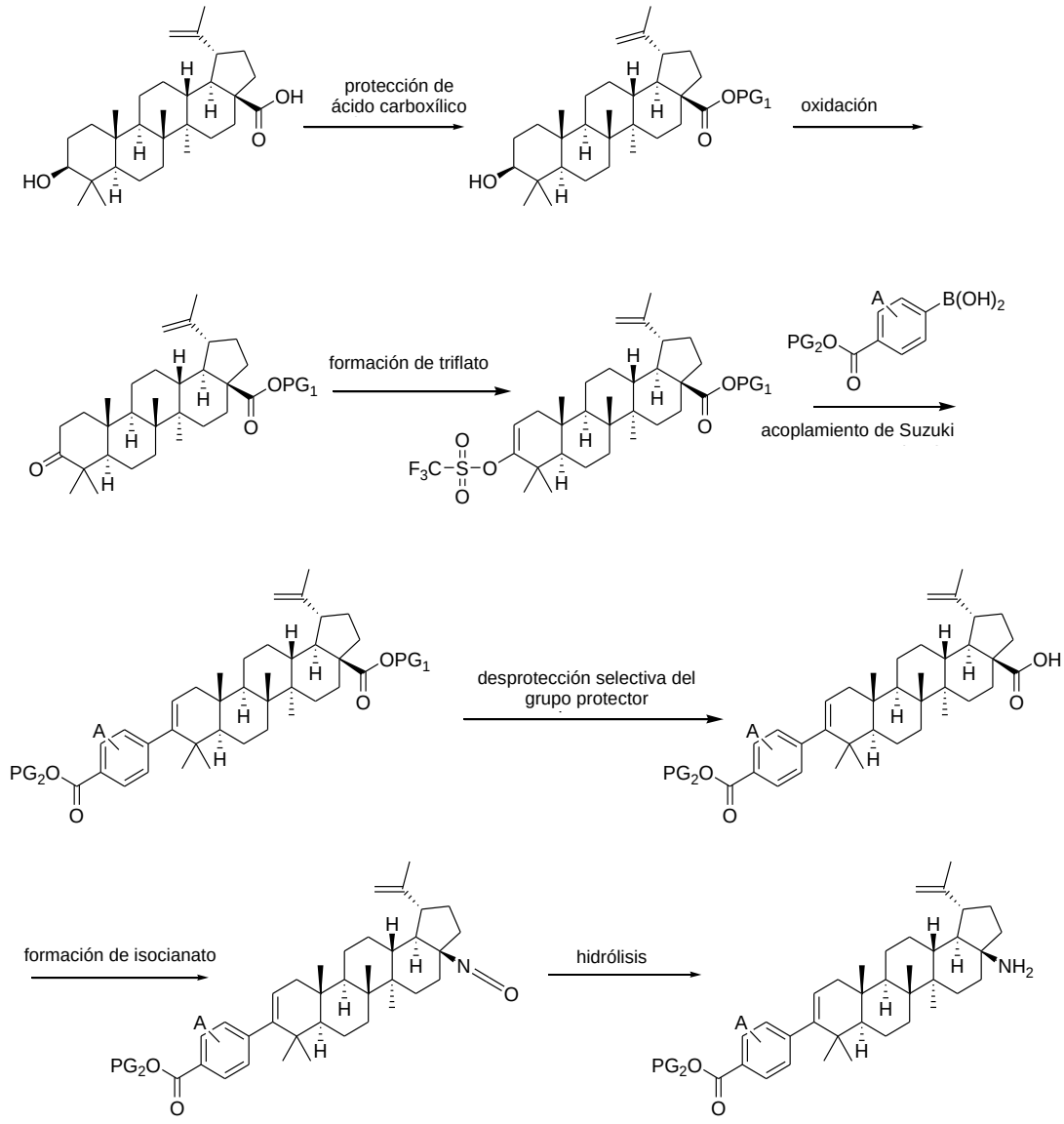
Preparación de compuestos de las Fórmulas I, II y III-Esquemas de reacción de química general:

Preparación de compuestos de las Fórmulas I, II y III-Esquemas de reacción de química general:

Los compuestos de la Fórmula I se pueden preparar de ácido betulínico disponible en el comercio (Aldrich, otros) mediante la química descrita en los siguientes esquemas de reacción. Los compuestos de las Fórmulas II y III se describen más adelante.

Los esquemas de reacción general se indican de la siguiente manera:

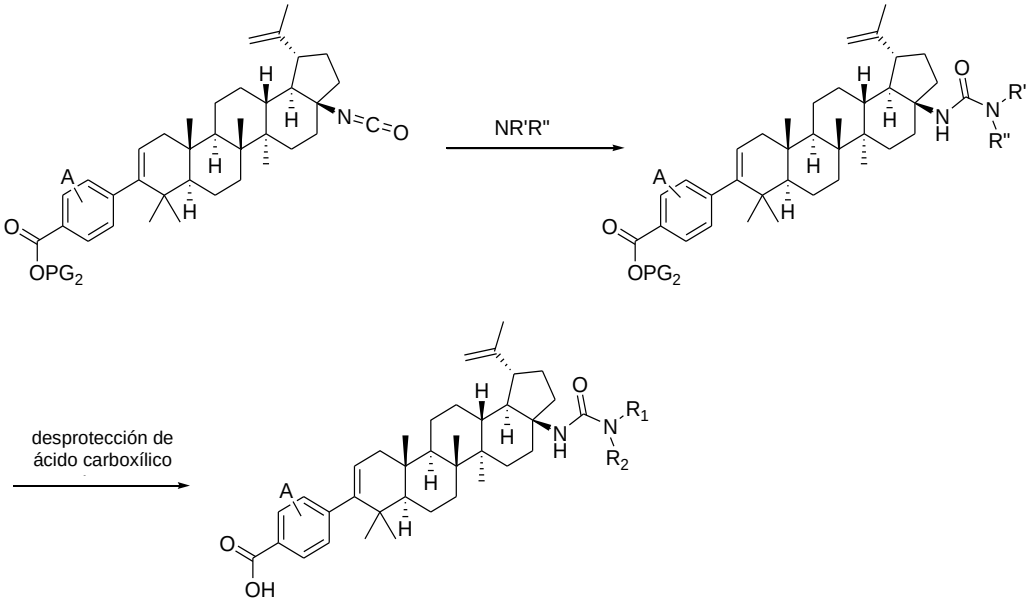
Esquema de reacción 1



El Esquema de reacción 1 describe la preparación del intermediario clave amina primaria C-17 del ácido betulínico. El ácido carboxílico presente en el ácido betulínico se protege con un grupo protector adecuado. La oxidación estándar (es decir, PCC, Dess-Martin) del grupo C-3 hidroxilo produce la cetona C-3 que luego se convierte en triflato mediante las condiciones conocidas por los expertos

en el arte. El acoplamiento cruzado catalizado por paladio con un derivado del ácido borónico (también se puede usar acoplamiento de Stille con estananos) produce los correspondientes derivados del ácido betulínico C-3 modificados. El éster carboxílico C-28 luego se desprotege selectivamente y se somete a condiciones de redisposición de Curtius para obtener la amina primaria C-17. Esta reacción se puede realizar en una sola etapa o en varias etapas mediante el aislamiento del intermediario de isocianato, como se indica en el Esquema de reacción 1.

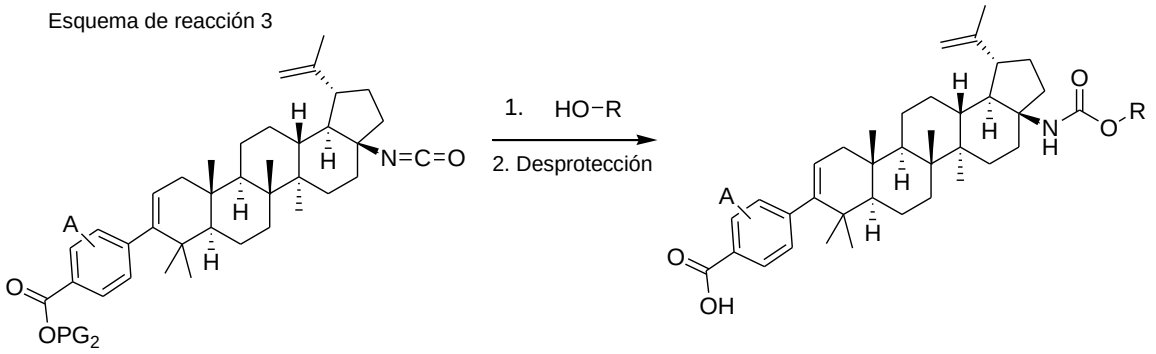
Esquema de reacción 2



El isocianato también se puede modificar para preparar ureas como se indica en el Esquema de reacción 2. La adición de una amina a una solución del isocianato en un solvente, tal como THF o dioxano, en presencia de la base de Hunig o TEA a temperatura ambiente o calentamiento, si es

necesario, produce la urea C-17 correspondiente. La hidrólisis del éster benzoico produce el derivado del ácido benzoico.

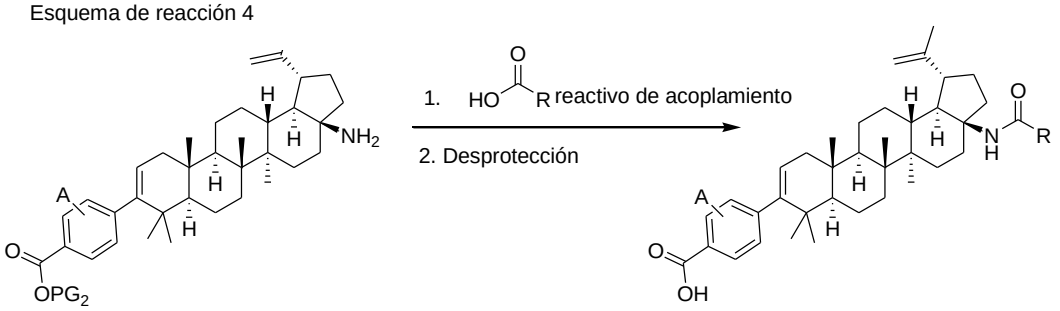
Esquema de reacción 3



De modo similar, los carbamatos se pueden preparar mediante la adición de un alcohol al isocianato en una solución de THF o dioxano en presencia de una base, tal como hidruro de sodio a temperatura ambiente o calentamiento, si es necesario, seguido de la hidrólisis del éster carboxílico. La desprotección también puede ocurrir en las condiciones de la primera reacción, por lo cual no se requieren etapas adicionales.

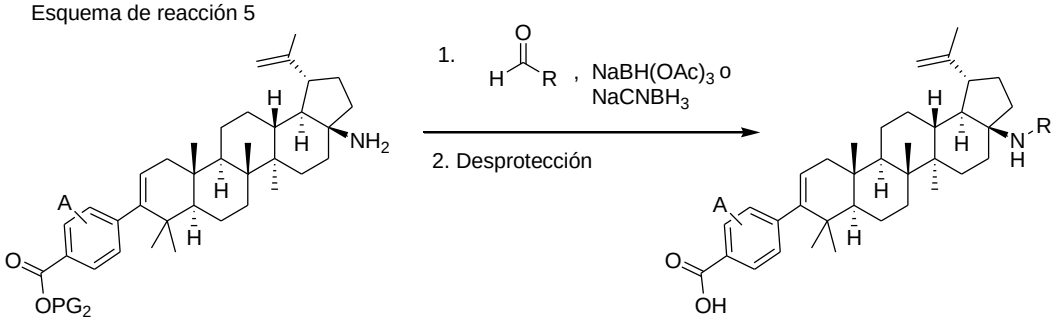
La amina primaria C-17 también se puede modificar con métodos estándares conocidos por los expertos en el arte. Algunos ejemplos se muestran en los siguientes esquemas de reacción.

Esquema de reacción 4



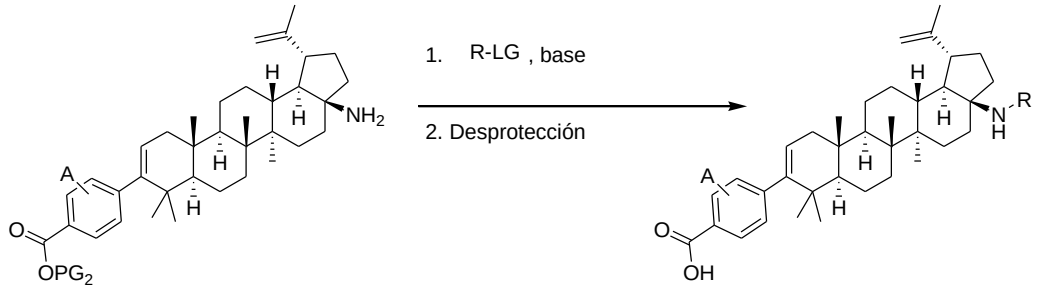
Las amidas C-17 se pueden preparar mediante la reacción de un ácido carboxílico con la amina primaria C-17 en presencia de un reactivo de acoplamiento adecuado, tal como HATU, DCC y otros conocidos por los expertos en el arte, en presencia de una base, tal como base de Hunig, TEA, etc., en el solvente adecuado (DCM, THF, DMF, etc.). La hidrólisis del éster carboxílico produce el ácido benzoico. Alternativamente, algunas amidas se pueden preparar tratando la amina primaria C-17 con el cloruro de ácido carboxílico correspondiente en lugar de un ácido. De modo similar, las sulfonamidas se pueden preparar de la amina primaria C-17 usando un cloruro de sulfonilo como agente de sulfonilación.

Esquema de reacción 5



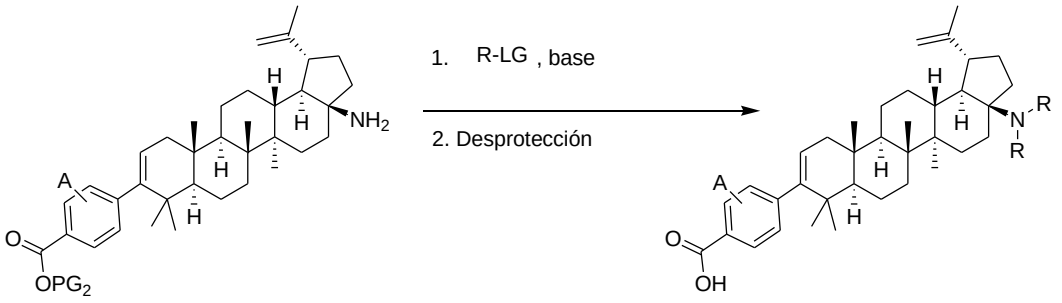
La amina primaria C-17 se puede tratar con un aldehído en condiciones de aminación reductora (por ejemplo, $NaBH(OAc)_3$) en presencia de AcOH/NaOAc o $Ti(OPr)_4$ en un solvente, tal como THF, 1,4-dioxano, DCE o DCM) para obtener aminas secundarias C-17. La hidrólisis del éster carboxílico produce el compuesto de ácido benzoico.

Esquema de reacción 6



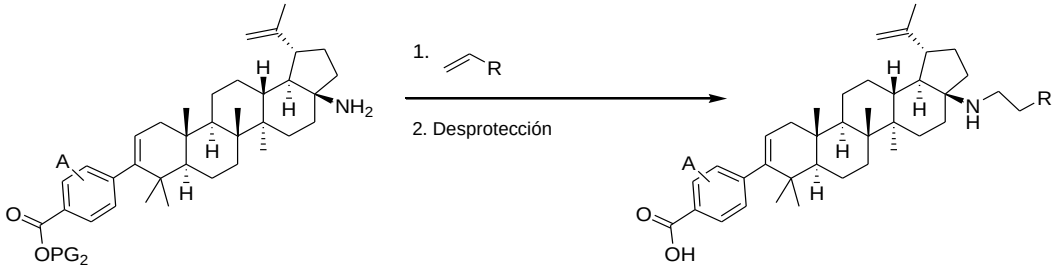
Algunas aminas C-17 se pueden preparar mediante la alquilación de la amina primaria C-17 con un agente alquilante (R-LG), en donde LG es un grupo saliente, por ejemplo, Br, Cl, I, mesilato, tosilato o triflato, en presencia de una base. En algunos casos puede ser necesario el calentamiento. La hidrólisis del éster carboxílico genera el producto de ácido benzoico.

Esquema de reacción 7



En algunos casos, al prolongar los tiempos de reacción y calentar la mezcla de reacción, también se puede formar el producto dialquilado.

Esquema de reacción 8



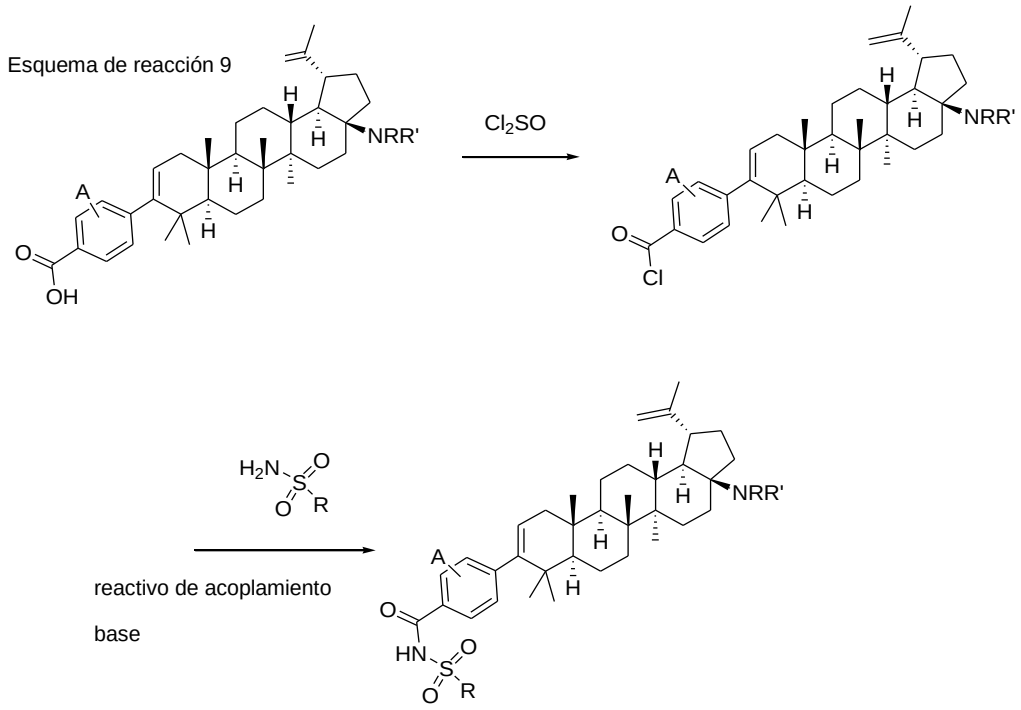
Alternativamente, algunas aminas C-17 se pueden preparar mediante la 1,4-adición a los aceptores de Michael, seguido de la hidrólisis del éster.

Los sustituyentes R, R' y R" pueden contener grupos funcionales (es decir, COOH, COOR, OH, NHR) que también se pueden modificar mediante métodos conocidos por los expertos en el arte. La modificación se puede realizar antes o después de la desprotección final del ácido carboxílico, según la naturaleza del grupo funcional.

Alternativamente, la amina secundaria C-17 también

se puede modificar (es decir, alquilada, acilada, sulfonilada, etc.) usando algunos de los métodos descritos anteriormente u otros métodos estándares conocidos por los expertos en el arte. La saturación del grupo isopropenilo se puede lograr mediante la hidrogenación en condiciones estándares de los productos finales.

Esquema de reacción 9

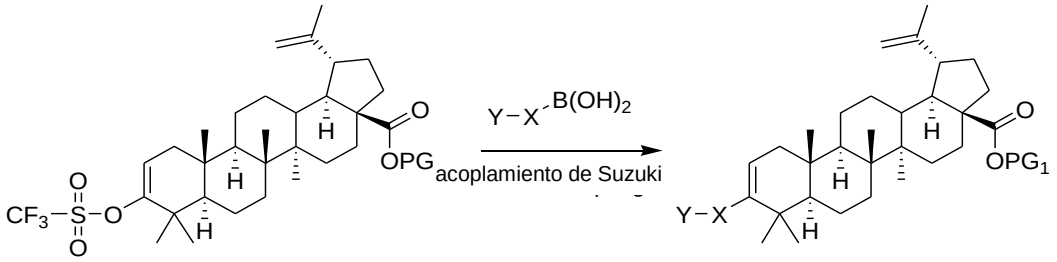


El ácido benzoico también se puede modificar con métodos conocidos por los expertos en el arte. Un ejemplo de tales modificaciones se muestra en el Esquema de reacción 9: El ácido benzoico libre se puede convertir en el cloruro ácido correspondiente y luego tratar con el nucleófilo adecuado, por ejemplo, una sulfonilamida o ureasulfamida, en presencia de una base para obtener un derivado de sulfonilamida o

acilsulfamida.

Los compuestos de la Fórmula I en los cuales la modificación en la posición C-3 difiere del ácido benzoico se pueden preparar seleccionando el ácido borónico correspondiente en la etapa de acoplamiento cruzado catalizado por paladio que se indica en el Esquema de reacción 1 (Esquema de reacción 10). Luego, la posición C-28 se puede modificar mediante los métodos de química descritos en los esquemas de reacción anteriores para obtener los derivados amino C-17 correspondientes.

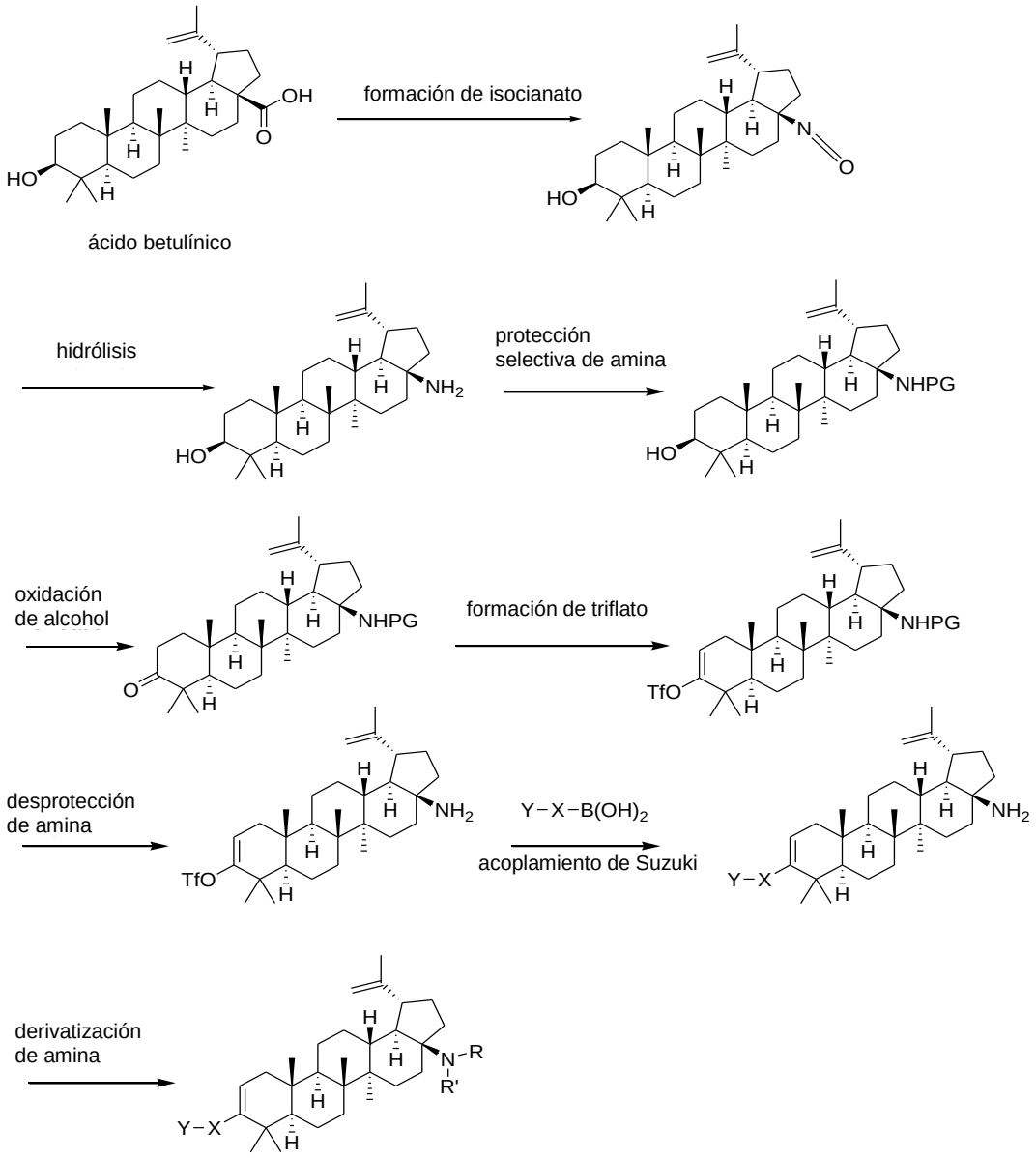
Esquema de reacción 10



Alternativamente, los compuestos de la Fórmula I se pueden preparar de ácido betulínico como se describe en el Esquema de reacción 11. La redisposición de Curtius del ácido betulínico se puede lograr sin la protección del grupo hidroxilo C-3 para obtener el isocianato C-17 que, luego de la hidrólisis del ácido, produce la amina C-17. La amina C-17 luego se protege

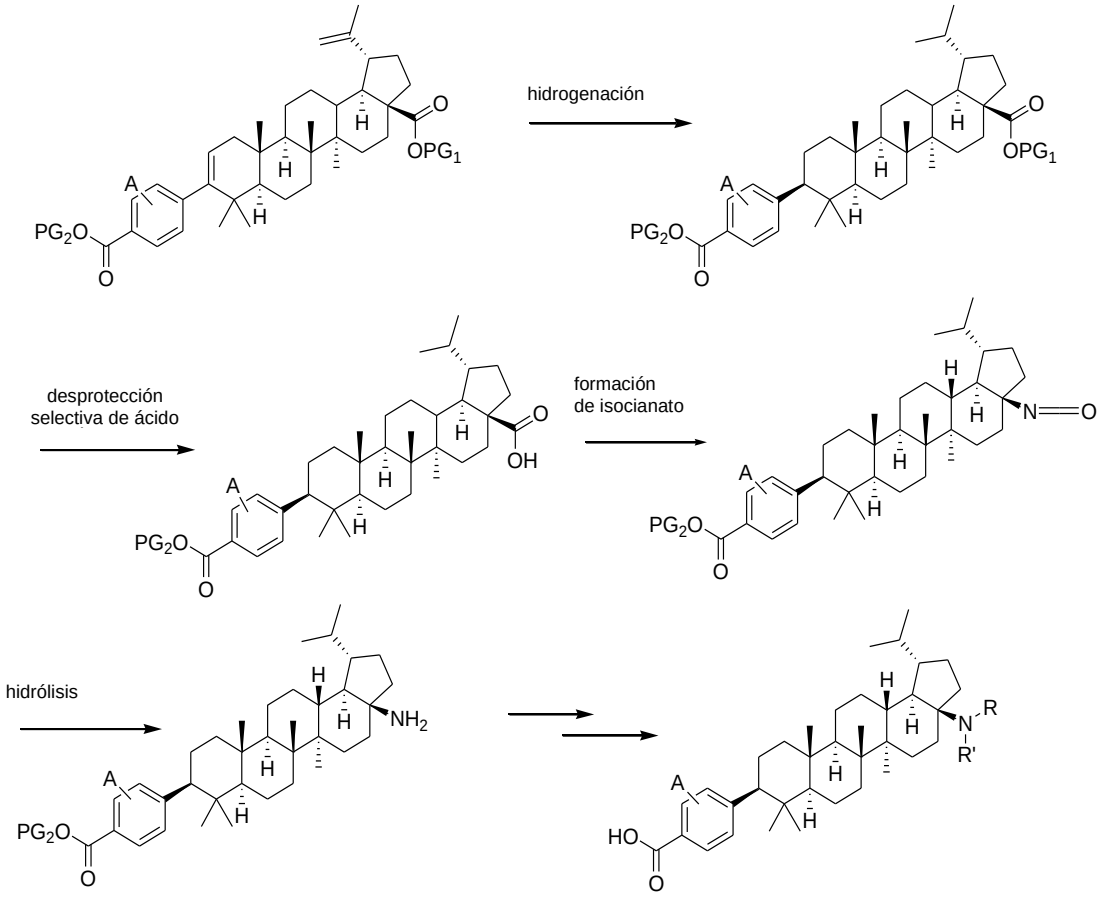
selectivamente con un grupo protector amina (es decir, F-moc, Boc) para realizar la oxidación del grupo hidroxi C-3 en una cetona en condiciones estándares (es decir, PCC, reactivo de Dess-Martin, etc.). La conversión de la cetona en su triflato se puede lograr mediante métodos conocidos por los expertos en el arte. Luego, el grupo protector en el grupo amino se retira para producir la amina C-17 no sustituida. La instalación de la porción C-3 se logra mediante el acoplamiento de Suzuki del triflato con el ácido borónico correspondiente descrito con anterioridad. Luego, el grupo amino C-17 se puede derivatizar como se indicó en los esquemas de reacción anteriores (alquilación, acilación, etc).

Esquema de reacción 11



Los compuestos de la Fórmula II se pueden preparar usando los métodos de química descritos anteriormente para los compuestos de la Fórmula I, con una etapa adicional que consiste en la saturación de los enlaces dobles, como se muestra más adelante en el Esquema de reacción 12:

Esquema de reacción 12



Los compuesto de la Fórmula III se pueden preparar de la misma manera que se describió anteriormente para los compuestos de las Fórmulas I y II usando ácido oleanoico o ursólico como materiales de inicio, en lugar de ácido betulínico.

EJEMPLOS

Los siguientes ejemplos ilustran síntesis típicas de los compuestos de las Fórmulas I, II y III antes descritos en términos generales. Estos ejemplos son solo ilustrativos y

no pretenden limitar la descripción de ninguna manera. Los reactivos y los materiales de inicio son fácilmente accesibles para los expertos en el arte.

Química

Procedimientos típicos y caracterización de ejemplos seleccionados:

A menos que se indique de otro modo, los solventes y los reactivos se usaron directamente como se obtuvieron de fuentes comerciales, y las reacciones se realizaron en una atmósfera de nitrógeno. La cromatografía instantánea se realizó en gel de sílice 60 (tamaño de partícula 0.040-0.063; suministro EM Science). Los espectros de ^{1}H NMR se registraron en Bruker DRX-500f a 500 MHz (o Bruker AV 400 MHz, Bruker DPX-300B o Varian Gemini 300 a 300 MHz como se indicó). Los cambios químicos se informaron en ppm en la escala δ con respecto a δTMS = 0. Se usaron las siguientes referencias internas para los protones residuales en los siguientes solventes: $CDCl_3$ (δ_H 7.26), CD_3OD (δ_H 3.30), d4 acético (*ácido acético d_4*) (δ_H 11.6, 2.07), mezcla DMSO o DMSO-D6_$CDCl_3$ (($_H$ 2.50 y 8.25) (relación 75 %:25 %) y DMSO-D6 (δ_H 2.50). Se usaron acrónimos estándar para describir los patrones de multiplicidad: s (singulete), br. s (singulete amplio), d (doblete), t (triplete), q (cuartete), m (multiplete), b (amplio), app (aparente). La constante de acoplamiento (*J*) es en Hertz. Todos los datos de cromatografía líquida (LC) se

registraron en un cromatógrafo de líquidos Shimadzu LC-10AS con un detector SPD-10AV UV-Vis y los datos de espectrometría de masa (MS, por sus siglas en inglés) se determinaron con Micromass Platform LC en modo electro-rocío.

Métodos LC/MS:

Método 1

Inicio % B = 0, final % B = 100 durante 2 minutos de gradiente, retención a 100 % B

Velocidad de flujo = 4 mL / min

Longitud de onda = 220 nm

Solvente A = 95 % de agua, 5 % de metanol, 10 mM de acetato de amonio

Solvente B = 5 % de agua, 95 % de metanol, 10 mM de acetato de amonio

Columna = Phenomenex Luna C18, 5 µm, 3.0 x 50 mm

Método 2

Inicio % B = 0, final % B = 100 durante 2 minutos de gradiente, retención a 100 % B

Velocidad de flujo = 1 mL / min

Longitud de onda = 220 nm

Solvente A = 90 % de agua, 10 % de acetonitrilo, 0.1 % de TFA

Solvente B = 10 % de agua, 90 % de acetonitrilo, 0.1 % de TFA

Columna = Phenomenex Luna C18, 3 µm, 2.0 x 30 mm

Método 3

Inicio % B = 0, final % B = 100 durante 2 minutos de gradiente, retención a 100 % B

Velocidad de flujo = 4 mL / min

Longitud de onda = 220 nm

Solvente A = 95 % de agua, 5 % de metanol, 10 mM de acetato de amonio

Solvente B = 5 % de agua, 95 % de metanol, 10 mM de acetato de amonio

Columna = Waters Xbridge C18, 5 µm, 4.6 x 50 mm

Método 4

Inicio % B = 0, final % B = 100 durante 2 minutos de gradiente, retención a 100 % B

Velocidad de flujo = 0.8 mL / min

Longitud de onda = 220 nm

Solvente A = 95 % de agua, 5 % de metanol, 10 mM de acetato de amonio

Solvente B = 5 % de agua, 95 % de metanol, 10 mM de acetato de amonio

Columna = Waters Xbridge C18, 3.5 µm, 2.1 x 50 mm

Método 5

Inicio % B = 15, final % B = 100 durante 2 minutos de gradiente, retención a 100 % B

Velocidad de flujo = 1 mL / min

Longitud de onda = 220 nm

Solvente A = 95 % de agua, 5 % de acetonitrilo, 10 mM de acetato de amonio

Solvente B = 5 % de agua, 95 % de acetonitrilo, 10 mM de acetato de amonio

Columna = Phenomenex Luna C18, 3 µm, 2.0 x 30 mm

Método 6

Inicio % B = 0, final % B = 100 durante 2 minutos de gradiente, retención a 100 % B

Velocidad de flujo = 1 ml/min

Longitud de onda = 220 nm

Solvente A = 95 % de agua, 5 % de acetonitrilo, 10 mM de acetato de amonio

Solvente B = 5 % de agua, 95 % de acetonitrilo, 10 mM de acetato de amonio

Columna = Phenomenex Luna C18, 3 µm, 2.0 x 30 mm

Método 7

Inicio % B = 25, final % B = 100 durante 2 minutos de gradiente, retención a 100 % B

Velocidad de flujo = 1 ml/min

Longitud de onda = 220 nm

Solvente A = 95 % de agua, 5% de acetonitrilo, 10 mM de acetato de amonio

Solvente B = 5 % de agua, 95 % de acetonitrilo, 10 mM de acetato de amonio

Columna = Phenomenex Luna C18, 3 µm, 2.0 x 30 mm

Método 8

Inicio % B = 0, final % B = 100 durante 4 minutos de gradiente, retención a 100 % B

Velocidad de flujo = 5 ml/min

Longitud de onda = 220 nm

Solvente A = 90 % de agua, 10 % de metanol, 0.1 % de TFA

Solvente B = 10 % de agua, 90 % de metanol, 0.1 % de TFA

Columna = Phenomenex Luna C18, 10 µm, 3.0 x 50 mm

Método 9

Inicio % B = 20, final % B = 100 durante 2 minutos de gradiente, retención a 100 % B

Velocidad de flujo = 1 ml/min

Longitud de onda = 220 nm

Solvente A = 95 % de agua, 5% de acetonitrilo, 10 mM de acetato de amonio

Solvente B = 5 % de agua, 95 % de acetonitrilo, 10 mM de acetato de amonio

Columna = Phenomenex Luna C18, 3 µm, 2.0 x 30 mm

Método 10

Inicio % B = 0, final % B = 100 durante 2 minutos de gradiente, retención a 100 % B

Velocidad de flujo = 1 mL / min

Longitud de onda = 220 nm

Solvente A = 95 % de agua, 5 % de metanol, 10 mM de acetato de amonio

Solvente B = 5 % de agua, 95 % de metanol, 10 mM de acetato de amonio

Columna = Phenomenex Luna C18, 3 µm, 2.0 x 30 mm

Método 11

Inicio % B = 0, final % B = 100 durante 2 minutos de gradiente, retención a 100 % B

Velocidad de flujo = 1 mL / min

Longitud de onda = 220 nm

Solvente A = 90 % de agua, 10 % de metanol, 0.1 % de TFA

Solvente B = 10 % de agua, 90 % de metanol, 0.1 % de TFA

Columna = Phenomenex Luna C18, 3 µm, 2.0 x 30 mm

Método 12

Inicio % B = 30, final % B = 100 durante 1 minuto de gradiente

Velocidad de flujo = 0.8 mL / min

Longitud de onda = 220 nm

Solvente A = 90 % de agua, 10 % de metanol, 0.1 % de TFA

Solvente B = 10 % de agua, 90 % de metanol, 0.1 % de TFA

Columna = Xbridge Phenyl 2.1 x 50 mm 2.5 µm

Método 13

Inicio % B = 20, final % B = 100 durante 2 minuto de gradiente

Velocidad de flujo = 0.8 mL / min

Longitud de onda = 254 nm

Solvente A = 90 % de agua, 10 % de metanol, 0.1 % de TFA

Solvente B = 10 % de agua, 90 % de metanol, 0.1 % de TFA

Columna = Xbridge Phenyl 2.1 x 50 mm 2.5 µm

Método 14

Inicio % B = 0, final % B = 100 durante 4 minutos de gradiente, retención a 100 % B

Velocidad de flujo = 1 mL / min

Longitud de onda = 220 nm

Solvente A = 95 % de agua, 5% de acetonitrilo, 10 mM de acetato de amonio

Solvente B = 5 % de agua, 95 % de acetonitrilo, 10 mM de acetato de amonio

Columna = Waters BEH C18, 1.7 µm, 2.0 x 50 mm

Método 15

Inicio % B = 0, final % B = 100 durante 4 minutos de gradiente, retención a 100 % B

Velocidad de flujo = 0.5 mL / min

Longitud de onda = 220 nm

Solvente A = 95 % de agua, 5 % de metanol, 10 mM de acetato de amonio

Solvente B = 5 % de agua, 95 % de metanol, 10 mM de acetato de amonio

Columna = Waters BEH C18, 1.7 µm, 2.0 x 50 mm

Método 16

Inicio % B = 0, final % B = 100 durante 4 minutos de gradiente, retención a 100 % B

Velocidad de flujo = 1 mL / min

Longitud de onda = 220 nm

Solvente A = 90 % de agua, 10 % de metanol, 0.1 % de TFA

Solvente B = 10 % de agua, 90 % de metanol, 0.1 % de TFA

Columna = Phenomenex Luna C18, 3 µm, 2.0 x 30 mm

Método 17

Inicio % B = 10, final % B = 100 durante 1 minuto de gradiente, retención a 100 % B

Velocidad de flujo = 0.8 mL / min

Longitud de onda = 220 nm

Solvente A = 90 % de agua, 10 % de metanol, 0.1 % de TFA

Solvente B = 10 % de agua, 90 % de metanol, 0.1 % de TFA

Columna = Phenomenex-luna, 2.0 x 30 mm, 3.0 µm

Métodos de HPLC preparativa:

Método 1 de HPLC preparativa

Inicio % B = 35, final % B = 100 durante 10 minutos de gradiente, retención a 100 % B durante 8 minutos

Velocidad de flujo = 100 mL / min

Solvente A = 90 % de agua, 10 % de acetonitrilo, 0.1 % de TFA

Solvente B = 10 % de agua, 90 % de acetonitrilo, 0.1 % de TFA

Columna = Phenomenex Luna C8(2), 10 µm, 50 x 250 mm (100A)

Método 2 de HPLC preparativa

Inicio % B = 15, final % B = 100 durante 12 minutos de gradiente, retención a 100 % B durante 6 minutos

Velocidad de flujo = 50 mL / min

Solvente A = 90 % de agua, 10 % de acetonitrilo, 0.1 % de TFA

Solvente B = 10 % de agua, 90 % de acetonitrilo, 0.1 % de TFA

Columna = Waters Sunfire C18, 5 µm, 30 x 100 mm

Método 3 de HPLC preparativa

Inicio % B = 20, final % B = 100 durante 8 minutos de gradiente, retención a 100 % B durante 10 minutos

Velocidad de flujo = 50 mL / min

Solvente A = 90 % de agua, 10 % de acetonitrilo,

0.1 % de TFA

Solvente B = 10 % de agua, 90 % de acetonitrilo, 0.1 % de TFA

Columna = Waters Sunfire C18, 5 µm, 30 x 100 mm

Método 4 de HPLC preparativa

Inicio % B = 20, final % B = 100 durante 15 minutos de gradiente, retención a 100 % B durante 8 minutos

Velocidad de flujo = 100 mL / min

Solvente A = 90 % de agua, 10 % de acetonitrilo, 0.1 % de TFA

Solvente B = 10 % de agua, 90 % de acetonitrilo, 0.1 % de TFA

Columna = Phenomenex Luna C8(2), 10 µm, 50 x 250 mm (100A)

Método 5 de HPLC preparativa:

Inicio % B = 15, final % B = 100 durante 20 minutos de gradiente, retención a 100 % B durante 4 minutos

Velocidad de flujo = 50 mL / min

Solvente A = 90 % de agua, 10 % de acetonitrilo, 0.1 % de TFA

Solvente B = 10 % de agua, 90 % de acetonitrilo, 0.1 % de TFA

Columna = Waters Sunfire C18, 5 µm, 30 x 100 mm

Método 6 de HPLC preparativa

Inicio % B = 30, final % B = 100 durante 20 minutos

de gradiente, retención a 100 % B durante 6 minutos

Velocidad de flujo = 40 mL / min

Solvente A = 90 % de agua, 10 % de metanol, 0.1 % de TFA

Solvente B = 10 % de agua, 90 % de metanol, 0.1 % de TFA

Columna = Phenomenex Luna C18(2), 5 µm, 30 x 100 mm

Método 7 de HPLC preparativa

Inicio % B = 0, final % B = 100 durante 30 minutos de gradiente, retención a 100 % B durante 8 minutos

Velocidad de flujo = 50 mL / min

Solvente A = 90 % de agua, 10 % de acetonitrilo, 0.1 % de TFA

Solvente B = 10 % de agua, 90 % de acetonitrilo, 0.1 % de TFA

Columna = Waters Xbridge Phenyl, 5 µm, 30 x 100 mm

Método 8 de HPLC preparativa

Inicio % B = 0, final % B = 100 durante 15 minutos de gradiente, retención a 100 % B durante 10 minutos

Velocidad de flujo = 50 mL / min

Solvente A = 90 % de agua, 10 % de acetonitrilo, 0.1 % de TFA

Solvente B = 10 % de agua, 90 % de acetonitrilo, 0.1 % de TFA

Columna = Waters Xbridge Phenyl, 5 µm, 30 x 100 mm

Método 9 de HPLC preparativa

Inicio % B = 30, final % B = 100 durante 20 minutos de gradiente, retención a 100 % B durante 10 minutos

Velocidad de flujo = 50 mL / min

Solvente A = 90 % de agua, 10 % de acetonitrilo, 0.1 % de TFA

Solvente B = 10 % de agua, 90 % de acetonitrilo, 0.1 % de TFA

Columna = Waters Sunfire C18, 5 µm, 30 x 100 mm

Método 10 de HPLC preparativa

Inicio % B = 0, final % B = 100 durante 20 minutos de gradiente, retención a 100 % B durante 4 minutos

Velocidad de flujo = 50 mL / min

Solvente A = 90 % de agua, 10 % de acetonitrilo, 0.1 % de TFA

Solvente B = 10 % de agua, 90 % de acetonitrilo, 0.1 % de TFA

Columna = Waters Xbridge Phenyl, 5 µm, 30 x 100 mm

Método 11 de HPLC preparativa

Inicio % B = 20, Final % B = 100 durante 10 minutos de gradiente, retención a 100% B durante 15 minutos

Velocidad de flujo = 50 ml/min

Longitud de onda = 220

Par de solventes = agua-metanol-TFA

Solvente A = 90 % de agua, 10 % de metanol, 0.1 %

de TFA

Solvente B = 10 % de agua, 90 % de metanol, 0.1 % de TFA

Columna = Waters Sunfire C18, 5 µm, 30 x 150 mm

Método de HPLC analítica:

Método 1 de HPLC analítica

Inicio % B = 10

Final % B = 100

Tiempo de gradiente = 15 min

Velocidad de flujo = 1 ml/min

Longitud de onda 1 = 220

Longitud de onda 2 = 254

Solvente A = 10 mM de bicarbonato de amonio (pH = 9.5)/95 % de agua/5 % de metanol

Solvente B = 10 mM de bicarbonato de amonio (pH = 9.5)/95 % de agua/5 % de metanol

Columna = Xbridge Phenyl, 3.5 um, 3.0 x 150 mm

Método 2 de HPLC analítica

Inicio % B = 10

Final % B = 100

Tiempo de gradiente = 15 min

Velocidad de flujo = 1 ml/min

Longitud de onda 1 = 220

Longitud de onda 2 = 254

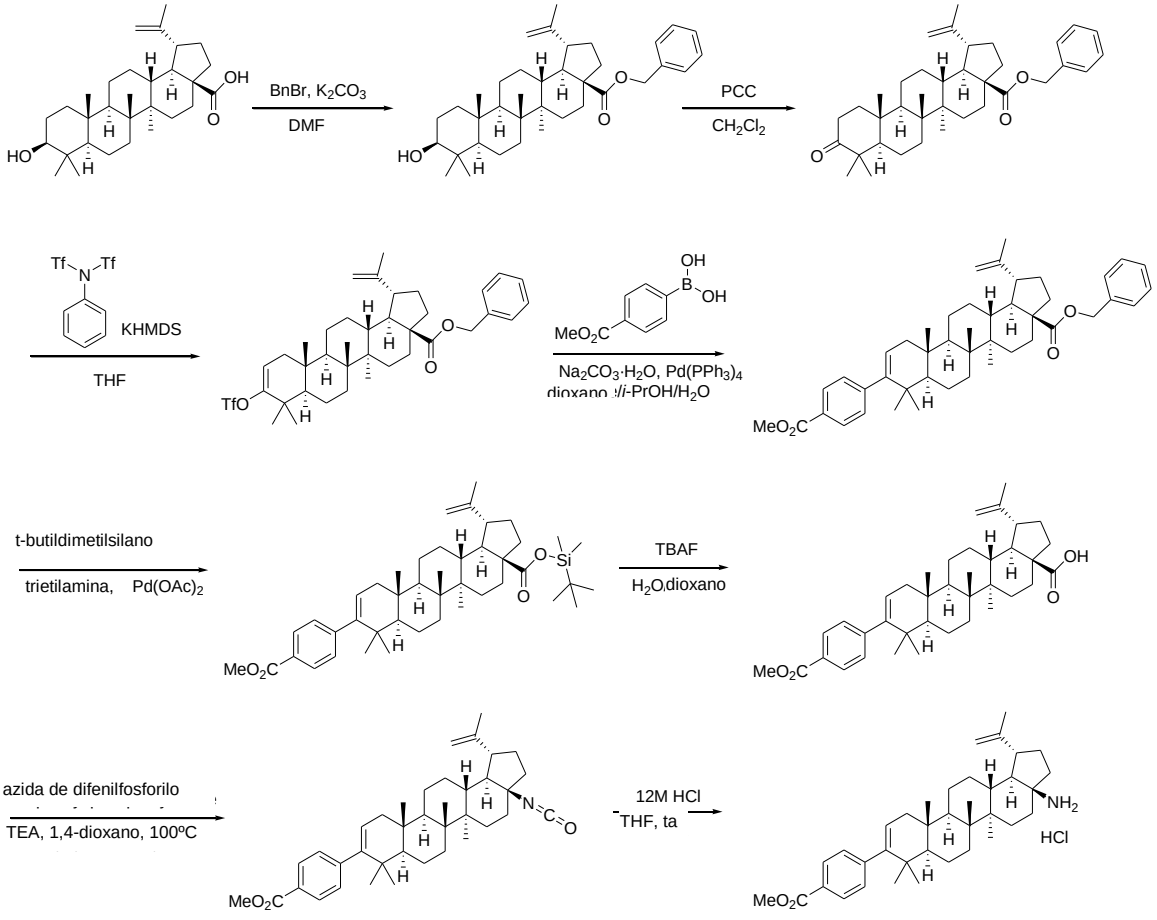
Solvente A = 0.1 % de TFA/95 % de agua/5 % de

acetonitrilo

Solvente B = 0.1 % de TFA/5 % de agua/95 % de acetonitrilo

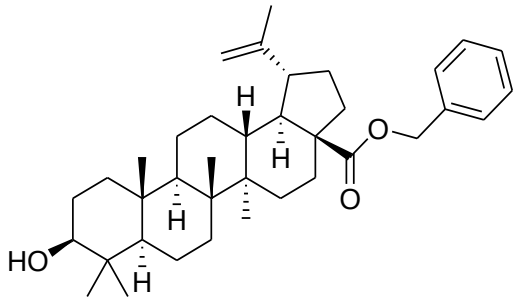
Columna = Xbridge Phenyl, 3.5 um, 3.0 x 150 mm

Preparación de compuestos:



Preparación de 9-hidroxi-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)icosahidro-1H-ciclopenta[a]crisen-3a-carboxilato de

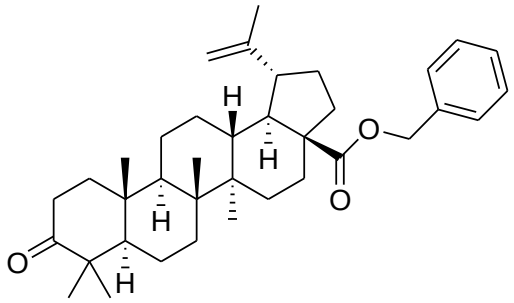
(1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-bencilo.



A una suspensión de ácido betulínico (12 g, 26.3 mmol) y carbonato de potasio (7.26 g, 52.6 mmol) en DMF (150 mL) se agregó bromuro de bencilo (3.28 mL, 27.6 mmol). La mezcla se calentó a 60 °C durante 3.5 h y luego se enfrió a temperatura ambiente. Los sólidos comenzaron a precipitar luego del enfriamiento. La mezcla se diluyó con agua (200 mL), y los sólidos que se formaron se recolectaron mediante filtración para obtener el compuesto del título (13.92 g, 25.5 mmol, 97% de rendimiento) como un sólido blanco. ^{1}H NMR (500 MHz, *CLOROFORMO-d*) δ ppm 7.39-7.28 (m, 5 H), 5.16-5.06 (m, 2 H), 4.71 (d, *J*=1.83 Hz, 1 H), 4.59 (s, 1 H), 3.17 (ddd, *J*=11.44, 5.65, 5.49 Hz, 1 H), 3.01 (td, *J*=10.99, 4.88 Hz, 1 H), 2.27 (ddd, *J*=12.36, 3.20, 3.05 Hz, 1 H), 2.21-2.13(m, 1 H), 1.93-1.81 (m, 2 H), 1.67 (s, 3 H), 0.95 (s, 3 H), 0.93 (s, 3 H), 1.71-0.82 (m, 20 H), 0.79 (s, 3 H), 0.75 (s, 3 H), 0.74 (s, 3 H).

Preparación de 5a,5b,8,8,11a-pentametil-9-oxo-1-(prop-1-en-2-il)icosahidro-1H-ciclopenta[a]crisen-3a-carboxilato de (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-

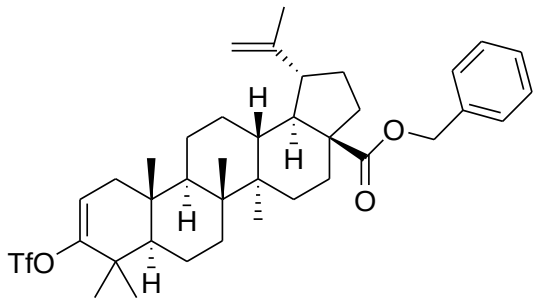
bencilo.



A una solución de 9-hidroxi-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)icosahidro-1H-ciclopenta[a]crisen-3a-carboxilato de (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-bencilo (7.1 g, 12.98 mmol) en diclorometano (100 mL) se agregó PCC (4.20 g, 19.48 mmol). Luego de agitar durante 5 minutos, la mezcla se volvió de color carmesí oscuro. La mezcla se agitó adicionalmente durante 5.5 horas. La mezcla se filtró a través de una almohadilla de celite y gel de sílice que se lavó con diclorometano y luego con una mezcla 1:1 de acetato de etilo:hexanos. El filtrado se concentró a presión reducida para obtener el compuesto del título (6.92 g, 12.7 mmol, 98 % de rendimiento) como una espuma blanca. ^{1}H NMR (500 MHz, *CLOROFORMO-d*) δ ppm 7.38-7.28 (m, 5 H), 5.17-5.06 (m, 2 H), 4.72 (d, *J*=1.83 Hz, 1 H), 4.59 (s, 1 H), 3.01 (td, *J*=10.99, 4.88 Hz, 1 H), 2.51-2.43 (m, 1 H), 2.42-2.34 (m, 1 H), 2.28 (dt, *J*=12.59, 3.17 Hz, 1 H), 2.21 (td, *J*=12.28, 3.51 Hz, 1 H), 1.94-1.82 (m, 3 H), 1.67 (s, 3 H), 1.05 (s, 3 H), 1.01 (s, 3 H), 1.73 – 0.95 (m, 17 H), 0.94 (s, 3 H), 0.89 (s, 3

H), 0.78 (s, 3 H).

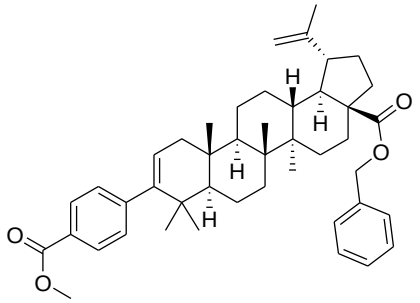
Preparación de 5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-9-(trifluorometilsulfoniloxi)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-carboxilato de (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-bencilo.



Se enfrió una solución de 5a,5b,8,8,11a-pentametil-9-oxo-1-(prop-1-en-2-il)icosahidro-1H-ciclopenta[a]crisene-3a-carboxilato de (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-bencilo (29.0 g, 53.2 mmol) en THF (200 mL) a -78 °C. A la solución, se agregó KHMDS (0.5 M en tolueno) (213 mL, 106 mmol). La solución amarilla se agitó a 78 °C durante 25 minutos, y se agregó una solución de 1,1,1-trifluoro-*N*-fenil-*N*-(trifluorometil)sulfonil metansulfonamida (20.92 g, 58.6 mmol) en THF (70 mL) y tolueno (30 mL) mediante una cánula. La solución se agitó a -78 °C durante 3 h. Luego, se agregó 1.0 g adicional de 1,1,1-trifluoro-*N*-fenil-*N*-(trifluorometil)sulfonil metansulfonamida, y la mezcla se agitó a -78 °C. Después de 1 h de agitación, la mezcla se inactivó con agua (300 mL) y se extrajo con acetato de etilo

(3 x 200 mL). Las capas orgánicas combinadas se secaron con $MgSO_4$. El agente de secado se retiró mediante filtración, y el filtrado se concentró a presión reducida para obtener el compuesto del título (40.0 g, 59.1 mmol) como un sólido amarillo. Rf de producto = 0.57 mediante TLC en gel de sílice, 5 % de EtOAc en hexanos, visualizado con tinción de Hanessian. ^{1}H NMR (500 MHz, *CLOROFORMO-d*) δ ppm 7.29-7.41 (m, 5 H), 5.54 (dd, *J* = 6.71, 1.53 Hz, 1 H), 5.13-5.18 (m, 1 H), 5.05-5.12 (m, 1 H), 4.72 (d, *J* = 1.53 Hz, 1 H), 4.59 (s, 1 H), 3.02 (td, *J* = 10.99, 4.58 Hz, 1 H), 2.25-2.31 (m, 1 H), 2.22 (td, *J* = 12.21, 3.36 Hz, 1 H), 2.14 (dd, *J* = 17.09, 6.71 Hz, 1 H), 1.81-1.96 (m, 2 H), 1.67 (s, 3 H), 1.10 (s, 3 H), 1.00 (s, 3 H), 0.94 (s, 3 H), 0.91-1.77 (m, 17 H), 0.88 (s, 3 H), 0.77 (s, 3 H).

Preparación de 9-(4-(metoxicarbonil)fenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-carboxilato de (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-bencilo.

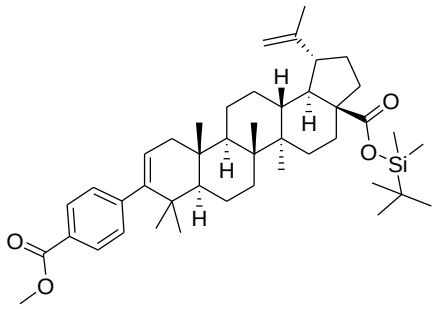


A una solución de 5a,5b,8,8,11a-pentametil-1-(prop-

1-en-2-il)-9-(trifluorometilsulfoniloxi)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-carboxilato de (1R,3aS,5aR,5bR,7aR,11aR,11bR,13bR)-bencilo (6.21 g, 9.18 mmol) en dioxano (25 mL) se agregaron 2-propanol (25 mL) y agua (15mL) seguido de monohidrato de carbonato de sodio (3.42 g, 27.5 mmol), ácido 4-metoxicarbonilfenilborónico (2.478 g, 13.77 mmol) y tetrakis(trifenilfosfina)paladio(0) (0.318 g, 0.275 mmol). El recipiente se unió a un condensador de reflujo, se purgó con N_2 y se calentó a reflujo durante la noche. Luego, la mezcla se enfrió a temperatura ambiente y se diluyó con agua (75 mL). La mezcla se extrajo con acetato de etilo (3 x 75 mL) y se lavó con salmuera (75 mL). Las capas orgánicas combinadas se secaron con $MgSO_4$, se filtraron y se concentraron a presión reducida. El residuo se adsorbió en gel de sílice y se purificó mediante cromatografía instantánea en gel de sílice con gradiente 0-20 % acetato de etilo en hexanos. Las fracciones que contenían el producto previsto se combinaron y concentraron a presión reducida para producir el compuesto del título (4.16 g, 6.28 mmol, 68.4 % de rendimiento) como una espuma blanca. ^{1}H NMR (500 MHz, *CLOROFORMO-d*) δ ppm 7.92 (d, *J*=8.24 Hz, 2 H), 7.40-7.29 (m, 5 H), 7.19 (d, *J*=8.24 Hz, 2 H), 5.28 (dd, *J*=6.10, 1.83 Hz, 1 H), 5.19-5.07 (m, 2 H), 4.73 (d, *J*=1.83 Hz, 1 H), 4.60 (s, 1 H), 3.90 (s, 3 H), 3.04 (td, *J*=10.91, 4.73 Hz, 1 H), 2.20-2.32 (m,

2 H), 2.09 (dd, *J*=17.24, 6.26 Hz, 1 H), 1.95-1.82 (m, 2 H), 1.69 (s, 3 H), 0.97 (s, 3 H), 0.95 (s, 3 H), 0.92 (s, 3 H), 0.91 (s, 3 H), 1.75 – 0.87 (m, 17 H), 0.82 (s, 3 H).

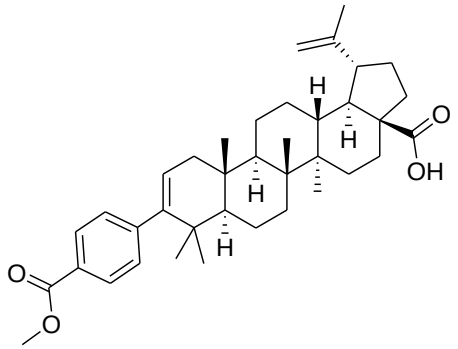
Preparación de 9-(4-(metoxicarbonil)fenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-carboxilato de (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-terc-butildimetilsililo.



A una solución de 9-(4-(metoxicarbonil)fenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisene-3a-carboxilato de (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-bencilo (3.82 g, 5.76 mmol) en dicloroetano (100 mL) se agregaron trietilamina (1.285 mL, 9.22 mmol), *terc-butil*dimetilsilano (1.912 mL, 11.52 mmol) y acetato de paladio(II) (0.647 g, 2.88 mmol). La mezcla se purgó con N_2 y se calentó a 60 °C. Después de 2 horas, la reacción se enfrió a temperatura ambiente, se filtró a través de una almohadilla de Celite y gel de sílice

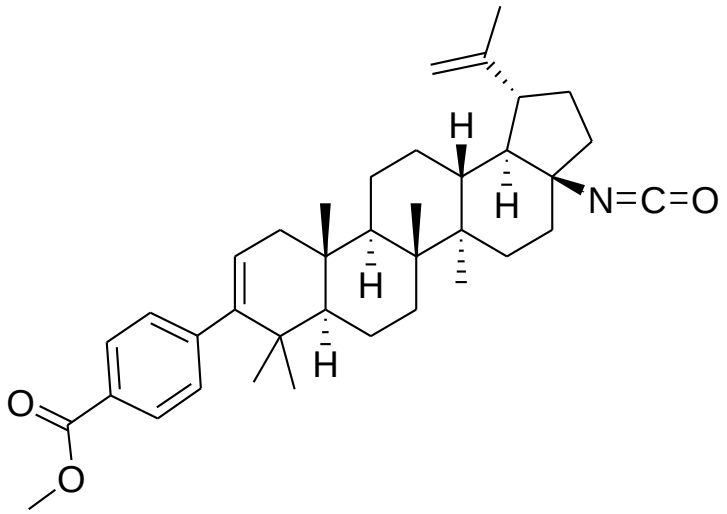
para retirar los sólidos que se lavaron con 25 % de EtOAc en hexanos. El filtrado se concentró a presión reducida y se trató con ácido acético (25 mL), THF (10 mL) y agua (3 mL). Después de 1 h de agitación, los sólidos formados se recolectaron mediante filtración y se lavaron con agua para obtener el compuesto del título (3.62 g, 5.27 mmol, 91 % de rendimiento) como un sólido blanco. ^{1}H NMR (400 MHz, *CLOROFORMO-d*) δ ppm 7.94 (d, *J*=8.28 Hz, 2 H), 7.21 (d, *J*=8.28 Hz, 2 H), 5.30 (dd, *J*=6.15, 1.63 Hz, 1 H), 4.75 (d, *J*=1.76 Hz, 1 H), 4.62 (s, 1 H), 3.92 (s, 4 H), 3.08 (td, *J*=10.92, 4.27 Hz, 1 H), 2.35-2.22 (m, 2 H), 2.17-2.06 (m, 1 H), 2.02 – 1.84 (m, 2 H), 1.71 (s, 3 H), 1.01 (s, 6 H), 0.99 (br. s., 3 H), 0.98 (s, 9 H), 0.94 (s, 6 H), 1.78 – 0.90 (m, 16 H), 0.32-0.28 (m, 6 H).

Preparación de ácido (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(metoxicarbonil)fenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-carboxílico.



A una solución de 9-(4-(metoxicarbonil)fenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-carboxilato de (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-terc-butildimetilsililo (3.12 g, 4.54 mmol) en dioxano (25 mL) se agregó TBAF (75 % en peso de agua) (2.375 g, 6.81 mmol), y la mezcla se agitó a temperatura ambiente durante 4 h. La mezcla de reacción se diluyó con HCl 1N (25 mL) y agua (5 mL) y se extrajo con diclorometano (3 x 100 mL). Las capas orgánicas combinadas se secaron en Na_2SO_4, se filtraron y se concentraron parcialmente a presión reducida a alrededor de 10 mL de volumen. A la mezcla parcialmente concentrada, se agregó HCl 1N (50 mL). Los sólidos que se formaron se recolectaron por filtración y se lavaron con agua para obtener el compuesto del título (2.58 g, 4.50 mmol, 99 % de rendimiento) como un sólido blanco. LCMS: m/e 571.47 $(M-H)^-$, 3.60 min (método 1). ^{1}H NMR (500 MHz, *CLOROFORMO-d*) δ ppm 9.80 (br. s., 1 H), 7.92 (d, *J*=8.24 Hz, 2 H), 7.18 (d, *J*=8.24 Hz, 2 H), 5.32-5.26 (m, 1 H), 4.75 (s, 1 H), 4.62 (br. s., 1 H), 3.90 (s, 3 H), 3.07 – 2.99 (m, 1 H), 2.33-2.21 (m, 2 H), 2.10 (dd, *J*=17.09, 6.10 Hz, 1 H), 2.06–1.94 (m, 2 H), 1.70 (s, 3 H), 1.01 (br. s., 3 H), 1.00 (br. s., 3 H), 0.98 (s, 3 H), 0.91 (s, 6 H), 1.79–0.89 (m, 17 H).

Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocianato-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

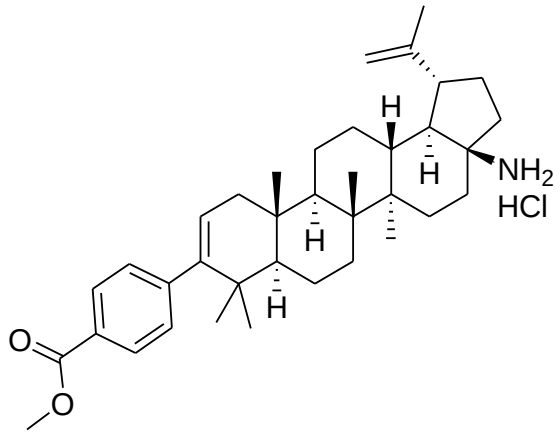


A una suspensión de ácido (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(metoxicarbonil)fenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-carboxílico (10 g, 17.46 mmol) en 1,4-dioxano (200 mL) se agregaron trietilamina (4.38 mL, 31.4 mmol) y luego azida de difenilfosforilo (5.82 mL, 26.2 mmol). La suspensión blanca resultante se calentó a 100 °C. Después de 5 h, la reacción se enfrió a temperatura ambiente, luego se diluyó con EtOAc y se lavó con NaOH 1N (2 x 70 mL). La capa acuosa combinada se extrajo con EtOAc (2 x 150 mL). La capa orgánica combinada se secó en Na_2SO_4, se

filtró y se concentró hasta obtener una suspensión (75 mL) que se almacenó en un refrigerador durante la noche. La suspensión se filtró, y el producto sólido blanco se lavó con Et_2O. El filtrado líquido se concentró hasta obtener una suspensión amarilla que se filtró y se lavó con Et_2O para producir más producto sólido blanco. Los dos lotes de sólido blanco se combinaron y se secaron al vacío para producir el compuesto del título (8.6 g, 15.09 mmol, 86 % de rendimiento) como un sólido blanco. ^{1}H NMR (500 MHz, *CLOROFORMO-d*) δ ppm 8.0 (2 H, d, *J*= 8.2 Hz), 7.2 (2 H, d, *J*= 8.2 Hz), 5.3 (1 H, d, *J*= 4.6 Hz), 4.8 (1 H, s), 4.7 (1 H, s), 3.9 (3 H, s), 2.6 (1 H, td, *J*= 10.8, 5.8 Hz), 2.1-2.2 (2 H, m), 1.8-2.0 (4 H, m), 1.7-1.8 (1 H, m), 1.7 (3 H, s), 1.5-1.7 (5 H, m), 1.4-1.5 (5 H, m), 1.3-1.4 (2 H, m), 1.2-1.3 (2 H, m), 1.1 (3 H, s), 1.1-1.1 (1 H, m), 1.0 (3 H, s), 1.0 (3 H, s), 1.0 (3 H, br. s.), 1.0 (3 H, br. s.). ^{13}C NMR (*CLOROFORMO-d*) δ ppm 14.2, 15.4, 16.2, 19.2, 19.5, 20.8, 21.0, 24.7, 27.4, 29.0, 29.2, 33.3, 36.0, 37.2, 39.0, 39.0, 40.3, 41.5, 41.8, 47.8, 49.0, 49.2, 51.7, 52.6, 66.8, 71.3, 110.2, 121.3, 123.7, 127.6, 128.2, 129.8, 146.0, 148.4, 148.6, 166.9.

Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de

metilo.

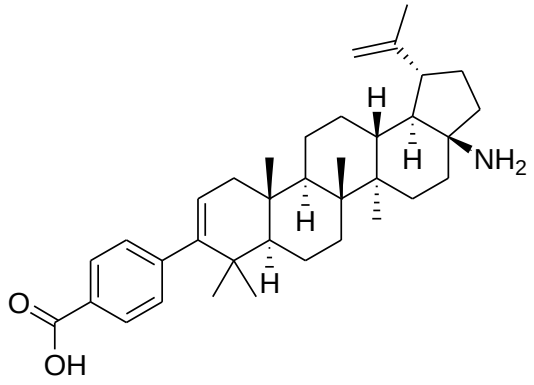


A una solución turbia de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocianato-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (5.47 g, 9.60 mmol) en THF (100 mL) se agregó ácido clorhídrico concentrado (19.83 mL, 240 mmol). La mezcla homogénea resultante se agitó a temperatura ambiente durante 72 h; la mezcla de reacción se concentró hasta secarse para obtener 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo, HCl (4.98 g, 8.58 mmol, 89 % de rendimiento) como un sólido blanco. LCMS: m/e 544.5 $(M+H)^+$, 3.26 min (método

6). ^{1}H NMR (500 MHz, 1:1 *$CDCl_3$*:*MeOD*, estabilización *MeOD*) δ ppm 7.9 (2 H, d, *J*= 8.5 Hz), 7.3 (1 H, t, *J*= 7.8 Hz), 7.2 (2 H, d, *J*= 8.5 Hz), 7.1 (1 H, t, *J*= 7.3 Hz), 5.3 (1 H, d, *J*= 4.6 Hz), 4.8 (1 H, s), 4.7 (1 H, br. s.), 3.9 (2 H, s), 3.6 (2 H, dt, *J*= 15.6, 6.6 Hz), 3.3 (1 H, dt, *J*= 3.1, 1.6 Hz), 2.6 (1 H, td, *J*= 11.0, 6.1 Hz), 2.1 (1 H, dd, *J*= 17.1, 6.4 Hz), 2.0 (1 H, d, *J*= 13.4 Hz), 1.9-2.0 (1 H, m), 1.8-1.9 (2 H, m), 1.7-1.7 (3 H, m), 1.6-1.7 (3 H, m), 1.5-1.6 (3 H, m), 1.5-1.5 (2 H, m), 1.4 (1 H, br. s.), 1.3-1.4 (1 H, m), 1.2-1.3 (1 H, m), 1.1-1.2 (2 H, m), 1.1-1.1 (1 H, m), 1.0 (3 H, s), 1.0 (3 H, s), 0.9 (3 H, s), 0.9 (3 H, s).

Ejemplo 1

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



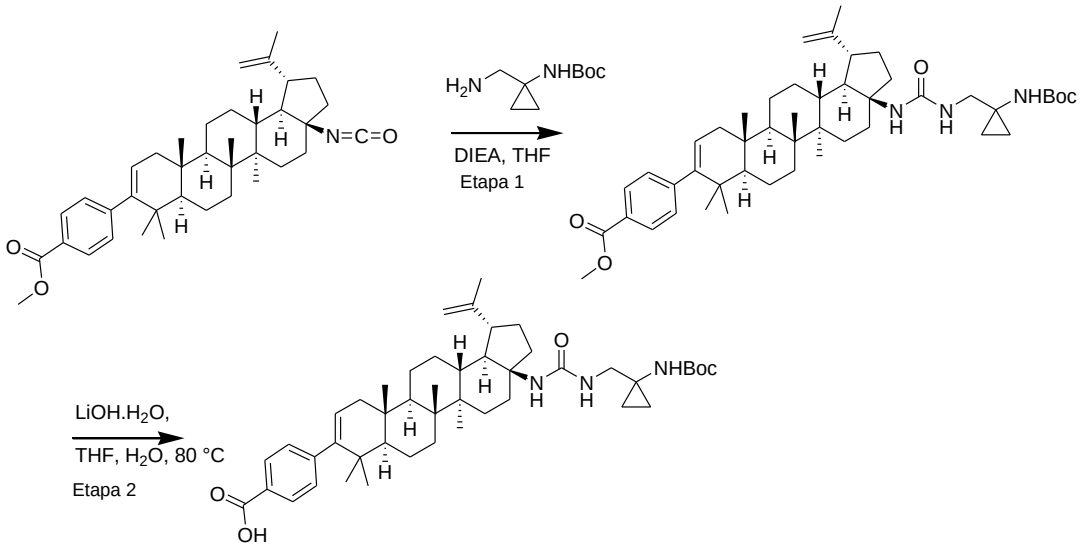
El compuesto del título se formó como un subproducto durante la preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo. La purificación por HPLC preparativa de fase inversa produjo una sal de mono-TFA sólida blancuzca (100 mg, 3.5 % de rendimiento). LCMS: m/z 530 ($M+H^+$), tiempo de retención 2.29 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.94 (br. s., 3 H) 0.95 (br. s., 3 H) 1.02 (s, 3 H) 1.06 (s, 3 H) 1.09-1.22 (m, 4 H) 1.22-1.30 (m, 1 H) 1.30-1.47 (m, 3 H) 1.49-1.57 (m, 4 H) 1.58-1.72 (m, 6 H) 1.73 (s, 3 H) 1.74-1.91 (m, 4 H) 1.91-1.99 (m, 1 H) 2.02-2.18 (m, 2 H) 2.51-2.63 (m, 1 H) 4.71 (s, 1 H) 4.81 (s, 1 H) 5.29 (d, *J*= 4.88 Hz, 1 H) 7.20 (d, *J*= 8.24 Hz, 2 H) 7.92 (d, *J*= 8.24 Hz, 2 H).

Sección 1. Ureas

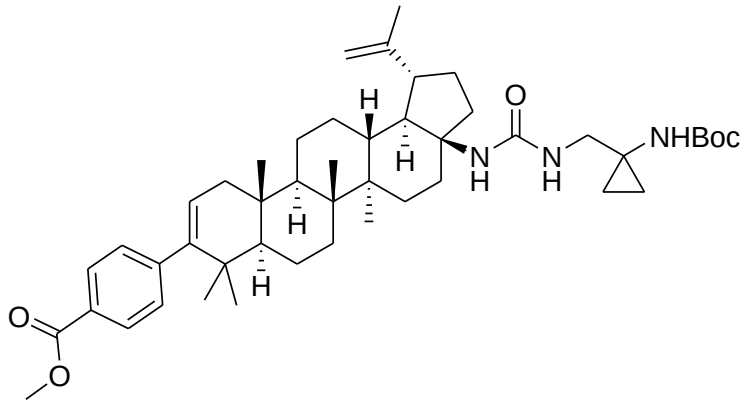
Ejemplo 2

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1-(terc-butoxicarbonilamino)ciclopropil)metilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1-(terc-butoxicarbonilamino)ciclopropil)metilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

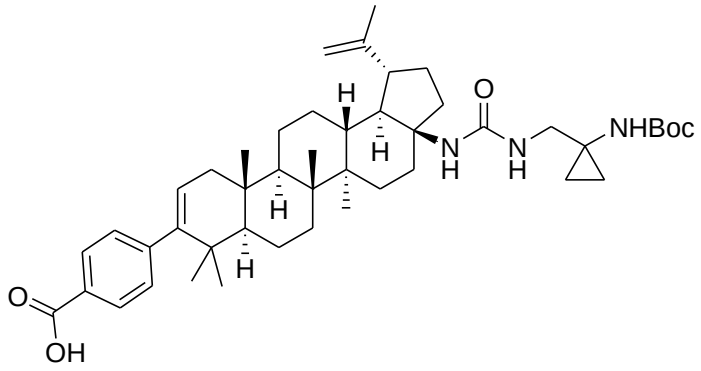


A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocianato-

5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (600 mg, 1.053 mmol) y *N,N*-diisopropietilamina (0.734 mL, 4.21 mmol) en THF (6 mL) se agregó 1-(aminometil)ciclopropilcarbamato de *terc-butilo* (294 mg, 1.579 mmol). La mezcla resultante se agitó a temperatura ambiente. Después de 16 h, se concentró el solvente. El material crudo se disolvió en THF (1 mL) y MeOH (2 mL), se filtró y se purificó mediante HPLC preparativa de fase inversa (método 1) para obtener el compuesto del título (499.5 mg, 58 % de rendimiento) como un sólido blanco. LCMS: m/e 756.7 $(M+H)^+$, 2.75 min (método 7). ^{1}H NMR (500 MHz, *CLOROFORMO-d*) δ ppm 8.0 (2 H, d, *J*= 8.5 Hz), 7.2 (2 H, d, *J*= 8.5 Hz), 5.3-5.3 (1 H, m), 5.1 (1 H, br. s.), 4.8 (1 H, s), 4.7 (1 H, s), 3.9 (3 H, s), 3.5-3.5 (1 H, m), 3.4 (1 H, d, *J*= 14.3 Hz), 2.8 (1 H, br. s.), 2.6 (1 H, d, *J*= 12.8 Hz), 2.4 (1 H, dd, *J*= 12.2, 8.2 Hz), 2.1 (1 H, dd, *J*= 17.4, 6.4 Hz), 1.9-2.1 (2 H, m), 1.8 (1 H, d, *J*= 13.4 Hz), 1.7-1.8 (1 H, m), 1.7 (3 H, s), 1.7-1.7 (2 H, m), 1.5-1.7 (3 H, m), 1.5 (9 H, s), 1.4-1.5 (5 H, m), 1.2-1.3 (1 H, m), 1.1-1.2 (2 H, m), 1.1 (3 H, s), 1.0 (3 H, s), 1.0 (3 H, s), 0.9 (6 H, s), 0.8-0.9 (3 H, m). ^{13}C NMR (*CLOROFORMO-d*) δ ppm 14.1, 15.4, 16.1, 19.0, 19.5, 20.7, 20.8, 24.8, 27.0, 28.1, 29.1, 29.2, 29.4, 31.4, 33.2, 35.1, 36.0, 36.6, 37.2, 40.4, 41.4, 41.6, 46.0, 49.1,

49.6, 51.7, 52.5, 77.3, 80.1, 109.9, 123.7, 127.6, 128.2, 129.8, 146.0, 148.4, 149.2, 167.0.

Etapa 2. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1-(terc-butoxicarbonilamino)ciclopropil)metilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



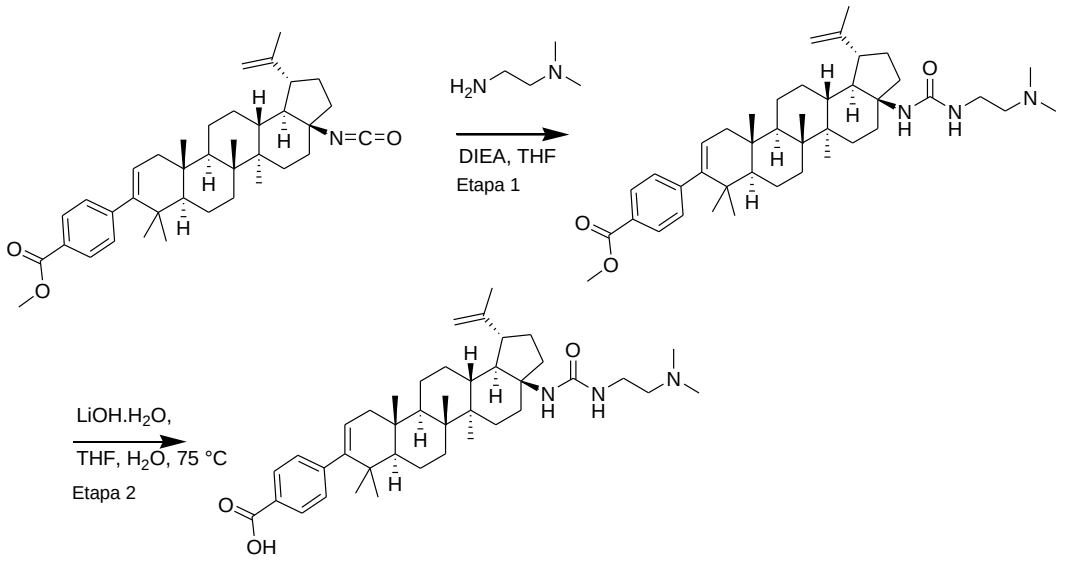
A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-((1-(terc-butoxicarbonilamino)ciclopropil)metil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (91 mg, 0.12 mmol) en THF (5 mL) se agregó una solución de hidróxido de litio monohidrato (20.2 mg, 0.481 mmol) en agua (1.00 mL). La mezcla de reacción se agitó a 80 °C durante 3 h. La reacción se concentró y se purificó mediante HPLC preparatoria de fase inversa mediante el método de HPLC

preparativa 2. Las fracciones de HPLC que contenían picos de producto se trataron con solución de $NaHCO_3$ acuoso saturado (100 mL), se combinaron y se concentraron. El residuo resultante se trituró con H_2O (8 mL) y se extrajo con una mezcla de THF (30 mL) y EtOAc (50 mL). La capa orgánica se lavó con salmuera, se secó en $MgSO_4$, se filtró y se concentró para obtener el compuesto del título (58.1 mg, 0.069 mmol, 57.7 % de rendimiento) como un sólido blanco. LCMS: m/e 742.6 $(M+H)^+$, 2.13 min (método 6). ^1H NMR (500 MHz, *MeOD*) δ ppm 7.9 (2 H, d, *J*= 7.9 Hz), 7.2 (2 H, d, *J*= 8.2 Hz), 5.3 (1 H, d, *J*= 6.1 Hz), 4.8 (1 H, s), 4.6 (1 H, s), 3.9-4.0 (1 H, m), 3.3 (2 H, d, *J*= 9.5 Hz), 2.7 (1 H, br. s.), 2.6 (1 H, d, *J*= 13.4 Hz), 2.4 (1 H, dd, *J*= 11.7, 8.7 Hz), 2.2 (1 H, dd, *J*= 17.2, 6.3 Hz), 1.9-2.0 (3 H, m), 1.7-1.8 (2 H, m), 1.7 (3 H, s), 1.7-1.7 (1 H, m), 1.5-1.6 (3 H, m), 1.5-1.5 (6 H, m), 1.5 (9 H, s), 1.4 (2 H, d, *J*= 2.1 Hz), 1.2-1.4 (6 H, m), 1.2 (3 H, s), 1.1-1.1 (2 H, m), 1.0 (6 H, br. s.), 1.0 (3 H, s), 1.0 (3 H, s), 0.9-0.9 (1 H, m). ^{13}C NMR (*MeOD*) δ ppm 11.2, 13.9, 15.5, 16.1, 18.4, 18.6, 20.0, 20.7, 21.6, 23.9, 25.6, 27.5, 27.8, 29.1, 29.1, 29.8, 29.9, 30.0, 33.8, 35.7, 36.5, 37.6, 37.7, 40.8, 41.9, 42.1, 49.9, 49.9, 53.3, 63.8, 67.3, 79.2, 109.5, 124.1, 128.7, 130.1, 146.8, 150.4, 157.5, 159.2.

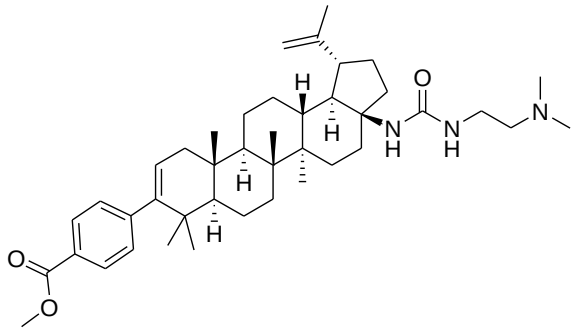
Ejemplo 3

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-

(dimetilamino)etil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimetilamino)etil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

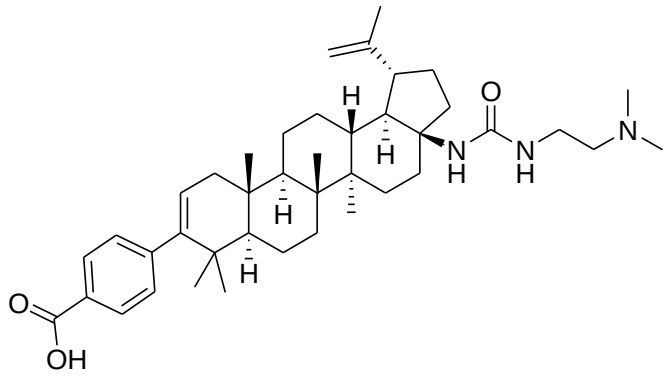


A una solución de 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocianato-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (610.0 mg, 1.071 mmol) en THF (10 mL) se agregaron *N,N*-diisopropiletilamina (0.559 mL, 3.21 mmol) y *N,N*-dimetiletilendiamina (0.353 mL, 3.21 mmol). La mezcla de reacción se agitó a 25 °C. Después de 18 h, la mezcla de reacción se diluyó con EtOAc (50 mL) y se trató con HCl 1N (5 mL). La mezcla se concentró hasta obtener una pasta y luego se trituró con EtOAc, se filtró y se lavó con Et_2O. Se reservó el sólido blanco, y se concentró el filtrado líquido; las etapas de trituración y filtración se repitieron dos veces más. El producto sólido blanco combinado se secó en un horno al vacío para obtener el compuesto del título (650.0 mg, 0.958 mmol, 90 % de rendimiento). LCMS: m/e 658.4 $(M+H)^+$, 4.25 min (método 8). ^{1}H NMR (500 MHz, *CLOROFORMO-d*) δ ppm 7.9 (2 H, d, *J*= 8.5 Hz), 7.2 (2 H, d, *J*= 8.2 Hz), 5.3 (1 H, dd, *J*= 6.3, 1.7 Hz), 4.8 (1 H, s), 4.6 (1 H, s), 3.9 (3 H, s), 3.7-3.8 (1 H, m), 3.5-3.6 (1 H, m), 3.2 (2 H, br. s.), 2.9 (6 H, br. s.), 2.7-2.7 (1 H, m), 2.6 (1 H, d, *J*= 13.4 Hz), 2.4 (1 H, dd, *J*= 11.6, 8.2 Hz), 2.1 (1 H, dd, *J*= 17.2, 6.3 Hz), 2.0-2.1 (1 H, m), 1.8-1.9 (1 H, m), 1.8 (1 H, d, *J*= 12.8 Hz), 1.7 (3 H, s), 1.7 (1 H, d, *J*= 6.7 Hz), 1.6-1.7 (1 H, m), 1.5-1.6 (2 H, m), 1.5 (4 H, d, *J*= 2.7 Hz), 1.3-1.4 (5 H, m), 1.2-

1.3 (1 H, m), 1.1 (3 H, s), 1.0-1.1 (2 H, m), 1.0 (3 H, s), 1.0-1.0 (3 H, m), 0.9 (6 H, s). ^{13}C NMR (*CLOROFORMO-d*) δ ppm 14.2, 15.8, 16.3, 18.4, 19.2, 19.5, 20.7, 21.1, 25.0, 27.1, 29.1, 29.5, 29.6, 33.3, 35.3, 35.4, 36.0, 37.2, 37.3, 40.3, 41.4, 41.7, 43.4, 46.7, 49.3, 51.7, 52.6, 53.4, 58.9, 63.9, 77.3, 109.8, 123.9, 127.6, 128.2, 129.8, 145.9, 148.5, 149.4, 157.5, 167.0.

Etapa 2. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimetilamino)etil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

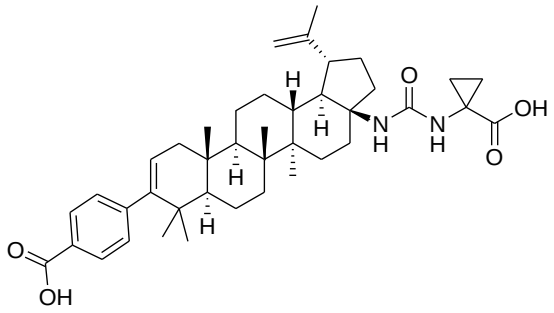


A una solución turbia de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimetilamino)etil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de

metilo (0.255 g, 0.388 mmol) en THF (5 mL) se agregó una solución de hidróxido de litio monohidrato (0.049 g, 1.16 mmol) en agua (1.00 mL). La mezcla de reacción se calentó a 75 °C durante 18 h. Luego, la reacción se trató con HCl 1N (1 mL) y se concentró al vacío, se absorbió en gel de sílice (3.5 g), se cargó en una columna de gel de sílice (cartucho de 12 g) y se eluyó con 90:10 de DCM:MeOH para obtener el compuesto del título (237 mg, 0.368 mmol, 95 % de rendimiento) como un sólido blanco. LCMS: m/e 644.4 $(M+H)^+$, 3.95 min (método 8). ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.9 (2 H, d, *J*= 8.2 Hz), 7.2 (2 H, d, *J*= 8.2 Hz), 5.9 (1 H, s), 5.3-5.3 (1 H, m), 4.8 (1 H, d, *J*= 1.8 Hz), 4.6 (1 H, s), 3.7-3.8 (1 H, m), 3.4-3.6 (2 H, m), 3.4 (1 H, s), 3.2-3.3 (2 H, m), 2.9 (6 H, s), 2.7 (1 H, td, *J*= 11.1, 5.0 Hz), 2.6 (1 H, dd, *J*= 10.2, 3.2 Hz), 2.4 (1 H, dd, *J*= 12.1, 8.1 Hz), 2.2 (1 H, dd, *J*= 17.4, 6.4 Hz), 1.9-2.0 (2 H, m), 1.8 (1 H, d, *J*= 13.4 Hz), 1.7 (3 H, s), 1.7 (1 H, br. s.), 1.7-1.7 (1 H, m), 1.6-1.6 (2 H, m), 1.5-1.6 (4 H, m), 1.4-1.4 (5 H, m), 1.3-1.4 (3 H, m), 1.2 (3 H, s), 1.1-1.1 (1 H, m), 1.0-1.1 (6 H, m), 1.0 (3 H, s), 1.0 (3 H, s). ^{13}C NMR (*MeOD*) δ ppm 14.5, 16.3, 16.8, 19.2, 20.6, 21.3, 22.2, 26.3, 28.2, 29.7, 30.4, 30.5, 34.5, 36.2, 36.4, 37.1, 38.2, 38.4, 41.5, 42.6, 42.8, 43.6, 48.1, 49.0, 49.3, 49.3, 50.4, 50.6, 54.0, 55.6, 59.9, 64.9, 110.3, 111.1, 124.8, 129.3, 130.7, 147.5, 150.9, 160.4.

Ejemplo 4

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(1-carboxiciclopropil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

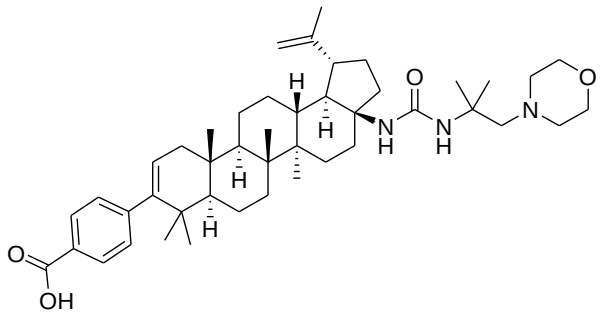


El compuesto del título se preparó en 25 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocianato-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimetilamino)etil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó clorhidrato de etiléster del ácido 1-

aminociclopropan-1-carboxílico en lugar de *N,N*-dimetiletilendiamina en la Etapa 1. LCMS: m/e 657.3 $(M+H)^+$, 4.18 min (método 8). ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.9 (2 H, d, *J*= 8.2 Hz), 7.2 (2 H, d, *J*= 8.2 Hz), 5.3-5.3 (1 H, m), 4.8 (1 H, br. s.), 4.6 (1 H, br. s.), 3.7-3.8 (1 H, m), 3.6-3.6 (1 H, m), 3.5-3.6 (1 H, m), 2.5-2.7 (2 H, m), 2.4 (1 H, dd, *J*= 12.1, 8.4 Hz), 2.2 (1 H, dd, *J*= 17.1, 6.4 Hz), 2.0 (1 H, d, *J*= 11.9 Hz), 1.9 (2 H, dt, *J*= 6.6, 3.2 Hz), 1.8-1.9 (2 H, m), 1.7-1.8 (4 H, m), 1.4-1.7 (7 H, m), 1.4 (3 H, td, *J*= 13.1, 4.0 Hz), 1.3 (3 H, t, *J*= 11.7 Hz), 1.2 (3 H, s), 1.1-1.1 (3 H, m), 1.1 (3 H, d, *J*= 2.4 Hz), 1.0 (3 H, s), 1.0 (2 H, s), 0.9 (1 H, m).

Ejemplo 5

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(3-(2-metil-1-morfolinopropan-2-il)ureido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



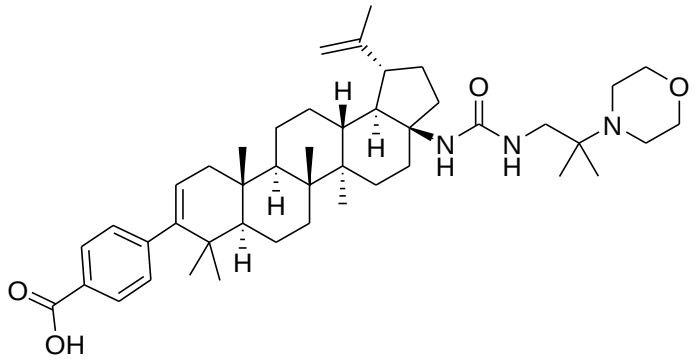
El compuesto del título se preparó en 16 % de

rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocianato-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimetilamino)etil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó 2-metil-2-morfolinopropan-1-amina en lugar de *N,N*-dimetiletilendiamina en la Etapa 1. LCMS: m/e 714.3 $(M+H)^+$, 3.97 min (método 8). ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.9 (2 H, d, *J*= 8.2 Hz), 7.2 (2 H, d, *J*= 8.2 Hz), 5.3 (1 H, d, *J*= 4.6 Hz), 4.7 (1 H, br. s.), 2.5-2.7 (1 H, m), 2.2 (1 H, dd, *J*= 16.9, 6.0 Hz), 2.1 (1 H, dd, *J*= 13.3, 9.9 Hz), 1.9-2.0 (2 H, m), 1.8-1.9 (3 H, m), 1.8 (3 H, br. s.), 1.7-1.8 (1 H, m), 1.6-1.7 (5 H, m), 1.5-1.6 (3 H, m), 1.4 (2 H, d, *J*= 13.4 Hz), 1.3-1.4 (1 H, m), 1.2 (3 H, br. s.), 1.1 (3 H, br. s.), 1.1 (3 H, br. s.), 1.0 (3 H, br. s.), 1.0 (3 H, br. s.).

Ejemplo 6

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(3-(2-metil-2-morfolinopropil)ureido)-1-(prop-

1-en-2-il)-
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

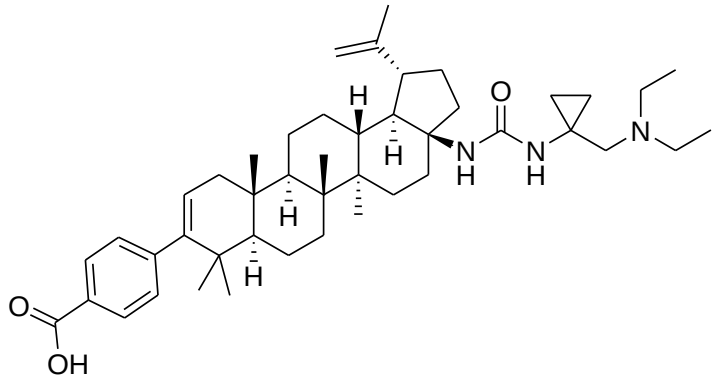


El compuesto del título se preparó en 20 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocianato-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimetilamino)etil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó 2-metil-2-morfolinopropan-1-amina en lugar de *N,N*-dimetiletilendiamina en la Etapa 1. LCMS: m/e 714.3 $(M+H)^+$, 3.95 min (método 8). ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.9 (2 H, d, *J*= 8.2 Hz), 7.2 (2 H, d, *J*= 8.2 Hz), 5.3 (1 H, d, *J*= 6.1

Hz), 4.8 (1 H, s), 4.7 (1 H, s), 4.1 (2 H, d, *J*= 12.2 Hz), 3.7-3.9 (2 H, m), 3.5-3.6 (2 H, m), 3.4-3.5 (2 H, m), 3.2 (2 H, t, *J*= 11.9 Hz), 2.6-2.7 (2 H, m), 2.4 (1 H, dd, *J*= 12.1, 8.4 Hz), 2.2 (1 H, dd, *J*= 17.1, 6.1 Hz), 2.0 (1 H, t, *J*= 10.8 Hz), 1.8-1.9 (1 H, m), 1.8 (1 H, br. s.), 1.7 (3 H, s), 1.7 (1 H, td, *J*= 13.3, 3.4 Hz), 1.6-1.6 (2 H, m), 1.5-1.6 (4 H, m), 1.4-1.5 (3 H, m), 1.4-1.4 (6 H, m), 1.3 (1 H, d, *J*= 9.5 Hz), 1.1 (3 H, s), 1.1 (3 H, br. s.), 1.1 (3 H, br. s.), 1.0 (3 H, s), 1.0 (3 H, s).

Ejemplo 7

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(1-((dietilamino)metil)ciclopropil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



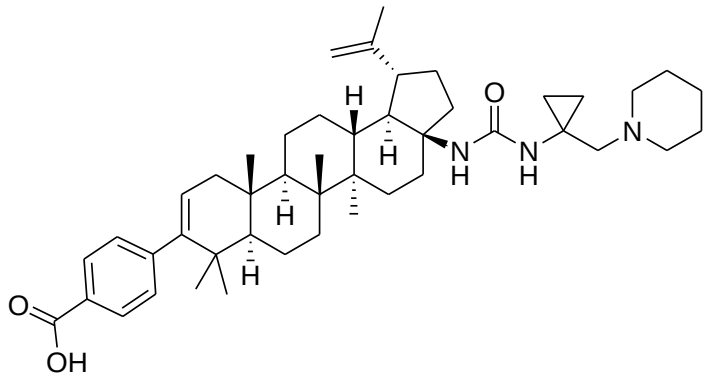
El compuesto del título se preparó en 25 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocianato-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimetilamino)etil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó 1-((dietilamino)metil)ciclopropanamina, 2 HCl en lugar de *N,N*-dimetiletilendiamina en la Etapa 1. LCMS: m/e 698.3 $(M+H)^+$, 3.97 min (método 8). ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.9-8.0 (2 H, m), 7.2-7.3 (2 H, m), 5.3 (1 H, dd, *J*= 4.0, 1.8 Hz), 4.8 (1 H, br. s.), 4.7 (1 H, br. s.), 3.2-3.3 (4 H, m), 2.6 (1 H, d, *J*= 12.8 Hz), 2.5-2.6 (1 H, m), 2.3-2.4 (1 H, m), 2.2 (1 H, dd, *J*= 16.0, 5.3 Hz), 1.9-2.0 (1 H, m), 1.7-1.8 (3 H, m), 1.7 (3 H, br. s.), 1.6-1.7 (4 H, m), 1.5 (4 H, d, *J*= 7.3 Hz), 1.4-1.5 (2 H, m), 1.4 (8 H, dd, *J*= 7.0, 5.2 Hz), 1.3 (2 H, br. s.), 1.1-1.2 (1 H, m), 1.1 (3 H, br. s.), 1.1 (6 H, br. s.), 1.0 (3 H, d, *J*= 1.5 Hz), 1.0 (3 H, br. s.), 0.9 (3 H, br. s.).

Ejemplo 8

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(3-(1-(piperidin-1-ilmetil)ciclopropil)ureido)-

1-(prop-1-en-2-il)-
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

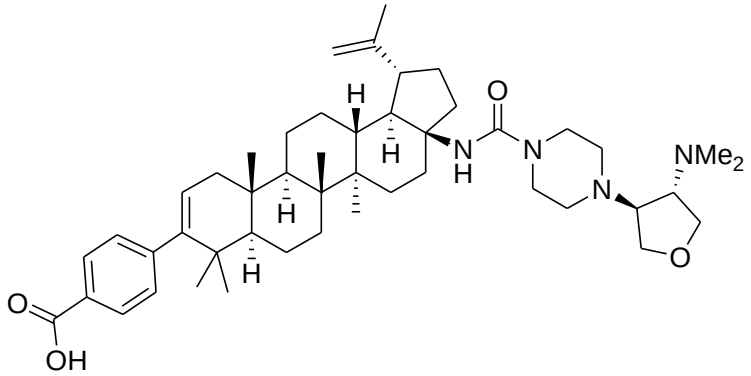


El compuesto del título se preparó de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocianato-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimetilamino)etil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó 1-(piperidin-1-ilmetil)ciclopropanamina, 2 HCl en lugar de *N,N*-dimetiletilendiamina en la Etapa 1. LCMS: m/e 710.6 $(M+H)^+$, 2.00 min (método 6). ^{1}H NMR (500 MHz, *MeOD*) δ ppm 7.9 (2 H, d, *J*= 7.9 Hz), 7.2 (2 H, d, *J*= 7.9 Hz), 5.3 (1

H, d, *J*= 4.9 Hz), 4.8 (1 H, s), 4.7 (1 H, s), 3.5-3.7 (2 H, m), 3.3 (1 H, s), 3.2-3.3 (2 H, m), 3.0 (2 H, ddd, *J*= 12.0, 8.5, 3.7 Hz), 2.6 (1 H, d, *J*= 13.4 Hz), 2.6 (1 H, td, *J*= 10.9, 5.0 Hz), 2.4 (1 H, dd, *J*= 11.9, 8.2 Hz), 2.2 (1 H, dd, *J*= 17.1, 6.4 Hz), 1.9-2.1 (3 H, m), 1.7-1.9 (5 H, m), 1.7 (3 H, s), 1.7-1.7 (1 H, m), 1.5-1.7 (8 H, m), 1.3-1.5 (6 H, m), 1.2-1.2 (1 H, m), 1.1 (1 H, d, *J*= 4.0 Hz), 1.1 (3 H, s), 1.1 (6 H, br. s.), 1.0 (3 H, s), 1.0 (3 H, s), 0.9-0.9 (2 H, m).

Ejemplo 9

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-((3S,4S)-4-(dimetilamino)tetrahidrofuran-3-il)piperazin-1-carboxamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

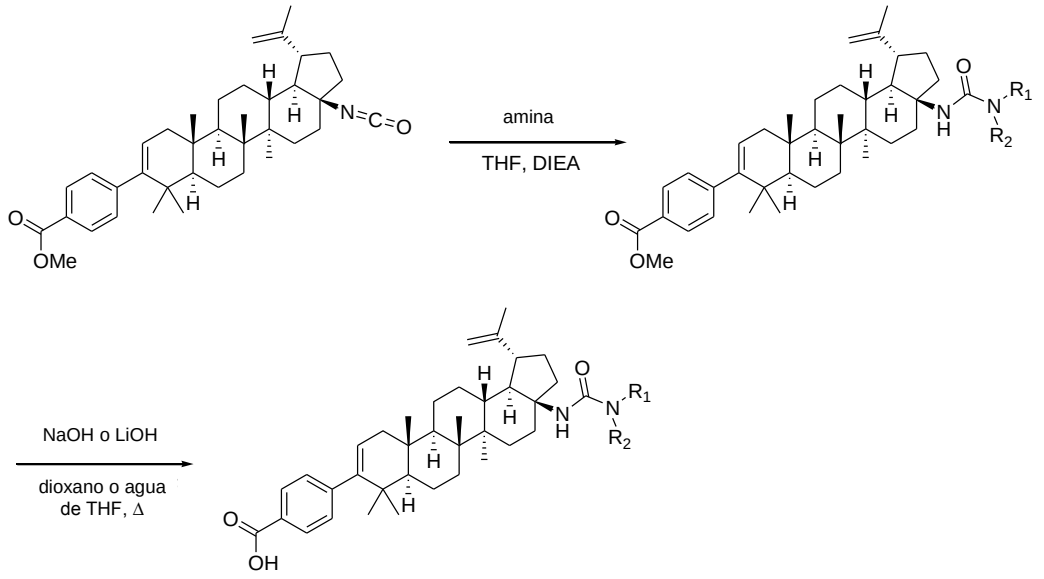


El compuesto del título se preparó en 20 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocianato-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimetilamino)etil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó (3S,4S)-N,N-dimetil-4-(piperazin-1-il)tetrahidrofuran-3-amina en lugar de *N,N*-dimetiletilendiamina en la Etapa 1. LCMS: m/e 755.6 $(M+H)^+$, 1.85 min (método 6). ^{1}H NMR (500MHz, *METANOL-d$_4$*) δ = 7.93 (d, *J* = 8.2 Hz, 2 H), 7.23 (d, *J* = 8.2 Hz, 2 H), 5.31 (d, *J* = 6.1 Hz, 1 H), 4.78 (s, 1 H), 4.64 (br. s., 1 H), 4.09 (d, *J* = 3.4 Hz, 1 H), 4.05 (d, *J* = 4.9 Hz, 2 H), 4.02 (td, *J* = 3.5, 6.8 Hz, 1 H), 3.96 (td, *J* = 5.1, 10.1 Hz, 1 H), 3.73 (d, *J* = 5.2 Hz, 1 H), 3.56-3.41 (m, 4 H), 2.96 (s, 6 H), 2.87-2.66 (m, 5 H), 2.59 (d, *J* = 13.1 Hz, 1 H), 2.45 (dd, *J* = 8.7, 11.7 Hz, 1 H), 2.16 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.97-1.90 (m, 1 H), 1.90-1.82 (m, 1 H), 1.82-1.74 (m, 2 H), 1.73 (s, 3 H), 1.66-1.54 (m, 3 H), 1.51 (d, *J* = 12.5 Hz, 4 H), 1.45-1.26 (m, 6 H), 1.23-1.15 (m, 2 H), 1.13 (s, 3 H), 1.10 (d, *J* = 13.4 Hz, 2 H), 1.06 (s, 3 H), 1.04 (s, 3 H), 0.97 (s, 3 H), 0.95 (s, 3 H).

Procedimiento general para la formación de

urea C-17:



Etapa 1: Procedimiento general para la preparación de metilésteres de urea C-17.

A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocianato-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo en THF (aproximadamente 0.1 M) se agregaron la base de Hunig (3-9 equiv.) y la amina (3 equiv.). La mezcla se agitó a temperatura ambiente durante 2-72 h. La mezcla de reacción se concentró y se volvió a disolver en una mezcla de THF y metanol, y con frecuencia se agregaron un par de gotas de agua. La mezcla se filtró y se purificó mediante HPLC preparativa de fase inversa.

Etapa 2: Procedimientos generales para la hidrólisis del éster benzoico con NaOH o $LiOH \cdot H_2O$.

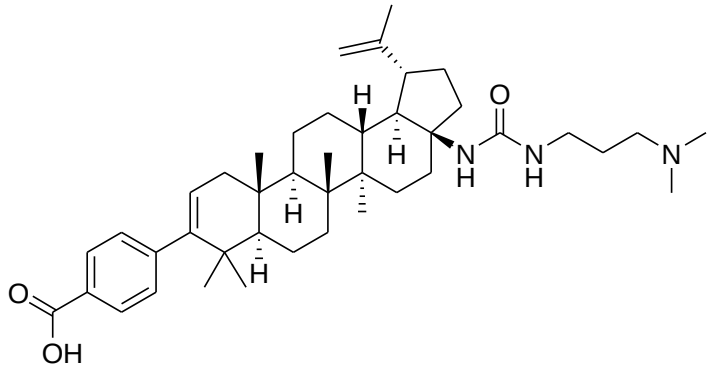
La urea C-17 formada en la Etapa 1 anterior se disolvió en 1,4-dioxano o THF para obtener aproximadamente una solución 0.1 M. Se agregó NaOH 1N acuoso (4 equiv.) a la mezcla y se calentó a 50-85 °C. Después de calentar durante 2-48 h, la mezcla se enfrió a temperatura ambiente. La mezcla cruda se purificó mediante HPLC preparativa de fase inversa.

Alternativamente, la hidrólisis del éster se puede realizar de la siguiente manera: La urea C-17 formada en la Etapa 1 anterior se disolvió en 1,4-dioxano o THF para obtener aproximadamente una solución 0.1 M. A la solución se agregó agua (relación 4:1 o 5:1 1,4-dioxano orgánico o THF: agua) y luego $LiOH \cdot H_2O$ (5-12 equiv.). La mezcla se calentó a 50-85 °C. Después del calentamiento durante un mínimo de 60 segundos hasta un máximo de 24 h, la mezcla se enfrió a temperatura ambiente. La mezcla cruda se purificó mediante HPLC preparativa de fase inversa.

Ejemplo 10

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(3-(dimetilamino)propil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-

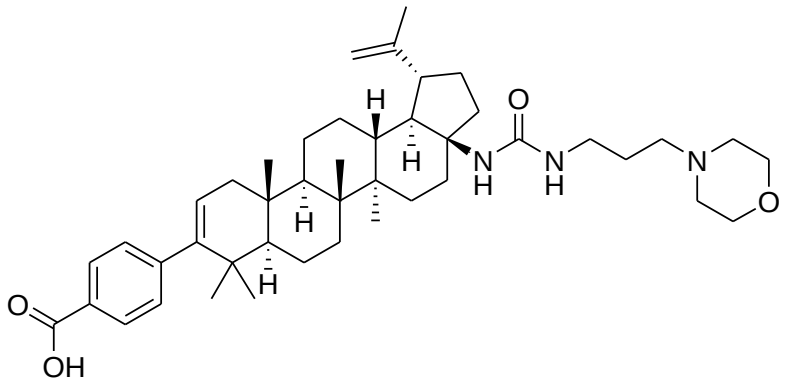
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando *N1*,*N1*-dimetilpropan-1,3-diamina como la amina reactiva. El producto salino de mono-TFA se aisló mediante purificación por HPLC preparativa de fase inversa como un sólido blanco (60 mg, 32.7 % de rendimiento). LCMS: m/z 658 ($M+H^+$), tiempo de retención 1.86 min (método 2). ^{1}H NMR (500 MHz, *MeOD*) δ ppm 0.97 (s, 3 H), 0.99 (s, 3 H), 1.07 (s, 6 H), 1.11-1.13 (m, 1 H), 1.15 (s, 3 H), 1.17-1.22 (m, 1 H), 1.28-1.48 (m, 5 H), 1.48-1.64 (m, 6 H), 1.64-1.83 (m, 7 H), 1.83-2.01 (m, 4 H), 2.18 (dd, *J*= 17.09, 6.41 Hz, 1 H), 2.37 (dd, *J*= 12.21, 8.24 Hz, 1 H), 2.58-2.68 (m, 2 H), 2.90 (s, 6 H), 3.13 (td, *J*= 7.02, 1.83 Hz, 2 H), 3.25 (td, *J*= 6.49, 0.76 Hz, 1 H), 4.66 (s, 1 H), 4.78 (d, *J*= 1.53 Hz, 1 H), 5.33 (dd, *J*= 6.10, 1.22 Hz, 1 H), 7.25 (m, *J*= 8.24 Hz, 2 H), 7.95 (m, *J*= 8.24 Hz, 2 H).

Ejemplo 11

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(3-(3-morfolinopropil)ureido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

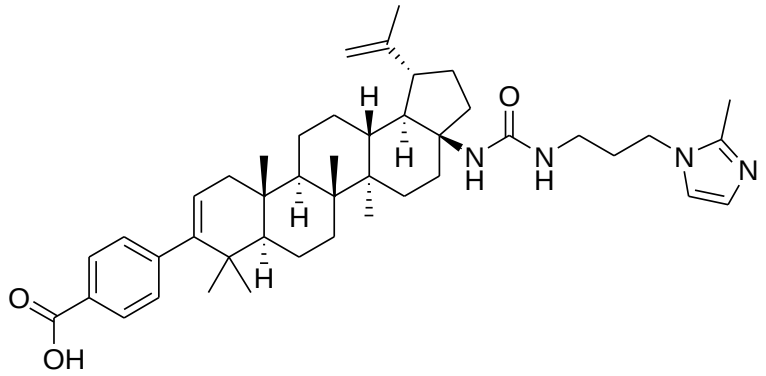


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando 3-morfolinopropan-1-amina como la amina reactiva. El producto salino de mono-TFA se aisló mediante purificación por HPLC preparativa de fase inversa como un sólido blanco (85 mg, 43 % de rendimiento). LCMS: m/z 700 ($M+H^+$), tiempo de retención 1.89 min (método 2). ^{1}H NMR (500 MHz, *MeOD*) δ ppm 0.97 (s, 3 H), 0.99 (s, 3 H), 1.07 (s, 6 H), 1.11-1.13 (m, 1 H), 1.15 (s, 3 H), 1.17-1.21 (m, 1 H), 1.28-1.47 (m, 5 H), 1.50-1.63 (m, 6 H), 1.64-1.72 (m, 1 H), 1.74 (br. s., 1 H), 1.75 (s, 3 H), 1.76-1.83 (m, 2 H), 1.87 (td, *J*= 12.21, 3.36 Hz, 1 H), 1.91-1.99 (m, 3 H), 2.18 (dd, *J*= 17.09, 6.41 Hz, 1

H), 2.35 (dd, *J*= 12.05, 8.09 Hz, 1 H), 2.58-2.67 (m, 2 H), 3.11-3.20 (m, 4 H), 3.25-3.31 (m, 2 H), 3.45 (t, *J*= 12.97 Hz, 2 H), 3.81 (t, *J*= 12.51 Hz, 2 H), 4.11 (d, *J*= 12.82 Hz, 2 H), 4.66 (s, 1 H), 4.78 (s, 1 H), 5.33 (dd, *J*= 6.10, 1.83 Hz, 1 H), 7.24 (m, *J*= 8.55 Hz, 2 H), 7.95 (m, *J*= 8.55 Hz, 2 H).

Ejemplo 12

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(3-(3-(2-metil-1H-imidazol-1-il)propil)ureido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

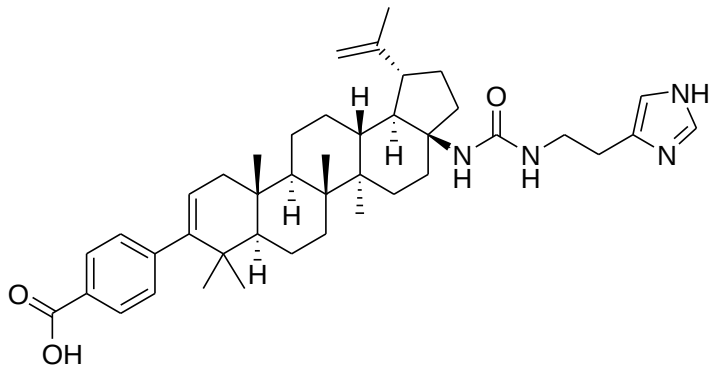


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando diclorhidrato de 3-(2-metil-1H-imidazol-1-il)propan-1-amina como la amina reactiva. El producto salino de mono-TFA se aisló mediante purificación por HPLC preparativa de fase inversa como un sólido blanco (40 mg, 21 % de rendimiento).

LCMS: m/z 709 ($M+H^+$), tiempo de retención 1.83 min (método 2). ^{1}H NMR (500 MHz, *MeOD*) δ ppm 0.97 (s, 3 H), 0.99 (s, 3 H), 1.07 (s, 6 H), 1.12 (d, *J*= 13.43 Hz, 1 H), 1.15 (s, 3 H), 1.17-1.22 (m, 1 H), 1.27-1.46 (m, 5 H), 1.47-1.64 (m, 6 H), 1.66-1.82 (m, 7 H), 1.83-1.98 (m, 2 H), 2.04 (quin, *J*= 6.94 Hz, 2 H), 2.18 (dd, *J*= 17.09, 6.41 Hz, 1 H), 2.38 (dd, *J*= 12.36, 8.09 Hz, 1 H), 2.58-2.65 (m, 2 H), 2.66 (s, 3 H), 3.18 (t, *J*= 6.71 Hz, 2 H), 4.18 (t, *J*= 7.17 Hz, 2 H), 4.66 (s, 1 H), 4.78 (d, *J*= 1.83 Hz, 1 H), 5.33 (dd, *J*= 6.26, 1.68 Hz, 1 H), 7.24 (m, *J*= 8.55 Hz, 2 H), 7.47 (d, *J*= 1.83 Hz, 1 H), 7.59 (d, *J*= 2.14 Hz, 1 H), 7.95 (m, *J*= 8.24 Hz, 2 H).

Ejemplo 13

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(1H-imidazol-4-il)etil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



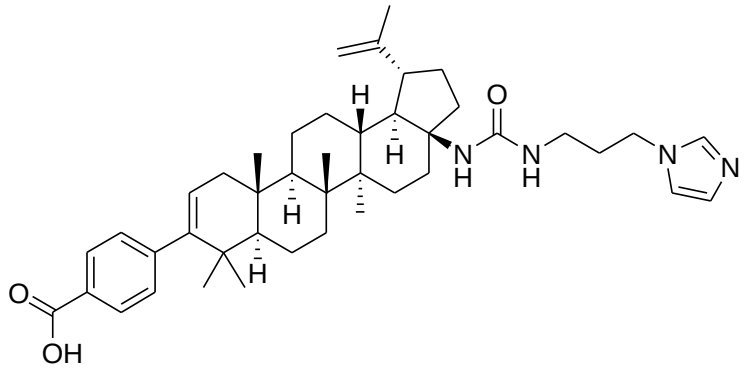
El compuesto del título se preparó de acuerdo

con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando histamina como la amina reactiva. El producto salino de mono-TFA se aisló mediante purificación por HPLC preparativa de fase inversa como un sólido blanco (23 mg, 11 % de rendimiento). LCMS: m/z 667 ($M+H^+$), tiempo de retención 1.79 min (método 2). ^1H NMR (500 MHz, *MeOD*) δ ppm 0.97 (s, 3 H), 0.99 (s, 3 H), 1.05 (s, 3 H), 1.06 (s, 3 H), 1.07-1.11 (m, 1 H), 1.12 (s, 3 H), 1.13-1.20 (m, 1 H), 1.26-1.45 (m, 5 H), 1.49-1.68 (m, 7 H), 1.71 (d, *J*= 11.60 Hz, 1 H), 1.74 (s, 3 H), 1.75-1.94 (m, 4 H), 2.17 (dd, *J*= 17.09, 6.41 Hz, 1 H), 2.31 (dd, *J*= 12.36, 8.09 Hz, 1 H), 2.54-2.64 (m, 2 H), 2.90 (t, *J*= 6.71 Hz, 2 H), 3.45 (t, *J*= 6.87 Hz, 2 H), 4.65 (s, 1 H), 4.76 (d, *J*= 1.83 Hz, 1 H), 5.33 (dd, *J*= 6.10, 1.83 Hz, 1 H), 7.24 (d, *J*= 8.24 Hz, 2 H), 7.34 (s, 1 H), 7.94 (d, *J*= 8.24 Hz, 2 H), 8.84 (d, *J*= 1.22 Hz, 1 H).

Ejemplo 14

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(3-(1H-imidazol-1-il)propil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

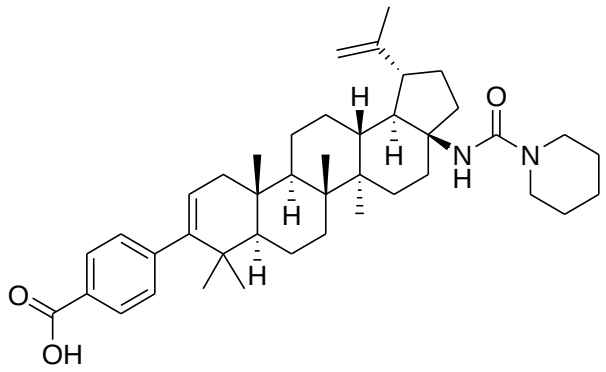
octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando 3-(1H-imidazol-1-il)propan-1-amina como la amina reactiva. El producto salino de mono-TFA se aisló mediante purificación por HPLC preparativa de fase inversa como un sólido blanco (109 mg, 53 % de rendimiento). LCMS: m/z 681 ($M+H^+$), tiempo de retención 1.82 min (método 2). ^{1}H NMR (500 MHz, *MeOD*) δ ppm 0.97 (s, 3 H), 0.99 (s, 3 H), 1.06 (s, 6 H), 1.09-1.14 (m, 1 H), 1.15 (s, 3 H), 1.17-1.21 (m, 1 H), 1.27-1.46 (m, 5 H), 1.47-1.63 (m, 6 H), 1.64-1.73 (m, 2 H), 1.75 (s, 3 H), 1.76-1.82 (m, 2 H), 1.83-2.00 (m, 2 H), 2.07 (qd, *J*= 7.07, 6.87 Hz, 2 H), 2.18 (dd, *J*= 17.09, 6.41 Hz, 1 H), 2.39 (dd, *J*= 12.36, 8.09 Hz, 1 H), 2.58-2.68 (m, 2 H), 3.11-3.23 (m, 2 H), 4.31 (t, *J*= 6.87 Hz, 2 H), 4.66 (s, 1 H), 4.78 (d, *J*= 1.83 Hz, 1 H), 5.33 (dd, *J*= 6.10, 1.83 Hz, 1 H), 7.24 (m, *J*= 8.54 Hz, 2 H), 7.60 (t, *J*= 1.53 Hz, 1 H), 7.71 (t, *J*= 1.68 Hz, 1 H), 7.94 (m, *J*= 8.54 Hz, 2 H), 9.00 (s, 1 H).

Ejemplo 15

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(piperidin-1-carboxamido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

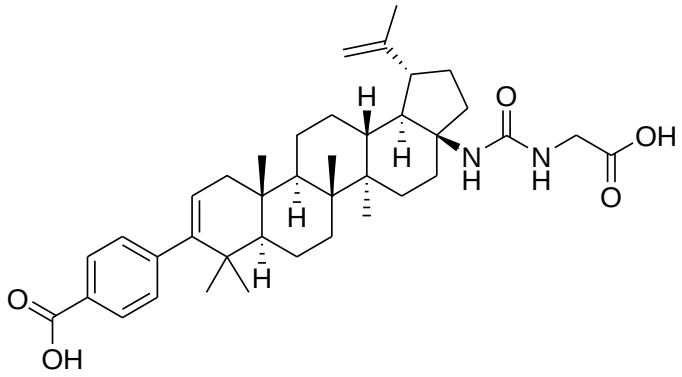


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando piperidina como la amina reactiva. El producto se aisló después de la purificación por HPLC preparativa de fase inversa como un sólido blanco (10 mg, 6 % de rendimiento). LCMS: m/z 641 ($M+H^+$), tiempo de retención 2.67 min (método 2). ^{1}H NMR (500 MHz, *MeOD*) δ ppm 0.97 (s, 3 H), 0.99 (s, 3 H), 1.07 (s, 3 H), 1.08 (s, 3 H), 1.12 (dt, *J*= 13.81, 3.17 Hz, 1 H), 1.16 (s, 3 H), 1.17-1.22 (m, 1 H), 1.28-1.47 (m, 5 H), 1.48-1.65 (m, 11 H), 1.65-1.70 (m, 2 H), 1.71-1.90 (m, 7 H), 1.91-2.02 (m, 1 H), 2.14-2.21 (m, 1 H), 2.49 (dd, *J*= 12.36, 8.09 Hz, 1 H), 2.59-2.71 (m, 2 H), 3.35-3.48 (m, 4 H),

4.63-4.67 (m, 1 H), 4.80 (d, *J*= 1.83 Hz, 1 H), 5.33 (dd, *J*= 6.10, 1.83 Hz, 1 H), 7.25 (m, *J*= 8.24 Hz, 2 H), 7.94 (m, *J*= 8.24 Hz, 2 H).

Ejemplo 16

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(carboximetil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

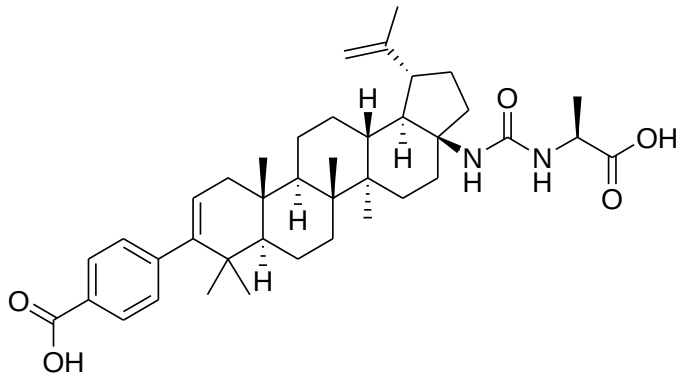


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando clorhidrato de metiléster de glicina como la amina reactiva. El producto se aisló después de la purificación por HPLC preparativa de fase inversa como un sólido blanco (59 mg, 45 % de rendimiento). LCMS: m/z 631 ($M+H^+$), tiempo de retención 2.17 min (método 2). 1H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.94 (s, 3 H), 0.95 (s, 3 H), 1.02 (s, 6 H), 1.04-1.11 (m, 2 H), 1.12 (s, 3 H),

1.23-1.41 (m, 5 H), 1.42-1.61 (m, 6 H), 1.65 (t, *J*= 11.60 Hz, 1 H), 1.68-1.79 (m, 6 H), 1.85 (td, *J*= 12.21, 3.36 Hz, 1 H), 1.92-2.05 (m, 1 H), 2.13 (dd, *J*= 17.09, 6.41 Hz, 1 H), 2.36 (dd, *J*= 12.36, 8.09 Hz, 1 H), 2.55-2.66 (m, 2 H), 3.80-3.95 (m, 2 H), 4.58-4.64 (m, 1 H), 4.74 (d, *J*= 1.83 Hz, 2 H), 5.29 (dd, *J*= 6.26, 1.68 Hz, 1 H), 7.19-7.23 (m, 2 H), 7.91-7.95 (m, 2 H).

Ejemplo 17

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-((S)-1-carboxietil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

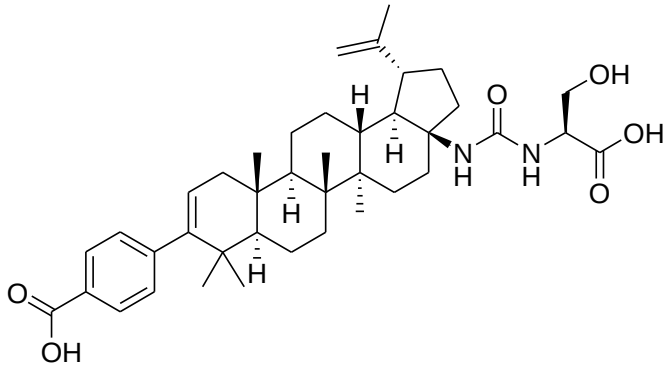


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando clorhidrato de metiléster de L-alanina como la amina reactiva. El producto se aisló después de la purificación por HPLC preparativa de fase inversa como un sólido blanco (74

mg, 54 % de rendimiento). LCMS: m/z 645 ($M+H^+$), tiempo de retención 2.26 min (método 2). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.93 (br. s., 3 H), 0.94 (br. s., 3 H), 0.99 (s, 6 H), 1.02-1.09 (m, 2 H), 1.10 (s, 3 H), 1.19-1.35 (m, 5 H), 1.37 (d, *J*= 7.32 Hz, 3 H), 1.39-1.57 (m, 6 H), 1.63 (t, *J*= 11.60 Hz, 1 H), 1.66-1.76 (m, 6 H), 1.76-1.85 (m, 1 H), 1.88-1.99 (m, 1 H), 2.11 (dd, *J*= 17.09, 6.41 Hz, 1 H), 2.35 (dd, *J*= 12.36, 8.09 Hz, 1 H), 2.50-2.61 (m, 2 H), 4.28 (q, *J*= 7.02 Hz, 1 H), 4.61 (br. s., 1 H), 4.72 (br. s., 1 H), 5.26-5.31 (m, 1 H), 7.20 (d, *J*= 8.24 Hz, 2 H), 7.92 (d, *J*= 8.55 Hz, 2 H).

Ejemplo 18

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-((S)-1-carboxi-2-hidroxietil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



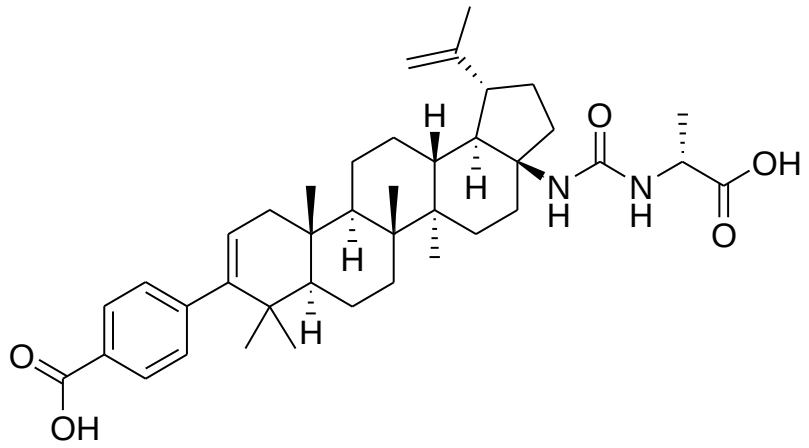
El compuesto del título se preparó de acuerdo con

los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando clorhidrato de metiléster de L-serina como la amina reactiva. El producto se aisló después de la purificación por HPLC preparativa de fase inversa como un sólido blanco (70 mg, 48 % de rendimiento). LCMS: m/z 661 ($M+H^+$), tiempo de retención 2.19 min (método 2). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.93 (br. s., 3 H), 0.93 (s, 3 H), 0.99 (br. s., 3 H), 1.00 (s, 3 H), 1.03-1.09 (m, 2 H), 1.11 (s, 3 H), 1.21-1.41 (m, 5 H), 1.41-1.57 (m, 6 H), 1.64 (t, *J*= 11.60 Hz, 1 H), 1.67-1.77 (m, 6 H), 1.84 (td, *J*= 12.21, 3.36 Hz, 1 H), 1.88-1.99 (m, 1 H), 2.11 (dd, *J*= 17.09, 6.41 Hz, 1 H), 2.35 (dd, *J*= 12.21, 8.24 Hz, 1 H), 2.54-2.63 (m, 2 H), 3.80 (dd, *J*= 10.99, 3.66 Hz, 1 H), 3.93 (dd, *J*= 10.99, 4.27 Hz, 1 H), 4.37 (t, *J*= 3.97 Hz, 1 H), 4.61 (br. s., 1 H), 4.72 (d, *J*= 1.53 Hz, 1 H), 5.28 (dd, *J*= 6.26, 1.68 Hz, 1 H), 7.20 (m, *J*= 8.54 Hz, 2 H), 7.92 (m, *J*= 8.24 Hz, 2 H).

Ejemplo 19

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-((R)-1-carboxietil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

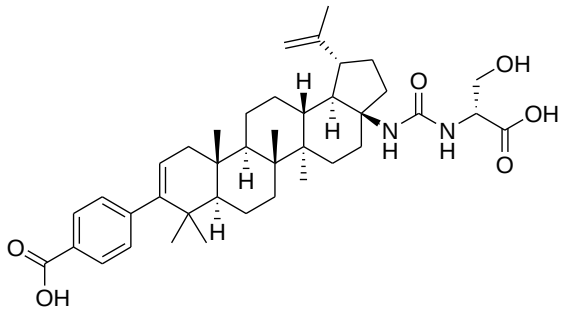
octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando clorhidrato de metiléster de *D*-alanina como la amina reactiva. El producto se aisló después de la purificación por HPLC preparativa de fase inversa como un sólido blanco (68 mg, 50 % de rendimiento). LCMS: m/z 645 ($M+H^+$), tiempo de retención 2.23 min (método 2). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.93 (br. s., 3 H), 0.94 (br. s., 3 H), 1.00 (s, 6 H), 1.03-1.14 (m, 5 H), 1.20-1.36 (m, 5 H), 1.37 (d, *J*= 7.02 Hz, 3 H), 1.40-1.58 (m, 6 H), 1.58-1.68 (m, 2 H), 1.68-1.75 (m, 5 H), 1.75-1.83 (m, 1 H), 1.92-2.03 (m, 1 H), 2.11 (dd, *J*= 17.09, 6.41 Hz, 1 H), 2.34 (dd, *J*= 12.21, 8.24 Hz, 1 H), 2.51-2.60 (m, 2 H), 4.27 (q, *J*= 7.32 Hz, 1 H), 4.60 (br. s., 2 H), 4.72 (d, *J*= 1.53 Hz, 1 H), 5.28 (dd, *J*= 6.10, 1.53 Hz, 1 H), 7.20 (m, *J*= 8.55 Hz, 2 H), 7.92 (m, *J*= 8.24 Hz, 2 H).

Ejemplo 20

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-((R)-1-carboxi-2-hidroxietil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

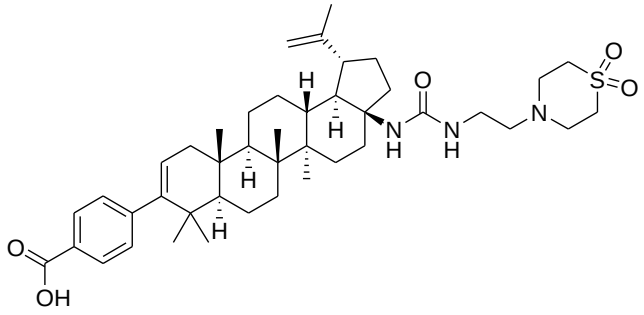


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando clorhidrato de metiléster de *D*-serina como la amina reactiva. El producto se aisló después de la purificación por HPLC preparativa de fase inversa como un sólido blanco (51 mg, 34 % de rendimiento). LCMS: m/z 661 ($M+H^+$), tiempo de retención 2.11 min (método 2). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.92 (br. s., 6 H), 0.98 (br. s., 6 H), 1.02-1.14 (m, 5 H), 1.17-1.38 (m, 5 H), 1.39-1.58 (m, 6 H), 1.58-1.75 (m, 7 H), 1.76-1.86 (m, 1 H), 1.90-2.04 (m, 1 H), 2.04-2.13 (m, 1 H), 2.36 (t, *J*= 9.77 Hz, 1 H), 2.56 (d, *J*= 12.51 Hz, 2 H), 3.81 (d, *J*= 10.99 Hz, 1 H),

3.94 (d, *J*= 10.99 Hz, 1 H), 4.35 (d, *J*= 2.44 Hz, 1 H), 4.60 (br. s., 1 H), 4.71 (br. s., 1 H), 5.28 (br. s., 1 H), 7.19 (m, *J*= 7.32 Hz, 2 H), 7.92 (m, *J*= 7.63 Hz, 2 H).

Ejemplo 21

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((2-(1,1-dioxido-4-tiomorfolinil)etil)carbamoil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

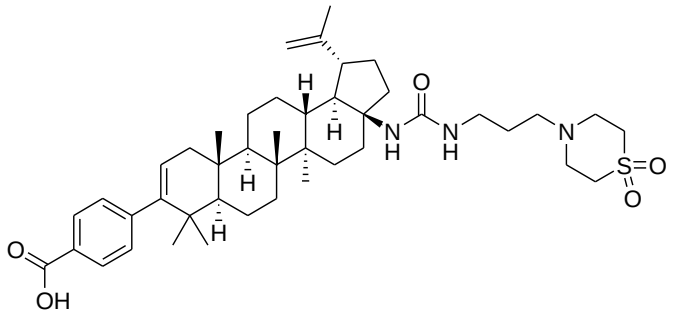


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando 1,1-dióxido de 4-(2-aminoetil)tiomorfolina como la amina reactiva. El producto salino de mono-TFA se aisló mediante purificación por HPLC preparativa de fase inversa como un sólido blanco (121 mg, 74 % de rendimiento). LCMS: m/z 734 ($M+H^+$), tiempo de retención 2.49 min (método 11). ^1H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.94 (s, 3 H), 0.95 (s, 3 H), 1.02 (br. s., 3 H),

1.03 (br. s., 3 H), 1.10 (s, 3 H), 1.11-1.17 (m, 2 H), 1.21-1.60 (m, 11 H), 1.63-1.82 (m, 8 H), 1.86-2.00 (m, 1 H), 2.13 (dd, *J*= 17.24, 6.26 Hz, 1 H), 2.35 (dd, *J*= 12.05, 8.39 Hz, 1 H), 2.52-2.63 (m, 2 H), 3.20 (br. s., 2 H), 3.39-3.52 (m, 6 H), 3.69 (br. s., 4 H), 4.63 (s, 1 H), 4.75 (d, *J*= 1.22 Hz, 1 H), 5.29 (d, *J*= 4.58 Hz, 1 H), 7.21 (m, *J*= 8.24 Hz, 2 H), 7.93 (m, *J*= 8.24 Hz, 2 H).

Ejemplo 22

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((3-(1,1-dioxido-4-tiomorfolinil)propil)carbamoil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

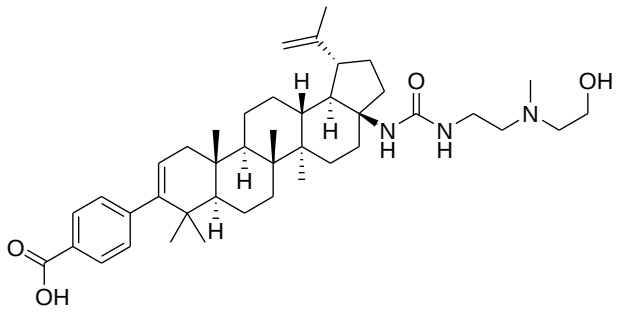


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando 1,1-dióxido de 4-(3-aminopropil)tiomorfolina como la amina reactiva. El producto salino de mono-TFA se aisló mediante purificación por HPLC preparativa de fase inversa

como un sólido blanco (115 mg, 59 % de rendimiento). LCMS: m/z 748 ($M+H^+$), tiempo de retención 2.44 min (método 11). 1H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.95 (s, 3 H), 0.96 (s, 3 H), 1.02 (br. s., 3 H), 1.03 (br. s., 3 H), 1.11 (s, 3 H), 1.12-1.18 (m, 2 H), 1.24-1.44 (m, 5 H), 1.44-1.60 (m, 6 H), 1.63-1.80 (m, 8 H), 1.85-1.99 (m, 3 H), 2.14 (dd, *J*= 17.09, 6.41 Hz, 1 H), 2.32 (dd, *J*= 12.05, 8.09 Hz, 1 H), 2.52-2.63 (m, 2 H), 3.14 (t, *J*= 7.02 Hz, 2 H), 3.19-3.30 (m, 2 H), 3.50 (d, *J*= 4.58 Hz, 4 H), 3.65 (d, *J*= 5.19 Hz, 4 H), 4.63 (s, 1 H), 4.75 (s, 1 H), 5.27-5.32 (m, 1 H), 7.21 (m, *J*= 8.24 Hz, 2 H), 7.93 (m, *J*= 8.24 Hz, 2 H).

Ejemplo 23

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-((2-hidroxietil)(metil)amino)etil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



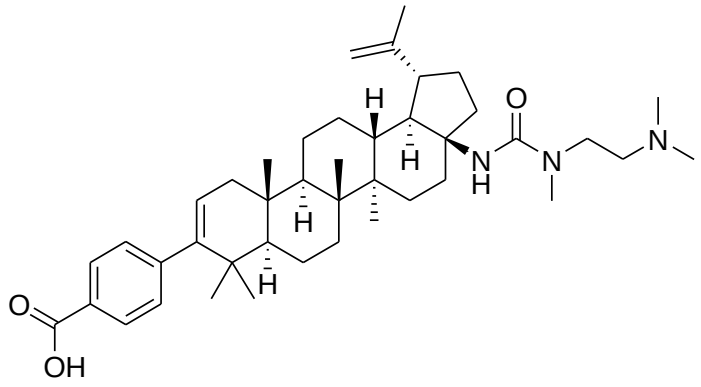
El compuesto del título se preparó de acuerdo

con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando 2-((2-aminoetil)(metil)amino)etanol como la amina reactiva. El producto salino de mono-TFA se aisló mediante purificación por HPLC preparativa de fase inversa como un sólido blanco (43 mg, 69 % de rendimiento). LCMS: m/z 674 ($M+H^+$), tiempo de retención 2.41 min (método 11). ^1H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.93 (br. s., 3 H), 0.94 (br. s., 3 H), 1.00 (br. s., 3 H), 1.00 (br. s., 3 H), 1.08 (s, 3 H), 1.08-1.15 (m, 2 H), 1.22-1.39 (m, 5 H), 1.40-1.56 (m, 6 H), 1.59-1.79 (m, 8 H), 1.85-1.99 (m, 1 H), 2.11 (dd, *J*= 17.09, 6.41 Hz, 1 H), 2.35 (br. s., 1 H), 2.48-2.61 (m, 2 H), 2.96 (s, 3 H), 3.09-3.61 (m, 6 H), 3.87 (t, *J*= 5.19 Hz, 2 H), 4.61 (br. s., 1 H), 4.73 (br. s., 1 H), 5.24-5.31 (m, 1 H), 7.20 (d, *J*= 8.24 Hz, 2 H), 7.92 (d, *J*= 8.24 Hz, 2 H).

Ejemplo 24

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimetilamino)etil)-3-metilureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-

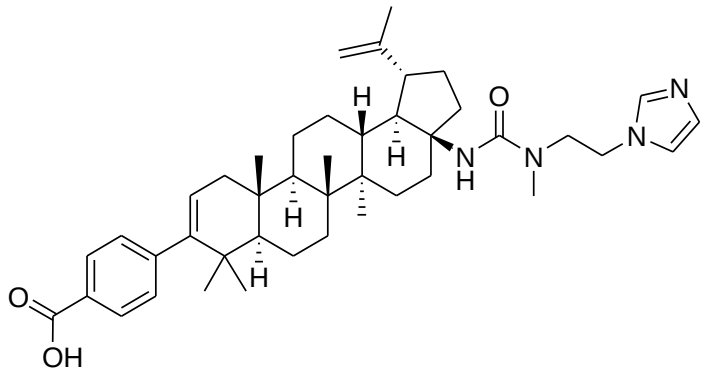
il)benzoico.



El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando *N1,N1,N2*-trimetiletan-1,2-diamina como la amina reactiva. El producto salino de mono-TFA se aisló mediante purificación por HPLC preparativa de fase inversa como un sólido blanco (34 mg, 57 % de rendimiento). LCMS: m/z 658 ($M+H^+$), tiempo de retención 2.41 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.93 (br. s., 3 H), 0.94 (br. s., 3 H), 1.00 (s, 3 H), 1.03 (s, 3 H), 1.10 (s, 3 H), 1.10-1.20 (m, 2 H), 1.20-1.28 (m, 1 H), 1.31-1.42 (m, 4 H), 1.44-1.58 (m, 7 H), 1.62-1.80 (m, 7 H), 1.88-2.01 (m, 1 H), 2.12 (dd, *J*= 17.09, 6.10 Hz, 1 H), 2.41-2.56 (m, 3 H), 2.92 (s, 6 H), 3.03 (s, 3 H), 3.18-3.31 (m, 2 H), 3.51 (ddd, *J*= 15.11, 5.95, 5.80 Hz, 1 H), 3.73-3.83 (m, 1 H), 4.54 (s, 1 H), 4.64 (br. s., 1 H), 4.75 (s, 1 H), 5.25-5.31 (m, 1 H), 7.20 (d, *J*= 8.24 Hz, 2 H), 7.92 (d, *J*= 8.24 Hz, 2 H).

Ejemplo 25

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(1H-imidazol-1-il)etil)-3-metilureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

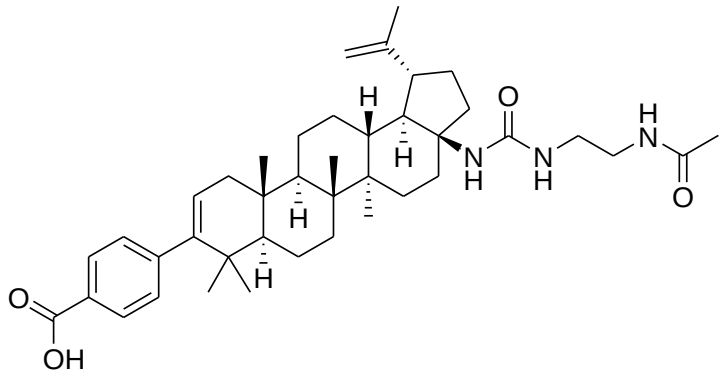


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando 2-(1H-imidazol-1-il)-N-metiletanamina, 2 HCl como la amina reactiva. El producto salino de mono-TFA se aisló mediante purificación por HPLC preparativa de fase inversa como un sólido blanco (35 mg, 56 % de rendimiento). LCMS: m/z 681 ($M+H^+$), tiempo de retención 2.39 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3 y MeOD*, estabilización *MeOD*) δ ppm 0.94 (br. s., 3 H), 0.94 (br. s., 3 H), 1.00 (s, 3 H), 1.02 (s, 3 H), 1.09 (s, 3 H), 1.09-1.19 (m, 2 H), 1.23-1.42 (m, 5 H), 1.43-1.54 (m, 6 H), 1.54-1.60 (m, 1 H), 1.61-1.76

(m, 7 H), 1.80-1.94 (m, 1 H), 2.12 (dd, *J*= 17.24, 6.26 Hz, 1 H), 2.29 (dd, *J*= 12.67, 8.09 Hz, 1 H), 2.35-2.51 (m, 2 H), 3.01 (s, 3 H), 3.65 (dt, *J*= 14.57, 5.84 Hz, 1 H), 3.79-3.89 (m, 1 H), 4.33-4.43 (m, 2 H), 4.64 (br. s., 1 H), 4.74 (br. s., 1 H), 5.25-5.31 (m, 1 H), 7.20 (d, *J*= 8.55 Hz, 2 H), 7.41 (t, *J*= 1.53 Hz, 1 H), 7.51 (t, *J*= 1.68 Hz, 1 H), 7.92 (d, *J*= 8.24 Hz, 2 H), 8.88 (d, *J*= 1.22 Hz, 1 H).

Ejemplo 26

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-acetamidoetil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

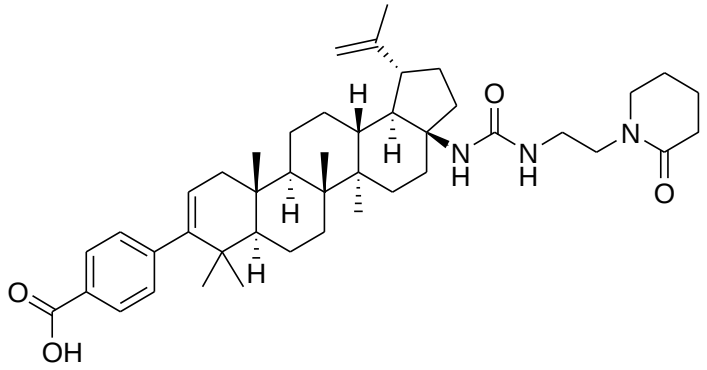


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando *N*-(2-aminoetil)acetamida como la amina reactiva. El producto se aisló después de la purificación por HPLC preparativa de fase inversa como un sólido blanco (24 mg, 48

% de rendimiento). LCMS: m/z 658 ($M+H^+$), tiempo de retención 2.73 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.93 (br. s., 3 H), 0.94 (br. s., 3 H), 1.00 (br. s., 3 H), 1.00 (br. s., 3 H), 1.04-1.15 (m, 5 H), 1.21-1.41 (m, 6 H), 1.41-1.58 (m, 6 H), 1.58-1.67 (m, 2 H), 1.70 (s, 3 H), 1.70-1.82 (m, 3 H), 1.86-1.94 (m, 1 H), 1.96 (s, 3 H), 2.11 (dd, *J*= 17.40, 6.41 Hz, 1 H), 2.34 (dd, *J*= 12.05, 8.09 Hz, 1 H), 2.49-2.61 (m, 2 H), 3.19-3.27 (m, 4 H), 4.61 (br. s., 1 H), 4.72 (s, 1 H), 5.25-5.31 (m, 1 H), 7.20 (d, *J*= 8.55 Hz, 2 H), 7.92 (d, *J*= 8.24 Hz, 2 H).

Ejemplo 27

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(3-(2-(2-oxopiperidin-1-il)etil)ureido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



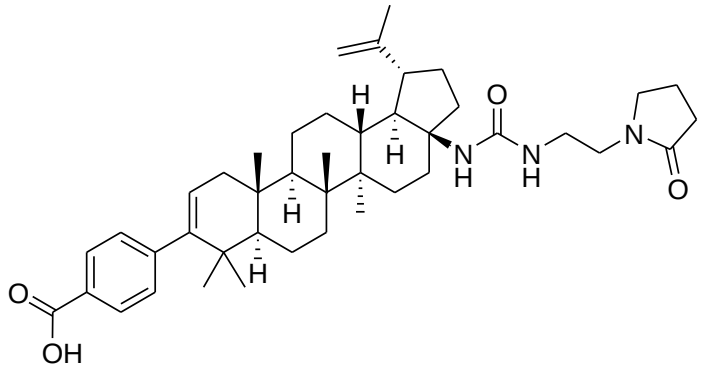
El compuesto del título se preparó de acuerdo

con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando bromhidrato de 1-(2-aminoetil)piperidin-2-ona como la amina reactiva. El producto se aisló después de la purificación por HPLC preparativa de fase inversa como un sólido blanco (37 mg, 68 % de rendimiento). LCMS: m/z 698 ($M+H^+$), tiempo de retención 2.83 min (método 11). ^1H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.93 (br. s., 3 H), 0.94 (br. s., 3 H), 1.00 (s, 6 H), 1.04-1.14 (m, 5 H), 1.21-1.41 (m, 5 H), 1.41-1.58 (m, 6 H), 1.58-1.67 (m, 2 H), 1.70 (s, 3 H), 1.70-1.85 (m, 7 H), 1.86-1.97 (m, 1 H), 2.11 (dd, *J*= 17.09, 6.10 Hz, 1 H), 2.29-2.39 (m, 3 H), 2.50-2.61 (m, 2 H), 3.30-3.32 (m, 1 H), 3.40 (t, *J*= 5.34 Hz, 2 H), 3.45 (t, *J*= 5.95 Hz, 2 H), 4.61 (br. s., 1 H), 4.72 (br. s., 1 H), 5.25-5.31 (m, 1 H), 7.20 (d, *J*= 8.24 Hz, 2 H), 7.92 (d, *J*= 8.24 Hz, 2 H).

Ejemplo 28

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(3-(2-(2-oxopirrolidin-1-il)etil)ureido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b

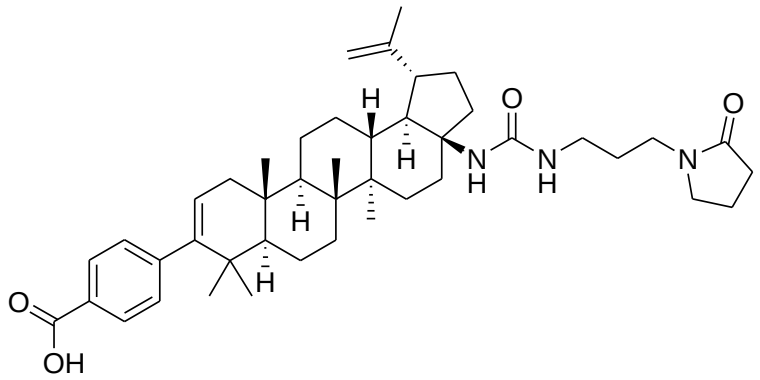
-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando sal del ácido 1-(2-aminoetil)pirrolidin-2-ona oxálico como la amina reactiva. El producto se aisló después de la purificación por HPLC preparativa de fase inversa como un sólido blanco (37 mg, 67 % de rendimiento). LCMS: m/z 684 ($M+H^+$), tiempo de retención 2.78 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.93 (s, 3 H), 0.94 (s, 3 H), 1.00 (s, 6 H), 1.04-1.15 (m, 5 H), 1.21-1.41 (m, 6 H), 1.41-1.59 (m, 6 H), 1.59-1.67 (m, 2 H), 1.67-1.81 (m, 6 H), 1.86-1.97 (m, 1 H), 2.00-2.08 (m, 2 H), 2.11 (dd, *J*= 17.09, 6.41 Hz, 1 H), 2.33 (dd, *J*= 12.36, 8.09 Hz, 1 H), 2.38 (t, *J*= 8.09 Hz, 2 H), 2.50-2.60 (m, 2 H), 3.28-3.32 (m, 2 H), 3.53 (t, *J*= 7.32 Hz, 2 H), 4.61 (s, 1 H), 4.72 (d, *J*= 1.53 Hz, 1 H), 5.28 (dd, *J*= 5.95, 1.68 Hz, 1 H), 7.20 (m, *J*= 8.54 Hz, 2 H), 7.92 (m, *J*= 8.24 Hz, 2 H).

Ejemplo 29

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(3-(3-(2-oxopirrolidin-1-il)propil)ureido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

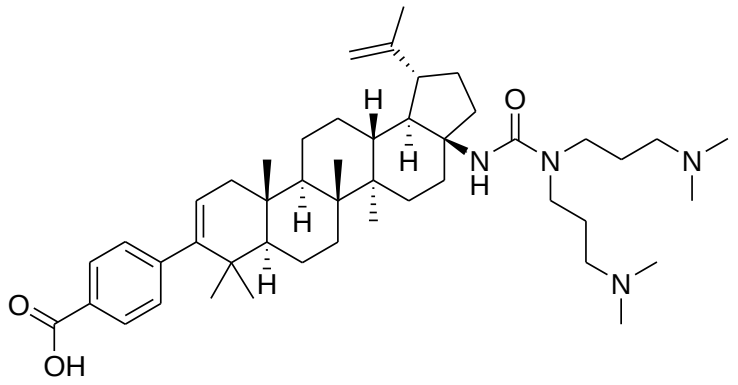


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando 1-(3-aminopropil)pirrolidin-2-ona como la amina reactiva. El producto se aisló después de la purificación por HPLC preparativa de fase inversa como un sólido blanco (38 mg, 69 % de rendimiento). LCMS: m/z 698 ($M+H^+$), tiempo de retención 2.79 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.93 (br. s., 3 H), 0.94 (br. s., 3 H), 1.00 (br. s., 3 H), 1.00 (s, 3 H), 1.04-1.16 (m, 5 H), 1.21-1.41 (m, 5 H), 1.41-1.59 (m, 6 H), 1.59-1.76 (m, 9 H), 1.80 (td, *J*= 12.21, 3.05 Hz, 1 H), 1.88-

2.00 (m, 1 H), 2.03-2.16 (m, 3 H), 2.36 (dd, *J*= 12.21, 8.24 Hz, 1 H), 2.42 (t, *J*= 8.09 Hz, 2 H), 2.51-2.64 (m, 2 H), 3.09 (t, *J*= 6.56 Hz, 2 H), 3.25-3.38 (m, 2 H), 3.47 (t, *J*= 7.17 Hz, 2 H), 4.61 (s, 1 H), 4.73 (d, *J*= 1.53 Hz, 1 H), 5.25-5.32 (m, 1 H), 7.20 (m, *J*= 8.24 Hz, 2 H), 7.92 (m, *J*= 8.24 Hz, 2 H).

Ejemplo 30

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3,3-bis(3-(dimetilamino)propil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

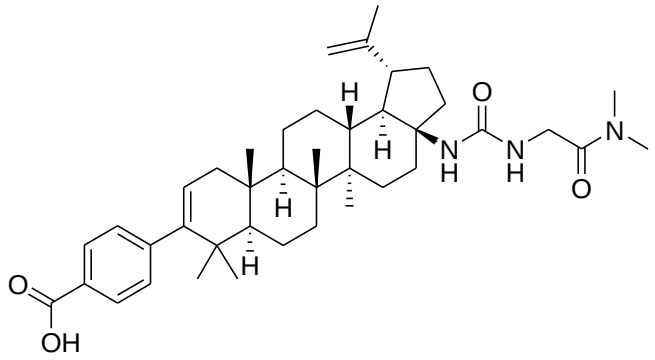


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando *N1*-(3-(dimetilamino)propil)-*N3*,*N3*-dimetilpropan-1,3-diamina como la amina reactiva. El producto salino de bis-TFA se aisló después de la purificación por HPLC preparativa de

fase inversa como un sólido blanco (15 mg, 20 % de rendimiento). LCMS: m/z 743 ($M+H^+$), tiempo de retención 2.27 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.94 (s, 3 H), 0.94 (s, 3 H), 1.00 (s, 3 H), 1.05 (s, 3 H), 1.09 (s, 3 H), 1.11-1.19 (m, 2 H), 1.26 (d, *J*= 6.71 Hz, 1 H), 1.30-1.44 (m, 3 H), 1.44-1.62 (m, 8 H), 1.63-1.81 (m, 7 H), 1.83-1.95 (m, 1 H), 2.02 (br. s., 4 H), 2.13 (dd, *J*= 17.09, 6.41 Hz, 1 H), 2.41 (dd, *J*= 12.51, 8.24 Hz, 1 H), 2.51 (td, *J*= 10.91, 5.04 Hz, 1 H), 2.59 (d, *J*= 13.43 Hz, 1 H), 2.89 (s, 12 H), 3.13 (t, *J*= 7.02 Hz, 4 H), 3.34-3.43 (m, 4 H), 4.76 (s, 1 H), 5.26-5.33 (m, 1 H), 7.20 (m, *J*= 8.55 Hz, 2 H), 7.92 (m, *J*= 8.24 Hz, 2 H).

Ejemplo 31

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimetilamino)-2-oxoetil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

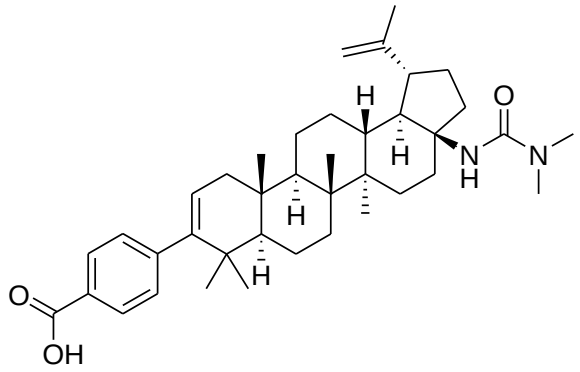


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando 2-amino-*N*,*N*-dimetilacetamida como la amina reactiva. El producto se aisló después de la purificación por HPLC preparativa de fase inversa como un sólido blanco (7 mg, 14 % de rendimiento). LCMS: m/z 658 ($M+H^+$), tiempo de retención 2.77 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.93 (s, 3 H), 0.94 (s, 3 H), 1.01 (s, 6 H), 1.05-1.16 (m, 5 H), 1.21-1.41 (m, 6 H), 1.41-1.57 (m, 6 H), 1.60-1.78 (m, 7 H), 1.84 (td, *J*= 12.28, 3.51 Hz, 1 H), 1.91-2.01 (m, 1 H), 2.12 (dd, *J*= 17.09, 6.41 Hz, 1 H), 2.36 (dd, *J*= 12.21, 7.93 Hz, 1 H), 2.55-2.64 (m, 2 H), 2.98 (s, 3 H), 3.03 (s, 3 H), 3.89-4.07 (m, 2 H), 4.61 (d, *J*= 1.22 Hz, 1 H), 4.73 (d, *J*= 1.83 Hz, 1 H), 5.29 (dd, *J*= 6.10, 1.83 Hz, 1 H), 7.20 (d, *J*= 8.54 Hz, 2 H), 7.92 (d, *J*= 8.24 Hz, 2 H).

Ejemplo 32

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3,3-dimetilureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

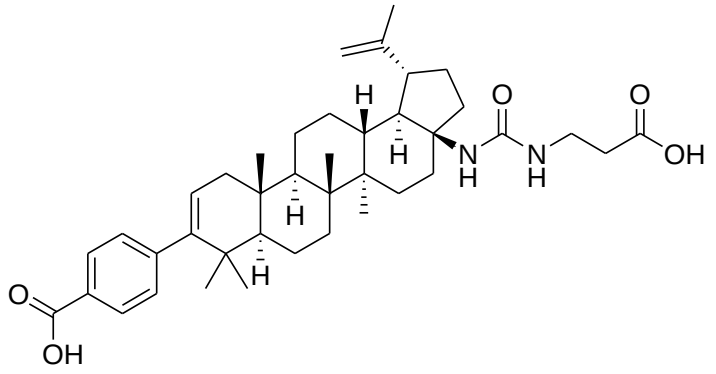


El compuesto del título se formó como un subproducto durante la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimetilamino)-2-oxoetil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico. La hidrólisis del penúltimo metiléster mediante el procedimiento general descrito y la purificación por HPLC preparativa de fase inversa produjo un sólido blanco (13 mg, 29 % de rendimiento). LCMS: m/z 601 ($M+H^+$), tiempo de retención 2.90 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.94 (s, 3 H), 0.94 (s, 3 H), 1.00 (s, 3 H), 1.03 (s, 3 H), 1.10 (s, 3 H), 1.11-1.19 (m, 2 H), 1.24-1.44 (m, 6 H), 1.45-1.60 (m, 7 H), 1.61-1.66 (m, 1 H), 1.69 (d, *J*= 5.49 Hz, 2 H), 1.71 (s, 3 H), 1.72-1.78 (m, 2 H), 1.91-2.01 (m, 1 H), 2.12 (dd, *J*= 17.09, 6.41 Hz, 1 H), 2.42-2.52 (m, 2 H), 2.56 (dt, *J*= 13.20, 3.32 Hz, 1 H), 2.95 (s, 6

H), 4.63 (d, *J*= 1.53 Hz, 1 H), 4.74 (d, *J*= 1.83 Hz, 1 H), 5.29 (dd, *J*= 6.26, 1.68 Hz, 1 H), 7.20 (m, *J*= 8.24 Hz, 2 H), 7.92 (m, *J*= 8.24 Hz, 2 H).

Ejemplo 33

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-carboxietil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

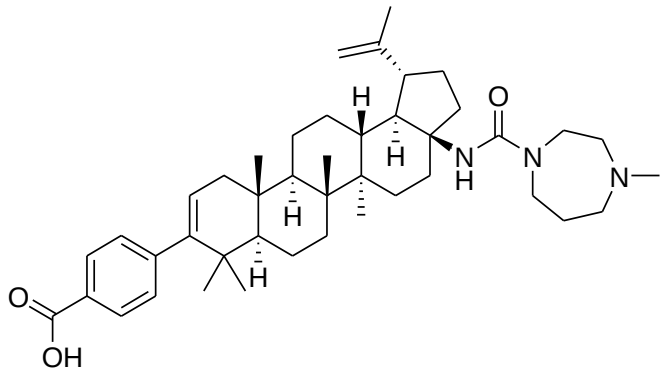


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando metil-3-aminopropanoato, HCl como la amina reactiva. El producto se aisló después de la purificación por HPLC preparativa de fase inversa como un sólido blanco (33 mg, 67 % de rendimiento). LCMS: m/z 645 ($M+H^+$), tiempo de retención 2.69 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.93 (br. s., 3 H), 0.94 (s, 3 H), 1.00 (s, 6 H), 1.03-1.14 (m, 5 H), 1.21-1.40 (m, 5 H),

1.40-1.58 (m, 6 H), 1.58-1.67 (m, 2 H), 1.67-1.75 (m, 5 H), 1.75-1.83 (m, 1 H), 1.87-1.98 (m, 1 H), 2.11 (dd, *J*= 17.09, 6.41 Hz, 1 H), 2.34 (dd, *J*= 12.05, 8.09 Hz, 1 H), 2.49 (t, *J*= 6.26 Hz, 2 H), 2.51-2.63 (m, 2 H), 3.37 (td, *J*= 6.33, 3.81 Hz, 2 H), 4.60 (s, 1 H), 4.72 (d, *J*= 1.83 Hz, 1 H), 5.28 (dd, *J*= 6.10, 1.53 Hz, 1 H), 7.20 (m, *J*= 8.54 Hz, 2 H), 7.92 (m, *J*= 8.24 Hz, 2 H).

Ejemplo 34

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(4-metil-1,4-diazepan-1-carboxamido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

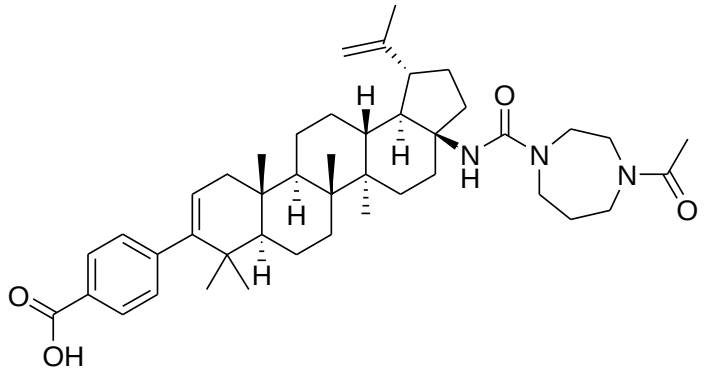


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando 1-metil-1,4-diazepano como la amina reactiva. El producto salino de mono-TFA se aisló mediante purificación por HPLC preparativa de fase inversa como un sólido blanco

(30 mg, 48 % de rendimiento). LCMS: m/z 670 ($M+H^+$), tiempo de retención 2.41 min (método 11). ^1H NMR (400 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.94 (s, 6 H), 1.00 (s, 3 H), 1.04 (s, 3 H), 1.09 (s, 3 H), 1.10-1.22 (m, 3 H), 1.22-1.45 (m, 5 H), 1.45-1.64 (m, 8 H), 1.64-1.81 (m, 7 H), 1.87-2.01 (m, 1 H), 2.12 (dd, *J*= 17.19, 6.40 Hz, 1 H), 2.33 (br. s., 2 H), 2.40-2.53 (m, 2 H), 2.58 (d, *J*= 13.30 Hz, 1 H), 2.92 (s, 3 H), 3.54 (br. s., 2 H), 4.64 (s, 1 H), 4.75 (d, *J*= 1.00 Hz, 1 H), 5.26-5.33 (m, 1 H), 7.20 (m, *J*= 8.28 Hz, 2 H), 7.92 (m, *J*= 8.28 Hz, 2 H).

Ejemplo 35

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-acetil-1,4-diazepan-1-carboxamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

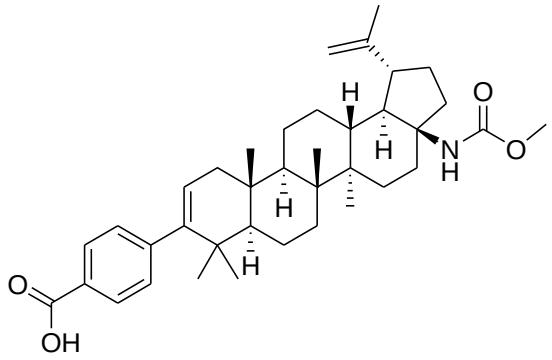


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster

usando 1-[1,4-diazepan1-il]etanona como la amina reactiva. El producto se aisló después de la purificación por HPLC preparativa de fase inversa como un sólido blanco (27 mg, 48 % de rendimiento). LCMS: m/z 698 ($M+H^+$), tiempo de retención 2.74 min (método 11). ^{1}H NMR (400 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.94 (br. s., 3 H), 0.94 (br. s., 3 H), 1.01 (s, 3 H), 1.03 (s, 3 H), 1.09 (s, 3 H), 1.10-1.19 (m, 2 H), 1.21-1.66 (m, 14 H), 1.67-1.78 (m, 6 H), 1.85-2.02 (m, 3 H), 2.11 (s, 2 H), 2.12-2.17 (m, 2 H), 2.34-2.50 (m, 2 H), 2.54-2.64 (m, 1 H), 3.41-3.48 (m, 2 H), 3.50-3.64 (m, 5 H), 4.63 (br. s., 1 H), 4.75 (d, *J*= 9.16 Hz, 1 H), 5.29 (d, *J*= 4.58 Hz, 1 H), 7.20 (d, *J*= 8.24 Hz, 2 H), 7.92 (d, *J*= 8.24 Hz, 2 H).

Ejemplo 36

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(metoxicarbonilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

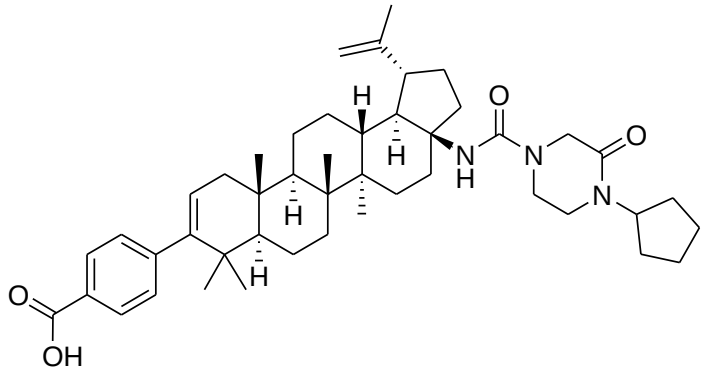


El compuesto del título se formó como un subproducto durante la etapa de formación de urea en la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-acetil-1,4-diazepan-1-carboxamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico. La hidrólisis del penúltimo metiléster mediante el procedimiento general descrito y la purificación por HPLC preparativa de fase inversa produjo un sólido blanco (6 mg, 13 % de rendimiento). LCMS: m/z 588 ($M+H^+$), tiempo de retención 3.07 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.93 (s, 3 H), 0.94 (s, 3 H), 1.00 (s, 3 H), 1.01 (s, 3 H), 1.09 (s, 3 H), 1.09-1.16 (m, 2 H), 1.23-1.27 (m, 1 H), 1.28-1.44 (m, 5 H), 1.45-1.57 (m, 6 H), 1.59-1.77 (m, 9 H), 1.88-2.00 (m, 1 H), 2.12 (dd, *J*= 17.09, 6.41 Hz, 1 H), 2.28-2.39 (m, 1 H), 2.45-2.58 (m, 2 H), 3.62 (br. s., 3 H), 4.62 (d, *J*= 1.53 Hz, 1 H), 4.74 (d, *J*= 1.83 Hz, 1 H), 5.29 (dd, *J*= 6.26, 1.68 Hz, 1 H), 7.20 (d, *J*= 8.24 Hz, 2 H), 7.92 (d, *J*= 8.24 Hz, 2 H).

Ejemplo 37

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-ciclopentil-3-oxopiperazin-1-carboxamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

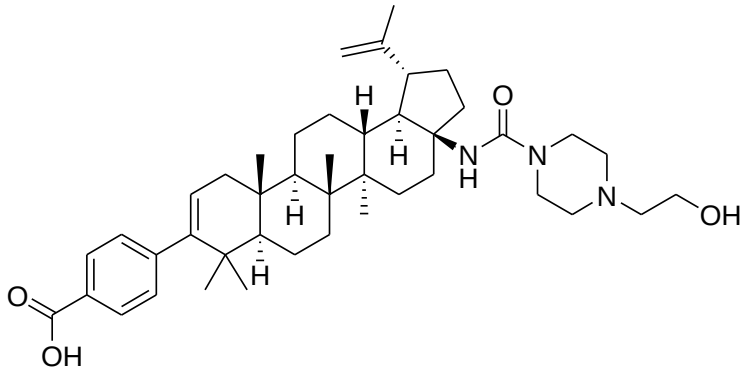


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando 1-ciclopentipiperazin-2-ona, HCl, 0.5 H_2O como la amina reactiva. El producto se aisló después de la purificación por HPLC preparativa de fase inversa como un sólido blanco (18 mg, 28 % de rendimiento). LCMS: m/z 724 ($M+H^+$), tiempo de retención 2.97 min (método 11). ^1H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.93 (br. s., 3 H), 0.94 (br. s., 3 H), 1.00 (s, 3 H), 1.03 (s, 3 H), 1.09 (s, 3 H), 1.11-1.19 (m, 2 H), 1.24 (d, *J*= 8.85 Hz, 1 H), 1.30-1.42 (m, 4 H), 1.43-1.60 (m, 10 H), 1.62-1.67 (m, 2 H), 1.67-1.80 (m, 9 H), 1.82-1.90 (m, 2 H), 1.90-2.00 (m, 1 H), 2.12 (dd, *J*= 17.09, 6.41 Hz, 1 H), 2.40-2.60 (m, 3 H), 3.35-3.41 (m, 2 H), 3.53-3.68 (m, 2 H), 3.94-4.04 (m, 1 H), 4.04-4.13 (m, 1 H), 4.63 (br. s., 1 H), 4.75 (s, 1 H), 4.90 (quin, *J*= 8.47 Hz, 1 H), 5.25-5.31 (m, 1 H), 5.34-5.38

(m, 1 H), 7.20 (d, *J*= 8.24 Hz, 2 H), 7.92 (d, *J*= 8.24 Hz, 2 H).

Ejemplo 38

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-(2-hidroxietil)piperazin-1-carboxamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

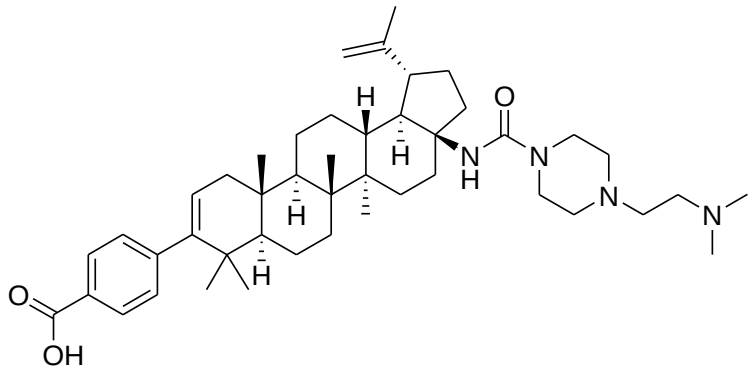


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando 2-(piperazin-1-il)etanol como la amina reactiva. El producto salino de mono-TFA se aisló mediante purificación por HPLC preparativa de fase inversa como un sólido blanco (12 mg, 18 % de rendimiento). LCMS: m/z 686 ($M+H^+$), tiempo de retención 2.41 min (método 11). 1H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.94 (s, 3 H), 0.94 (s, 3 H), 1.00 (s, 3 H), 1.04 (s, 3 H), 1.08 (s, 3 H),

1.09-1.19 (m, 2 H), 1.24-1.28 (m, 1 H), 1.32-1.43 (m, 4 H), 1.44-1.59 (m, 7 H), 1.67-1.80 (m, 7 H), 1.86-1.98 (m, 1 H), 2.12 (dd, *J*= 17.24, 6.26 Hz, 1 H), 2.42 (dd, *J*= 12.36, 8.09 Hz, 1 H), 2.53-2.65 (m, 2 H), 3.23-3.29 (m, 3 H), 3.92 (dd, *J*= 5.95, 4.43 Hz, 2 H), 4.75 (d, *J*= 1.53 Hz, 1 H), 5.29 (dd, *J*= 6.10, 1.83 Hz, 1 H), 7.20 (m, *J*= 8.24 Hz, 2 H), 7.92 (m, *J*= 8.54 Hz, 2 H).

Ejemplo 39

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-(2-(dimetilamino)etil)piperazin-1-carboxamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

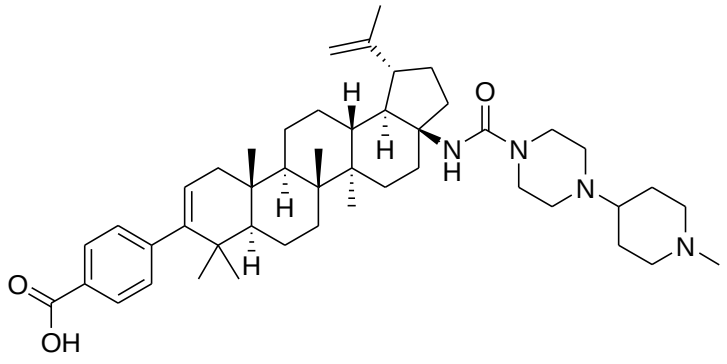


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando *N*,*N*-dimetil-2-(piperazin-1-il)etanamina como la amina reactiva. El producto salino de bis-TFA se aisló después de

la purificación por HPLC preparativa de fase inversa como un sólido blanco (15 mg, 19 % de rendimiento). LCMS: m/z 713 ($M+H^+$), tiempo de retención 2.44 min (método 11). 1H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.94 (s, 3 H), 0.94 (s, 3 H), 1.00 (s, 3 H), 1.03 (s, 3 H), 1.08 (s, 3 H), 1.09-1.20 (m, 2 H), 1.24-1.44 (m, 7 H), 1.44-1.62 (m, 7 H), 1.64-1.79 (m, 7 H), 1.88-2.00 (m, 1 H), 2.12 (dd, *J*= 17.09, 6.41 Hz, 1 H), 2.44 (dd, *J*= 12.21, 8.24 Hz, 1 H), 2.51 (dt, *J*= 10.15, 5.15 Hz, 1 H), 2.57 (d, *J*= 13.12 Hz, 1 H), 2.73 (br. s., 4 H), 2.87-2.99 (m, 8 H), 3.39-3.55 (m, 4 H), 4.75 (s, 1 H), 5.29 (d, *J*= 4.58 Hz, 1 H), 7.20 (m, *J*= 8.24 Hz, 2 H), 7.92 (m, *J*= 8.24 Hz, 2 H).

Ejemplo 40

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(4-(1-metilpiperidin-4-il)piperazin-1-carboxamido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

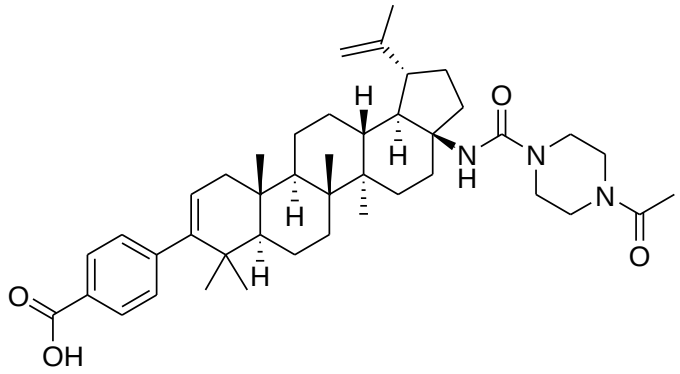


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando 1-(1-metilpiperidin-4-il)piperazina como la amina reactiva. El producto salino de bis-TFA se aisló después de la purificación por HPLC preparativa de fase inversa como un sólido blanco (48 mg, 61 % de rendimiento). LCMS: m/z 739 ($M+H^+$), tiempo de retención 2.41 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.93 (s, 3 H), 0.94 (s, 3 H), 1.00 (s, 3 H), 1.03 (s, 3 H), 1.08 (s, 3 H), 1.09-1.19 (m, 2 H), 1.23-1.28 (m, 1 H), 1.29-1.44 (m, 4 H), 1.44-1.64 (m, 9 H), 1.65-1.79 (m, 7 H), 1.87-1.99 (m, 1 H), 1.99-2.08 (m, 2 H), 2.12 (dd, *J*= 17.09, 6.41 Hz, 1 H), 2.40-2.60 (m, 3 H), 2.77-2.93 (m, 5 H), 3.03-3.13 (m, 1 H), 3.35 (br. s., 4 H), 3.47 (br. s., 4 H), 3.99-4.15 (m, 2 H), 4.63 (s, 1 H), 4.75 (d, *J*= 1.22 Hz, 1 H), 5.29 (dd, *J*= 6.10, 1.53 Hz, 1 H), 7.20 (m, *J*= 8.54 Hz, 2 H), 7.92 (m, *J*= 8.24 Hz, 2 H).

Ejemplo 41

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-acetilpiperazin-1-carboxamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

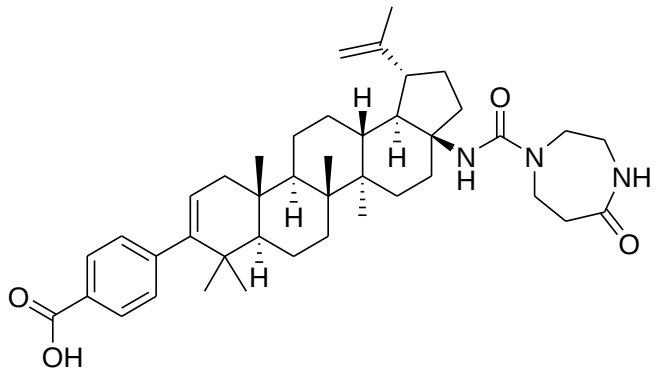
octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando 1-(piperazin-1-il)etanona como la amina reactiva. El producto se aisló después de la purificación por HPLC preparativa de fase inversa como un sólido blanco (6 mg, 11 % de rendimiento). LCMS: m/z 684 ($M+H^+$), tiempo de retención 2.81 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.94 (br. s., 3 H), 0.94 (s, 3 H), 1.01 (s, 3 H), 1.04 (s, 3 H), 1.09 (s, 3 H), 1.10-1.20 (m, 2 H), 1.24-1.28 (m, 2 H), 1.29-1.45 (m, 4 H), 1.45-1.62 (m, 7 H), 1.64-1.79 (m, 7 H), 1.89-2.00 (m, 1 H), 2.08-2.16 (m, 4 H), 2.46 (dd, *J*= 12.36, 8.09 Hz, 1 H), 2.52 (td, *J*= 10.60, 5.34 Hz, 1 H), 2.58 (ddd, *J*= 13.35, 3.36, 3.13 Hz, 1 H), 3.35-3.48 (m, 3 H), 3.49-3.60 (m, 3 H), 3.60-3.73 (m, 2 H), 4.75 (d, *J*= 1.53 Hz, 1 H), 5.29 (dd, *J*= 6.10, 1.53 Hz, 1 H), 7.20 (m, *J*= 8.54 Hz, 2 H), 7.92 (m, *J*= 8.54 Hz, 2 H).

Ejemplo 42

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(5-oxo-1,4-diazepan-1-carboxamido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

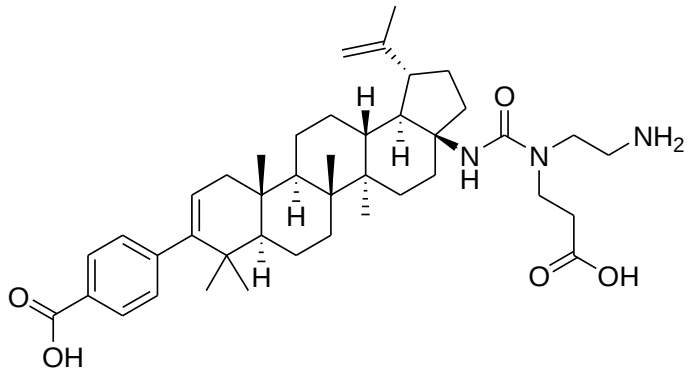


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando 1,4-diazepan-5-ona como la amina reactiva. El producto se aisló después de la purificación por HPLC preparativa de fase inversa como un sólido blanco (26 mg, 46 % de rendimiento). LCMS: m/z 670 ($M+H^+$), tiempo de retención 2.70 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.94 (s, 3 H), 0.94 (s, 3 H), 1.01 (s, 3 H), 1.04 (s, 3 H), 1.09 (s, 3 H), 1.10-1.19 (m, 2 H), 1.26 (dd, *J*= 7.17, 3.20 Hz, 1 H), 1.31-1.43 (m, 5 H), 1.45-1.54 (m, 6 H), 1.55-1.60 (m, 2 H), 1.63-1.80 (m, 7 H), 1.88-1.99 (m, 1 H), 2.13 (dd, *J*= 16.94, 6.26 Hz, 1 H), 2.44-2.53

(m, 2 H), 2.60 (ddd, *J*= 13.50, 2.82, 2.59 Hz, 1 H), 2.68 (t, *J*= 5.19 Hz, 2 H), 3.49-3.68 (m, 4 H), 4.57 (s, 1 H), 4.75 (d, *J*= 1.53 Hz, 1 H), 5.29 (dd, *J*= 6.10, 1.53 Hz, 1 H), 7.20 (d, *J*= 8.54 Hz, 2 H), 7.92 (d, *J*= 8.54 Hz, 2 H).

Ejemplo 43

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-aminoetil)-3-(2-carboxietil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

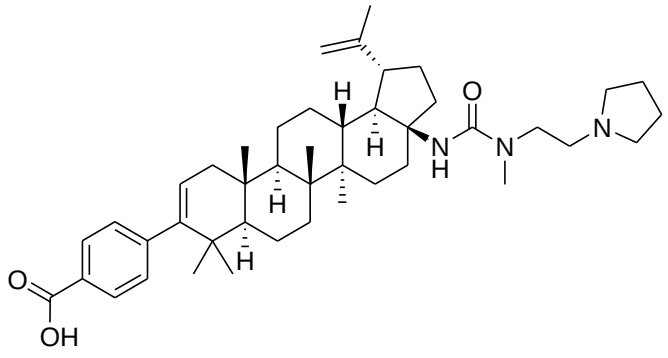


El compuesto del título se formó como un subproducto durante la etapa de hidrólisis del éster en la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(5-oxo-1,4-diazepan-1-carboxamido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico. La purificación mediante HPLC preparativa de fase inversa

produjo una sal de mono-TFA sólida blanca (10 mg, 15 % de rendimiento). LCMS: m/z 688 ($M+H^+$), tiempo de retención 2.40 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.94 (s, 6 H), 1.01 (s, 3 H), 1.04 (s, 3 H), 1.07-1.17 (m, 5 H), 1.23-1.42 (m, 7 H), 1.44-1.62 (m, 7 H), 1.67-1.81 (m, 6 H), 1.84-2.00 (m, 2 H), 2.13 (dd, *J*= 17.39, 6.41 Hz, 1 H), 2.38 (dd, *J*= 11.90, 7.93 Hz, 1 H), 2.51-2.58 (m, 1 H), 2.59-2.66 (m, 1 H), 2.66-2.73 (m, 1 H), 2.77 (td, *J*= 10.83, 4.58 Hz, 1 H), 2.99-3.10 (m, 2 H), 3.36-3.46 (m, 3 H), 3.76 (ddd, *J*= 15.56, 9.31, 3.81 Hz, 1 H), 4.76 (d, *J*= 1.83 Hz, 1 H), 5.29 (dd, *J*= 6.10, 1.53 Hz, 1 H), 7.20 (m, *J*= 8.24 Hz, 2 H), 7.92 (m, *J*= 8.24 Hz, 2 H).

Ejemplo 44

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(3-metil-3-(2-(pirrolidin-1-il)etil)ureido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

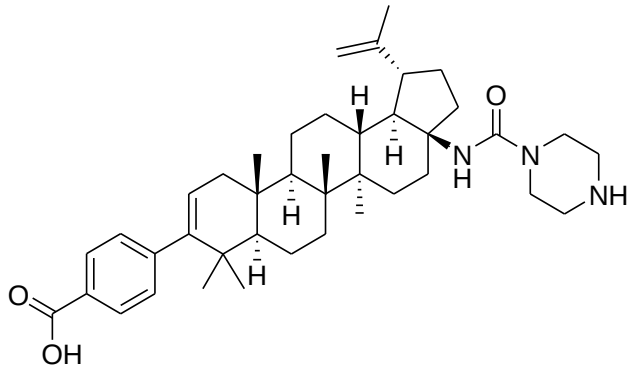


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando *N*-metil-2-(pirrolidin-1-il)etanamina como la amina reactiva. El producto se aisló mediante purificación por HPLC preparativa de fase inversa como una sal de mono-TFA sólida blanca (34 mg, 54 % de rendimiento). LCMS: m/z 684 ($M+H^+$), tiempo de retención 2.41 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.94 (br. s., 3 H), 0.94 (br. s., 3 H), 1.00 (s, 3 H), 1.04 (s, 3 H), 1.10 (s, 3 H), 1.10-1.21 (m, 2 H), 1.26 (dd, *J*= 10.68, 2.75 Hz, 1 H), 1.32-1.43 (m, 4 H), 1.45-1.59 (m, 7 H), 1.62-1.81 (m, 8 H), 1.87-2.00 (m, 1 H), 2.08 (br. s., 4 H), 2.12 (dd, *J*= 17.09, 6.41 Hz, 1 H), 2.41-2.57 (m, 3 H), 3.03 (s, 3 H), 3.06 (br. s., 2 H), 3.25-3.39 (m, 2 H), 3.52 (dt, *J*= 14.65, 6.26 Hz, 1 H), 3.63-3.83 (m, 3 H), 4.64 (br. s., 1 H), 4.75 (s, 1 H), 5.26-5.32 (m, 1 H), 7.20 (d, *J*= 7.93 Hz, 2 H), 7.92 (d, *J*= 8.24 Hz, 2 H).

Ejemplo 45

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(piperazin-1-carboxamido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

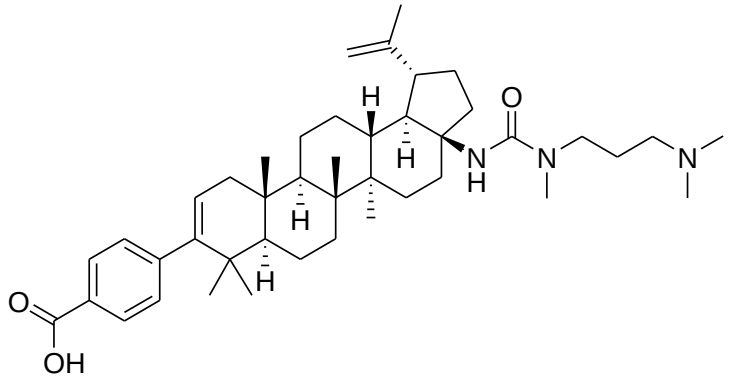
octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando 1-(piperazin-1-il)etanona como la amina reactiva. El producto se aisló mediante purificación por HPLC preparativa de fase inversa como una sal de mono-TFA sólida blanca (5 mg, 8 % de rendimiento). LCMS: m/z 642 ($M+H^+$), tiempo de retención 2.42 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.94 (s, 3 H), 0.94 (s, 3 H), 1.00 (s, 3 H), 1.04 (s, 3 H), 1.08 (s, 3 H), 1.09-1.19 (m, 2 H), 1.26 (dd, *J*= 8.09, 2.29 Hz, 1 H), 1.29-1.44 (m, 4 H), 1.44-1.51 (m, 4 H), 1.51-1.62 (m, 3 H), 1.67-1.80 (m, 7 H), 1.87-1.97 (m, 1 H), 2.12 (dd, *J*= 17.09, 6.41 Hz, 1 H), 2.43 (dd, *J*= 12.36, 8.09 Hz, 1 H), 2.53-2.63 (m, 2 H), 3.13-3.27 (m, 4 H), 3.55-3.68 (m, 4 H), 4.75 (d, *J*= 1.53 Hz, 1 H), 4.95 (s, 1 H), 5.29 (dd, *J*= 6.10, 1.53 Hz, 1 H), 7.20 (d, *J*= 8.54 Hz, 2 H), 7.92 (d, *J*= 8.24 Hz, 2 H).

Ejemplo 46

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(3-(dimetilamino)propil)-3-metilureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

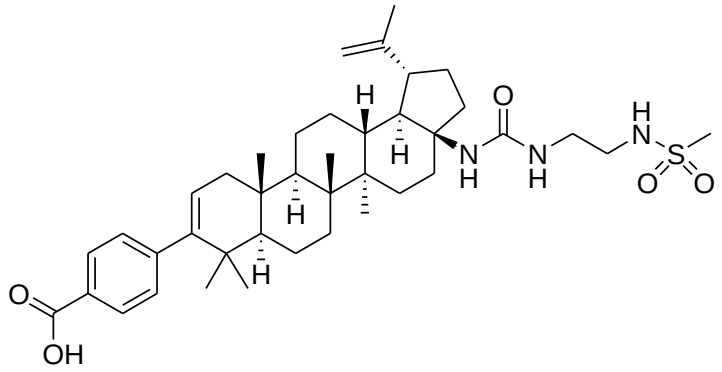


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando *N1,N1,N3*-trimetilpropan-1,3-diamina como la amina reactiva. El producto se aisló mediante purificación por HPLC preparativa de fase inversa como una sal de mono-TFA sólida blanca (21 mg, 31 % de rendimiento). LCMS: m/z 672 ($M+H^+$), tiempo de retención 1.86 min (método 2). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.94 (s, 3 H) 0.94 (s, 3 H) 1.01 (s, 3 H) 1.05 (s, 3 H) 1.07-1.20 (m, 5 H) 1.24-1.29 (m, 2 H) 1.33-1.39 (m, 2 H) 1.40-1.59 (m, 9 H) 1.62-1.80 (m, 7 H) 1.88-2.02 (m, 3 H) 2.13 (dd, *J*= 17.09,

6.41 Hz, 1 H) 2.43 (dd, *J*= 12.51, 8.24 Hz, 1 H) 2.46-2.55 (m, 2 H) 2.87 (s, 6 H) 2.98-3.10 (m, 5 H) 3.34-3.49 (m, 2 H) 4.76 (d, *J*= 1.22 Hz, 1 H) 5.29 (dd, *J*= 6.10, 1.83 Hz, 1 H) 7.20 (m, *J*= 8.24 Hz, 2 H) 7.92 (m, *J*= 8.24 Hz, 2 H).

Ejemplo 47

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(3-(2-(metilsulfonamido)etil)ureido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

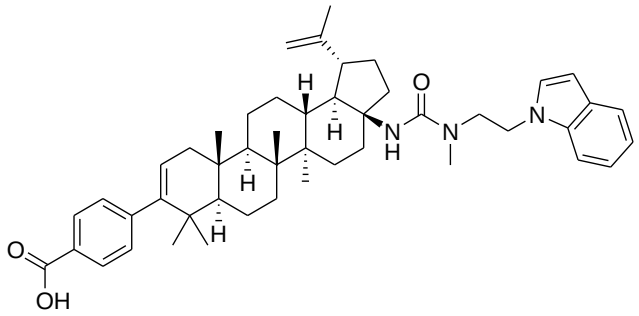


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando clorhidrato de *N*-(2-aminoetil)metansulfonamida como la amina reactiva. El producto se aisló después de la purificación por HPLC preparativa de fase inversa como un sólido blanco (28 mg, 51 % de rendimiento). LCMS: m/z 694 ($M+H^+$), tiempo de retención 2.17 min (método 2). ^{1}H NMR (400 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm

0.93 (br. s., 3 H) 0.94 (s, 3 H) 1.00 (s, 6 H) 1.04-1.16 (m, 5 H) 1.23-1.43 (m, 6 H) 1.45-1.56 (m, 5 H) 1.59-1.83 (m, 8 H) 1.87-2.00 (m, 1 H) 2.11 (dd, *J*= 17.19, 6.40 Hz, 1 H) 2.36 (dd, *J*= 12.05, 8.28 Hz, 1 H) 2.49-2.63 (m, 2 H) 2.95 (s, 3 H) 3.09-3.17 (m, 2 H) 3.20-3.30 (m, 2 H) 4.61 (s, 1 H) 4.72 (d, *J*= 1.76 Hz, 1 H) 5.29 (dd, *J*= 6.02, 1.51 Hz, 1 H) 7.20 (m, *J*= 8.28 Hz, 2 H) 7.92 (m, *J*= 8.28 Hz, 2 H).

Ejemplo 48

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(1H-indol-1-il)etil)-3-metilureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

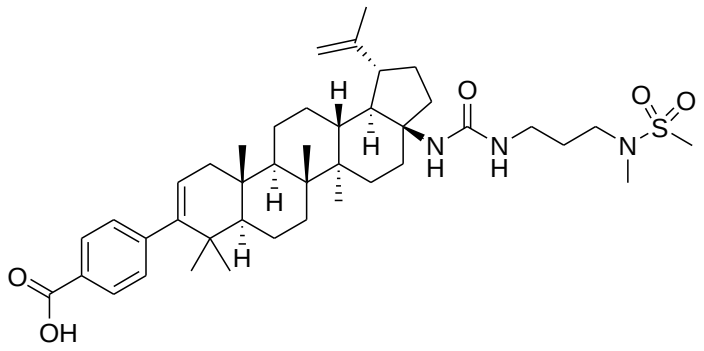


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando 2-(1H-indol-1-il)-*N*-metiletanamina como la amina reactiva. El producto se aisló mediante purificación por HPLC preparativa de fase inversa como una sal de mono-TFA sólida blanca (30 mg, 39 % de rendimiento). LCMS: m/z 730 ($M+H^+$),

tiempo de retención 2.73 min (método 2). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.94 (br. s., 3 H) 0.94 (br. s., 3 H) 0.95 (br. s., 3 H) 0.97 (s, 3 H) 0.99 (s, 3 H) 1.01-1.12 (m, 2 H) 1.21-1.29 (m, 3 H) 1.32-1.37 (m, 2 H) 1.38-1.53 (m, 7 H) 1.54-1.73 (m, 7 H) 1.79-1.92 (m, 1 H) 2.09 (dd, *J*= 17.09, 6.41 Hz, 1 H) 2.19 (td, *J*= 10.61, 4.43 Hz, 1 H) 2.42 (s, 3 H) 2.48-2.57 (m, 2 H) 3.60 (ddd, *J*= 14.50, 5.49, 5.34 Hz, 1 H) 3.71 (ddd, *J*= 14.65, 5.65, 5.34 Hz, 1 H) 4.28-4.39 (m, 2 H) 4.60 (br. s., 1 H) 4.69 (s, 1 H) 5.27 (d, *J*= 6.10 Hz, 1 H) 6.51 (d, *J*= 3.05 Hz, 1 H) 7.05-7.12 (m, 2 H) 7.15-7.22 (m, 3 H) 7.38 (d, *J*= 8.24 Hz, 1 H) 7.61 (d, *J*= 7.93 Hz, 1 H) 7.92 (d, *J*= 8.24 Hz, 2 H).

Ejemplo 49

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(3-(3-(*N*-metilmetilsulfonamido)propil)ureido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

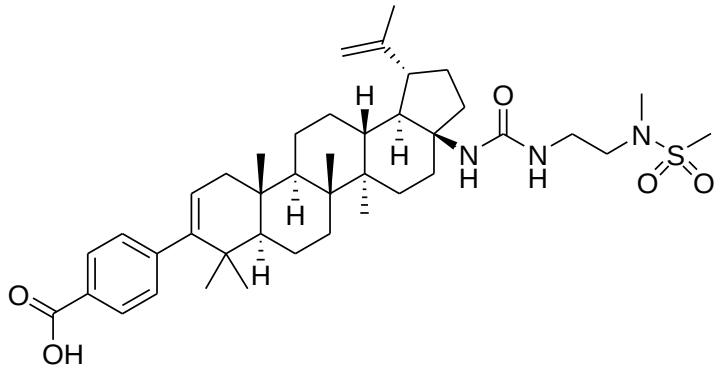


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando *N*-(3-aminopropil)-*N*-metilmetansulfonamida como la amina reactiva. El producto se aisló después de la purificación por HPLC preparativa de fase inversa como un sólido blanco (36 mg, 62 % de rendimiento). LCMS: m/z 730 ($M+H^+$), tiempo de retención 2.25 min (método 2). ^1H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.93 (s, 3 H) 0.94 (s, 3 H) 1.00 (s, 6 H) 1.05-1.15 (m, 5 H) 1.21-1.41 (m, 5 H) 1.41-1.59 (m, 6 H) 1.62-1.81 (m, 10 H) 1.88-1.99 (m, 1 H) 2.11 (dd, *J*= 17.09, 6.41 Hz, 1 H) 2.35 (dd, *J*= 12.36, 8.09 Hz, 1 H) 2.50-2.63 (m, 2 H) 2.85 (s, 3 H) 2.86 (s, 3 H) 3.12-3.23 (m, 4 H) 4.61 (s, 1 H) 4.72 (d, *J*= 1.53 Hz, 1 H) 5.25-5.32 (m, 1 H) 7.20 (m, *J*= 8.24 Hz, 2 H) 7.92 (m, *J*= 8.24 Hz, 2 H).

Ejemplo 50

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(3-(2-(N-metilmetilsulfonamido)etil)ureido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

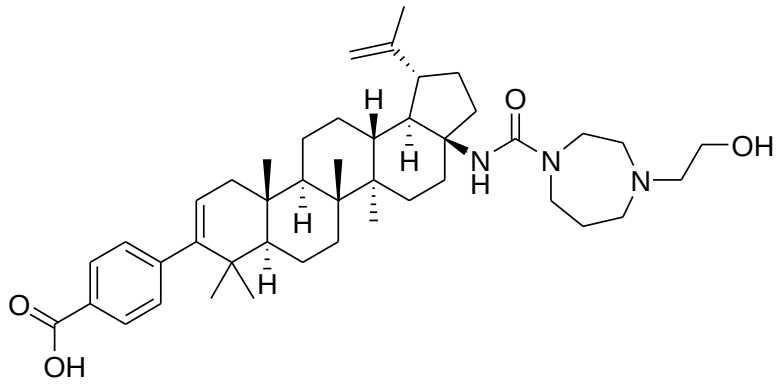
octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando *N*-(2-aminoetil)-*N*-metilmetansulfonamida como la amina reactiva. El producto se aisló después de la purificación por HPLC preparativa de fase inversa como un sólido blanco (37 mg, 65 % de rendimiento). LCMS: m/z 708 ($M+H^+$), tiempo de retención 2.25 min (método 2). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.93 (br. s., 3 H) 0.94 (s, 3 H) 1.00 (s, 6 H) 1.04-1.15 (m, 5 H) 1.21-1.41 (m, 5 H) 1.41-1.58 (m, 6 H) 1.59-1.75 (m, 7 H) 1.75-1.83 (m, 1 H) 1.88-2.00 (m, 1 H) 2.11 (dd, *J*= 17.09, 6.41 Hz, 1 H) 2.36 (dd, *J*= 12.36, 8.09 Hz, 1 H) 2.51-2.64 (m, 2 H) 2.86 (s, 3 H) 2.91 (s, 3 H) 3.18-3.25 (m, 2 H) 3.31 (t, *J*= 5.49 Hz, 2 H) 4.61 (s, 1 H) 4.72 (d, *J*= 1.53 Hz, 1 H) 5.28 (dd, *J*= 6.26, 1.68 Hz, 1 H) 7.20 (d, *J*= 8.54 Hz, 2 H) 7.92 (d, *J*= 8.24 Hz, 2 H).

Ejemplo 51

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-(2-hidroxietil)-1,4-diazepan-1-carboxamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

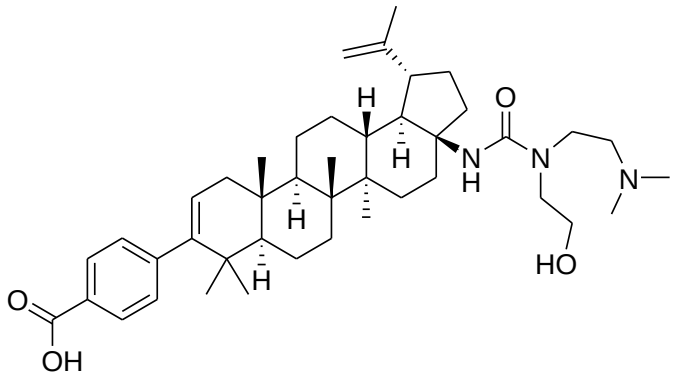


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando 2-(1,4-diazepan-1-il)etanol como la amina reactiva. El producto se aisló mediante purificación por HPLC preparativa de fase inversa como una sal de mono-TFA sólida blanca (49 mg, 72 % de rendimiento). LCMS: m/z 700 ($M+H^+$), tiempo de retención 1.77 min (método 2). ^{1}H NMR (400 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.94 (s, 3 H) 0.94 (s, 3 H) 1.00 (s, 3 H) 1.04 (s, 3 H) 1.09 (s, 3 H) 1.10-1.18 (m, 2 H) 1.18-1.64 (m, 13 H) 1.64-1.82 (m, 7 H) 1.85-2.01 (m, 1 H) 2.12 (dd, *J*= 17.19, 6.40 Hz, 1 H) 2.29-2.41 (m, 2 H)

2.41-2.53 (m, 2 H) 2.58 (d, *J*= 13.30 Hz, 1 H) 3.25-3.32 (m, 2 H) 3.35-3.63 (m, 6 H) 3.69-4.00 (m, 4 H) 4.64 (br. s., 1 H) 4.75 (s, 1 H) 5.29 (d, *J*= 4.77 Hz, 1 H) 7.19 (m, 2 H) 7.91 (m, 2 H).

Ejemplo 52

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-(dimetilamino)etil)-3-(2-hidroxietil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

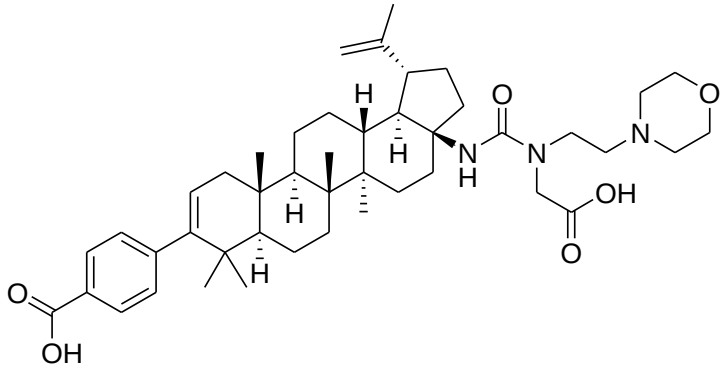


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando 2-(2-(dimetilamino)etilamino)etanol como la amina reactiva. El producto se aisló mediante purificación por HPLC preparativa de fase inversa como una sal de mono-TFA sólida blanca (35 mg, 51 % de rendimiento). LCMS: m/z 688 ($M+H^+$), tiempo de retención 1.79 min (método 2). ^{1}H NMR (500 MHz, 1:1

mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.93 (br. s., 3 H) 0.94 (br. s., 3 H) 1.01 (br. s., 3 H) 1.02 (br. s., 3 H) 1.06-1.18 (m, 5 H) 1.20-1.66 (m, 12 H) 1.66-1.81 (m, 7 H) 1.81-2.01 (m, 2 H) 2.12 (dd, *J*= 17.09, 6.41 Hz, 1 H) 2.37 (dd, *J*= 12.05, 8.09 Hz, 1 H) 2.46-2.61 (m, 2 H) 2.93 (s, 6 H) 3.21-3.31 (m, 2 H) 3.48-3.61 (m, 3 H) 3.72-3.79 (m, 2 H) 4.61 (br. s., 1 H) 4.74 (br. s., 1 H) 5.23-5.35 (m, 1 H) 7.20 (d, *J*= 8.24 Hz, 2 H) 7.92 (d, *J*= 8.24 Hz, 2 H).

Ejemplo 53

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(carboximetil)-3-(2-morfolinoetil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

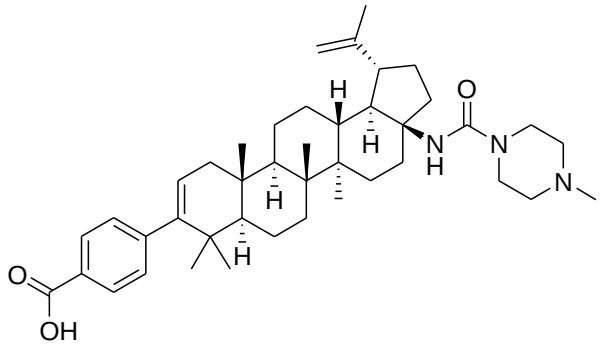


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando 2-(2-morfolinoetilamino)acetato de etilo como la amina

reactiva. El producto se aisló mediante purificación por HPLC preparativa de fase inversa como una sal de mono-TFA sólida blanca (5 mg, 6 % de rendimiento). LCMS: m/z 744 ($M+H^+$), tiempo de retención 1.81 min (método 2). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.94 (br. s., 3 H) 0.94 (s, 3 H) 1.01 (s, 3 H) 1.02 (s, 3 H) 1.10 (d, *J*= 2.44 Hz, 1 H) 1.11-1.16 (m, 4 H) 1.19-1.64 (m, 12 H) 1.64-1.80 (m, 7 H) 1.87-1.98 (m, 1 H) 2.13 (dd, *J*= 17.09, 6.41 Hz, 1 H) 2.35 (dd, *J*= 12.51, 8.24 Hz, 1 H) 2.47-2.59 (m, 2 H) 3.23-3.30 (m, 2 H) 3.37 (s, 3 H) 3.58 (td, *J*= 10.38, 4.88 Hz, 1 H) 3.70-4.03 (m, 6 H) 4.72 (s, 1 H) 4.78 (d, *J*= 1.53 Hz, 1 H) 5.29 (dd, *J*= 6.10, 1.53 Hz, 1 H) 7.20 (m, *J*= 8.24 Hz, 2 H) 7.92 (m, *J*= 8.24 Hz, 2 H).

Ejemplo 54

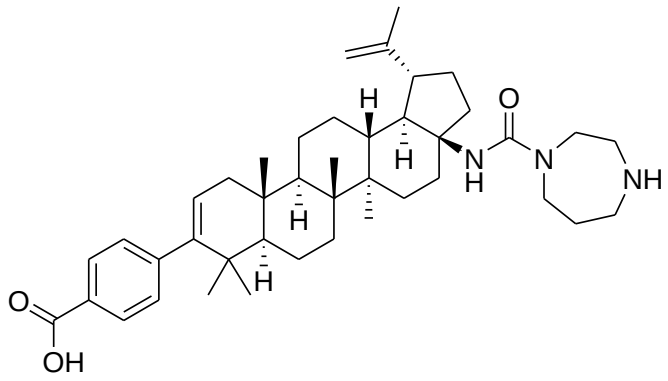
Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(4-metilpiperazin-1-carboxamido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando 1-metilpiperazina como la amina reactiva. El producto se aisló mediante purificación por HPLC preparativa de fase inversa como una sal de mono-TFA sólida blanca (49 mg, 75 % de rendimiento). LCMS: m/z 656 ($M+H^+$), tiempo de retención 2.44 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.94 (br. s., 3 H) 0.94 (s, 3 H) 1.00 (s, 3 H) 1.03 (s, 3 H) 1.05-1.19 (m, 5 H) 1.23-1.28 (m, 1 H) 1.31-1.42 (m, 4 H) 1.44-1.59 (m, 7 H) 1.64-1.81 (m, 7 H) 1.86-1.98 (m, 1 H) 2.12 (dd, *J*= 17.24, 6.26 Hz, 1 H) 2.42 (dd, *J*= 12.36, 8.39 Hz, 1 H) 2.51-2.65 (m, 2 H) 2.90 (s, 3 H) 3.34 (br. s., 4 H) 3.96 (br. s., 2 H) 4.64 (br. s., 1 H) 4.75 (d, *J*= 1.22 Hz, 1 H) 5.29 (dd, *J*= 6.26, 1.68 Hz, 1 H) 7.20 (m, *J*= 8.24 Hz, 2 H) 7.92 (m, *J*= 8.55 Hz, 2 H).

Ejemplo 55

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(1,4-diazepan-1-carboxamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

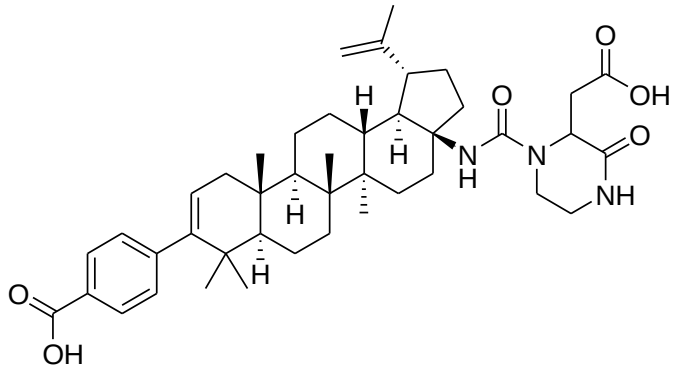


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando homopiperazina como la amina reactiva. El producto se aisló mediante purificación por HPLC preparativa de fase inversa como una sal de mono-TFA sólida blanca (33 mg, 53 % de rendimiento). LCMS: m/z 656 ($M+H^+$), tiempo de retención 2.43 min (método 11). ^{1}H NMR (400 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.94 (s, 6 H) 1.00 (s, 3 H) 1.04 (s, 3 H) 1.09 (s, 3 H) 1.10-1.22 (m, 2 H) 1.24-1.30 (m, 1 H) 1.34-1.59 (m, 11 H) 1.64-1.82 (m, 7 H) 1.86-2.01 (m, 1 H) 2.12 (dd, *J*= 17.07, 6.27 Hz, 1 H) 2.18-2.29 (m, 2 H) 2.42-2.53 (m, 2 H) 2.59 (d, *J*= 13.30 Hz, 1 H) 3.20-3.31 (m, 4 H)

3.48-3.62 (m, 2 H) 3.76 (t, *J*= 4.27 Hz, 2 H) 4.47 (s, 1 H) 4.64 (s, 1 H) 4.75 (s, 1 H) 5.29 (d, *J*= 4.77 Hz, 1 H) 7.20 (m, *J*= 8.03 Hz, 2 H) 7.92 (m, *J*= 8.03 Hz, 2 H).

Ejemplo 56

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(carboximetil)-3-oxopiperazin-1-carboxamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

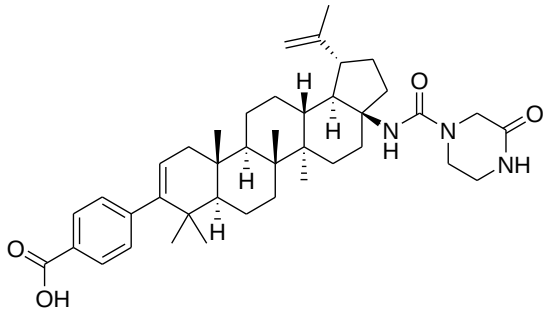


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando 2-(3-oxopiperazin-2-il)acetato de etilo como la amina reactiva. El producto se aisló después de la purificación por HPLC preparativa de fase inversa como un sólido blanco (38 mg, 64 % de rendimiento). LCMS: m/z 714 ($M+H^+$), tiempo de retención 2.66 min (método 11). Este material es una mezcla diastereomérica en una relación de aproximadamente 1:1. ^1H

NMR (400 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.91-0.97 (m, 6 H) 0.97-1.04 (m, 6 H) 1.05-1.17 (m, 5 H) 1.19-1.64 (m, 13 H) 1.65-1.80 (m, 7 H) 1.80-2.08 (m, 3 H) 2.12 (dt, *J*= 17.07, 6.02 Hz, 1 H) 2.23 (dd, *J*= 12.30, 8.28 Hz, 0.5 H) 2.34-2.44 (m, 0.5 H) 2.58 (d, *J*= 13.30 Hz, 0.5 H) 2.65-2.76 (m, 1 H) 2.80-2.96 (m, 2 H) 2.97-3.13 (m, 2 H) 3.14-3.24 (m, 1 H) 3.50-3.64 (m, 1.5 H) 3.94-4.03 (m, 0.5 H) 4.07 (dd, *J*= 13.80, 2.76 Hz, 0.5 H) 4.70-4.80 (m, 2 H) 5.25-5.32 (m, 1 H) 7.19 (d, *J*= 8.03 Hz, 2 H) 7.92 (d, 2 H).

Ejemplo 57

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(3-oxopiperazin-1-carboxamido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

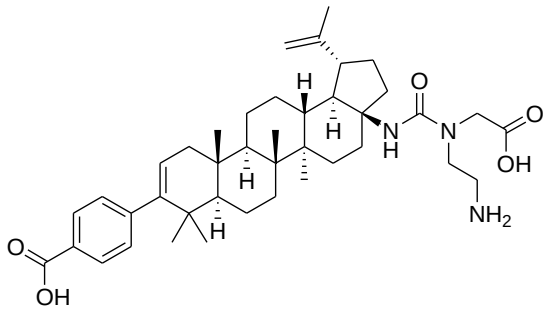


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando piperazin-2-ona como la amina reactiva. El producto se aisló después de la purificación por HPLC preparativa de fase

inversa como un sólido blanco (7 mg, 12 % de rendimiento). LCMS: m/z 656 ($M+H^+$), tiempo de retención 2.71 min (método 11). ^1H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.94 (s, 3 H) 0.94 (s, 3 H) 1.00 (s, 3 H) 1.03 (s, 3 H) 1.10 (s, 3 H) 1.10-1.20 (m, 2 H) 1.25 (d, *J*= 10.07 Hz, 1 H) 1.29-1.44 (m, 4 H) 1.44-1.63 (m, 7 H) 1.65-1.80 (m, 7 H) 1.89-2.00 (m, 1 H) 2.13 (dd, *J*= 17.09, 6.41 Hz, 1 H) 2.46 (dd, *J*= 12.51, 8.24 Hz, 1 H) 2.49-2.61 (m, 2 H) 3.36-3.45 (m, 2 H) 3.54-3.67 (m, 2 H) 3.91-4.02 (m, 1 H) 4.02-4.13 (m, 1 H) 4.64 (d, *J*= 1.22 Hz, 1 H) 4.76 (d, *J*= 1.22 Hz, 1 H) 5.29 (dd, *J*= 6.26, 1.68 Hz, 1 H) 7.20 (d, *J*= 8.24 Hz, 2 H) 7.92 (d, *J*= 8.55 Hz, 2 H).

Ejemplo 58

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(2-aminoetil)-3-(carboximetil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



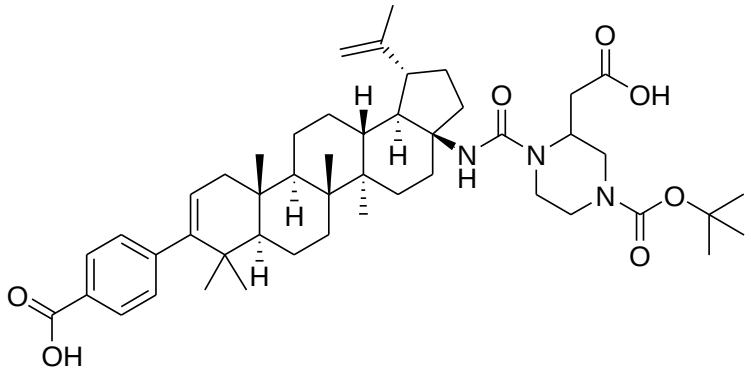
El compuesto del título se formó con un subproducto

durante la etapa de hidrólisis del éster en la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(3-oxopiperazin-1-carboxamido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico. La purificación mediante HPLC preparativa de fase inversa produjo una sal de mono-TFA sólida blanca (22 mg, 33 % de rendimiento). LCMS: m/z 674 ($M+H^+$), tiempo de retención 2.41 min (método 11). ^{1}H NMR (400 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.94 (s, 3 H) 0.94 (s, 3 H) 1.01 (s, 3 H) 1.02 (s, 3 H) 1.07-1.18 (m, 5 H) 1.20-1.59 (m, 12 H) 1.60-1.79 (m, 8 H) 1.86-2.01 (m, 1 H) 2.12 (dd, *J*= 17.07, 6.27 Hz, 1 H) 2.37-2.51 (m, 2 H) 2.51-2.60 (m, 1 H) 3.05-3.18 (m, 2 H) 3.47 (ddd, *J*= 15.37, 5.46, 5.27 Hz, 1 H) 3.70-3.82 (m, 1 H) 3.93-4.06 (m, 2 H) 4.62 (s, 1 H) 4.75 (d, *J*= 1.51 Hz, 1 H) 5.29 (dd, *J*= 6.02, 1.51 Hz, 1 H) 7.20 (m, *J*= 8.28 Hz, 2 H) 7.92 (m, *J*= 8.28 Hz, 2 H).

Ejemplo 59

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-(terc-butoxicarbonil)-2-(carboximetil)piperazin-1-carboxamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

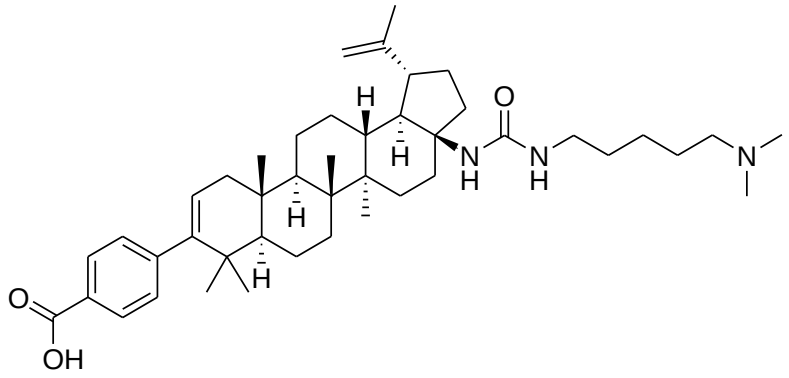


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando 3-(2-metoxi-2-oxoetil)piperazin-1-carboxilato de *terc-butilo* como la amina reactiva. El producto se aisló después de la purificación por HPLC preparativa de fase inversa como un sólido blanco (39 mg, 63 % de rendimiento). LCMS: m/z 800 ($M+H^+$), tiempo de retención 2.94 min (método 11). Este material es una mezcla diastereomérica en una relación de aproximadamente 2:1. ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 1H NMR (500 MHz, MeOD) δ ppm 0.89-0.97 (m, 6 H) 0.97-1.05 (m, 6 H) 1.05-1.18 (m, 5 H) 1.25 (d, *J*= 3.36 Hz, 1 H) 1.29-1.44 (m, 5 H) 1.48 (d, *J*= 5.80 Hz, 13 H) 1.51-1.62 (m, 3 H) 1.65-1.80 (m, 7 H) 1.81-2.00 (m, 2 H) 2.12 (ddd, *J*= 17.09, 6.10, 3.66 Hz, 1 H) 2.27-2.42 (m, 1 H) 2.57 (dd, *J*= 17.24, 4.12 Hz, 1 H) 2.63 (dd, *J*= 12.82, 9.77 Hz, 2 H) 2.75 (br. s., 0.5 H) 2.88 (d, *J*= 7.02 Hz, 1.5 H) 2.95-3.04 (m, 1 H) 3.09 (br. s., 0.5 H) 3.80 (d, *J*= 11.60 Hz,

0.5 H) 3.91 (d, *J*= 12.21 Hz, 0.5 H) 4.03 (d, *J*= 10.38 Hz, 1 H) 5.29 (dd, *J*= 4.27, 2.14 Hz, 1 H) 7.20 (dd, *J*= 8.24, 2.44 Hz, 2 H) 7.92 (d, *J*= 7.32 Hz, 2 H).

Ejemplo 60

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(5-(dimetilamino)pentil)ureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

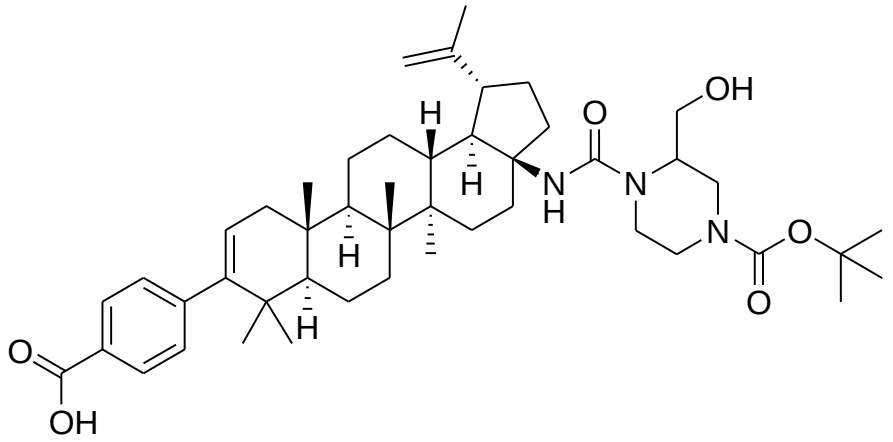


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando *N1,N1*-dimetilpentan-1,5-diamina como la amina reactiva. El producto salino de mono-TFA se aisló mediante purificación por HPLC preparativa de fase inversa como un sólido blanco (21 mg, 57 % de rendimiento). LCMS: m/z 686 ($M+H^+$), tiempo de retención 2.44 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm

0.93 (br. s., 3 H) 0.94 (s, 3 H) 1.00 (br. s., 3 H) 1.01 (br. s., 3 H) 1.04-1.16 (m, 5 H) 1.23-1.26 (m, 1 H) 1.28-1.44 (m, 7 H) 1.44-1.59 (m, 7 H) 1.59-1.67 (m, 2 H) 1.67-1.84 (m, 8 H) 1.86-1.98 (m, 1 H) 2.12 (dd, *J*= 17.40, 6.41 Hz, 1 H) 2.34 (dd, *J*= 12.21, 8.24 Hz, 1 H) 2.50-2.63 (m, 2 H) 2.86 (s, 6 H) 3.03-3.17 (m, 4 H) 4.61 (s, 1 H) 4.72 (d, *J*= 1.53 Hz, 1 H) 5.24-5.32 (m, 1 H) 7.20 (m, *J*= 8.24 Hz, 2 H) 7.92 (m, *J*= 8.24 Hz, 2 H).

Ejemplo 61

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-(terc-butoxicarbonil)-2-(hidroximetil)piperazin-1-carboxamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



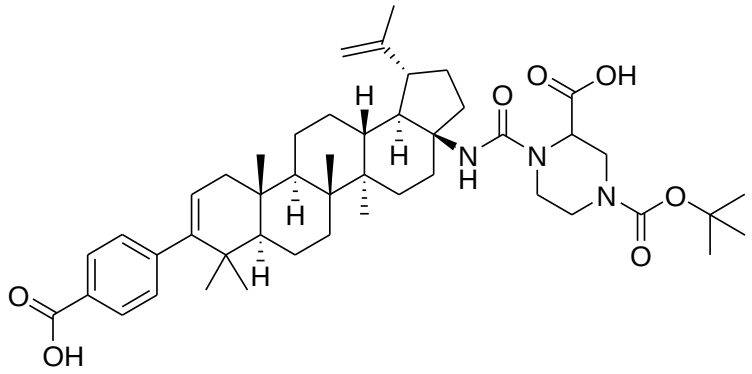
El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de

éster usando 3-(hidroximetil)piperazin-1-carboxilato de *terc-butilo* como la amina reactiva. El producto se aisló como una mezcla de dos diastereómeros después de la purificación por HPLC preparativa de fase inversa como un sólido blanco (68 mg, 60 % de rendimiento). LCMS: m/z 772 ($M+H^+$), tiempo de retención 2.91 y 2.99 min (método 11). Este material es una mezcla diastereomérica en una relación de aproximadamente 5:4. ^{1}H NMR (400 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.89-0.98 (m, 6 H) 0.98-1.04 (m, 6 H) 1.05-1.18 (m, 5 H) 1.20-1.44 (m, 6 H) 1.47 (d, *J*= 2.26 Hz, 9 H) 1.48-1.61 (m, 6 H) 1.62-1.77 (m, 7 H) 1.80-2.01 (m, 2 H) 2.12 (dd, *J*= 16.81, 6.02 Hz, 1 H) 2.32-2.42 (m, 1 H) 2.46-2.56 (m, 1 H) 2.60 (dd, *J*= 13.30, 2.51 Hz, 1 H) 2.98-3.15 (m, 2 H) 3.21 (ddd, *J*= 18.63, 13.87, 4.64 Hz, 1 H) 3.61-3.69 (m, 1 H) 3.71-3.91 (m, 4 H) 3.94-4.06 (m, 1 H) 4.61 (d, *J*= 8.78 Hz, 1 H) 4.74 (dd, *J*= 10.79, 1.25 Hz, 1 H) 5.24-5.33 (m, 1 H) 7.20 (dd, *J*= 8.41, 1.88 Hz, 2 H) 7.86-7.92 (m, 1 H) 7.93 (s, 1 H).

Ejemplo 62

Preparación de ácido 4-(terc-butoxicarbonil)-1-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-carboxifenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-

ilcarbamoil)piperazin-2-carboxílico.

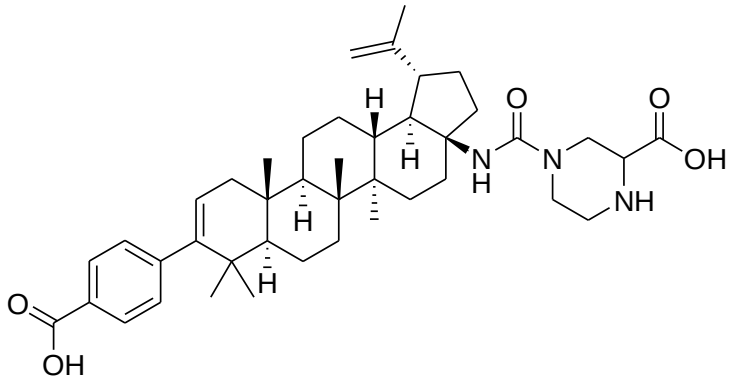


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando 1-terc-butil 3-metil piperazin-1,3-dicarboxilato como la amina reactiva. El producto se aisló como una mezcla de dos diastereómeros después de la purificación por HPLC preparativa de fase inversa como un sólido blanco (76 mg, 62 % de rendimiento). LCMS: m/z 786 ($M+H^+$), tiempo de retención 2.84 min (método 11). Este material es una mezcla diastereomérica en una relación de aproximadamente 1:1. ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.93 (br. s., 3 H) 0.94 (br. s., 3 H) 1.01 (s, 3 H) 1.02 (s, 3 H) 1.04-1.18 (m, 5 H) 1.19-1.43 (m, 6 H) 1.46 (d, *J*= 2.75 Hz, 9 H) 1.47-1.61 (m, 6 H) 1.61-1.80 (m, 8 H) 1.91-2.05 (m, 1 H) 2.12 (dd, *J*= 17.09, 6.41 Hz, 1 H) 2.43 (dd, *J*= 12.21, 8.24 Hz, 1 H) 2.46-2.53 (m, 1 H) 2.53-2.62 (m, 1 H) 2.98 (br. s., 1 H) 3.17 (d, *J*= 9.77 Hz, 1 H) 3.35-3.44 (m, 1 H) 3.50 (d, *J*= 9.77 Hz, 1 H) 4.09 (br. s., 1 H) 4.60 (d, *J*=

13.73 Hz, 1 H) 4.63 (br. s., 1 H) 4.68 (br. s., 1 H) 4.75 (br. s., 1 H) 5.29 (d, *J*= 4.58 Hz, 1 H) 7.20 (d, *J*= 8.24 Hz, 2 H) 7.92 (d, *J*= 8.24 Hz, 2 H).

Ejemplo 63

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-carboxifenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-ilcarbamoil)piperazin-2-carboxílico.

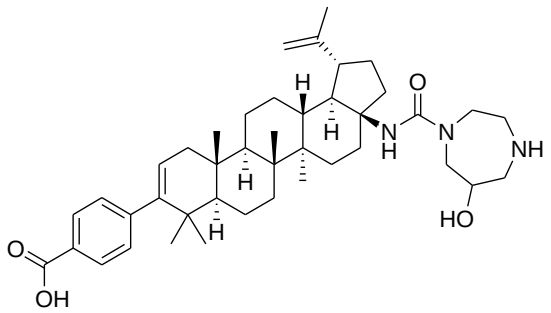


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando piperazin-2-carboxilato de metilo como la amina reactiva. El producto se aisló como una mezcla de dos diastereómeros después de la purificación por HPLC preparativa de fase inversa como una sal de mono-TFA sólida blanca (75 mg, 41 % de rendimiento). LCMS: m/z 686 ($M+H^+$), tiempo de retención 2.46 min (método 11). Este material es

una mezcla diastereomérica en una relación de aproximadamente 1:1. ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.93 (br. s., 3 H) 0.93 (br. s., 3 H) 0.99 (s, 3 H) 1.02 (s, 3 H) 1.05-1.18 (m, 5 H) 1.25 (d, *J*= 7.63 Hz, 1 H) 1.28-1.42 (m, 4 H) 1.42-1.52 (m, 5 H) 1.52-1.64 (m, 2 H) 1.65-1.84 (m, 7 H) 1.87-1.99 (m, 1 H) 2.11 (dd, *J*= 17.09, 6.41 Hz, 1 H) 2.41 (td, *J*= 11.90, 8.85 Hz, 1 H) 2.55 (dd, *J*= 13.43, 2.75 Hz, 1 H) 2.63 (tt, *J*= 10.72, 5.46 Hz, 1 H) 3.07-3.18 (m, 0.5 H) 3.19-3.27 (m, 0.5 H) 3.34-3.51 (m, 2 H) 3.57-3.71 (m, 1 H) 3.71-3.83 (m, 1 H) 3.98-4.05 (m, 0.5 H) 4.07-4.16 (m, 1 H) 4.16-4.25 (m, 0.5 H) 4.63 (s, 1 H) 4.76 (br. s., 1 H) 5.28 (d, *J*= 4.88 Hz, 1 H) 7.19 (m, *J*= 8.24 Hz, 2 H) 7.92 (m, *J*= 8.24 Hz, 2 H).

Ejemplo 64

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(6-hidroxi-1,4-diazepan-1-carboxamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



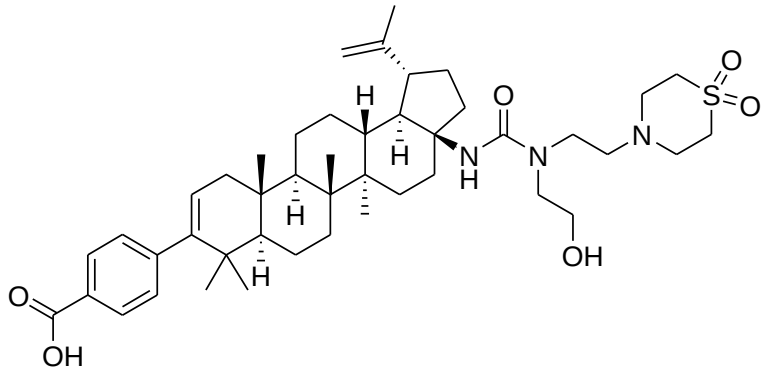
El compuesto del título se preparó de acuerdo con

los procedimientos generales descritos anteriormente para la formación de urea C-17 y la posterior hidrólisis de éster usando dibromhidrato de 1,4-diazepan-6-ol como la amina reactiva. El producto se aisló como una mezcla de dos diastereómeros después de la purificación por HPLC preparativa de fase inversa como una sal de mono-TFA sólida blanca (30 mg, 35 % de rendimiento). LCMS: m/z 672 ($M+H^+$), tiempo de retención 2.42 min (método 11). Este material es una mezcla diastereomérica en una relación de aproximadamente 1:1. ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.89-0.96 (m, 6 H) 0.97-1.05 (m, 6 H) 1.05-1.17 (m, 5 H) 1.22-1.42 (m, 6 H) 1.42-1.60 (m, 7 H) 1.64-1.80 (m, 7 H) 1.82-2.02 (m, 2 H) 2.12 (dd, *J*= 17.09, 6.10 Hz, 1 H) 2.49-2.65 (m, 2 H) 3.12-3.32 (m, 4 H) 3.36-3.44 (m, 1 H) 3.45-3.53 (m, 1 H) 3.78 (d, *J*= 15.56 Hz, 0.5 H) 3.95 (d, *J*= 15.56 Hz, 0.5 H) 4.25-4.44 (m, 2 H) 4.62 (d, *J*= 8.85 Hz, 1 H) 4.71 (br. s., 0.5 H) 4.75 (br. s., 0.5 H) 5.29 (d, *J*= 6.10 Hz, 1 H) 5.69 (s, 0.5 H) 5.74 (s, 0.5 H) 7.20 (dd, *J*= 8.24, 1.53 Hz, 2 H) 7.92 (d, *J*= 7.93 Hz, 2 H).

Ejemplo 65

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((2-(1,1-dioxido-4-tiomorfolinil)etil)(2-hidroxietil)carbamoil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

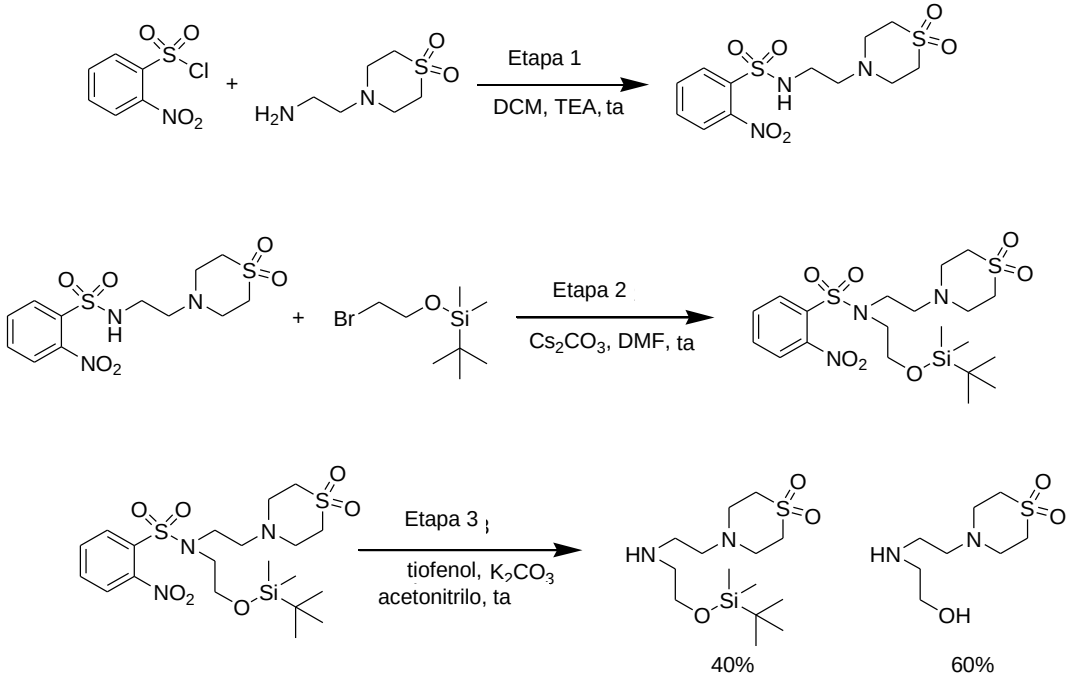
octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



El compuesto del título se preparó de acuerdo con los procedimientos generales descritos para la formación de urea C-17 y la posterior hidrólisis de éster usando la mezcla de 2-((*terc-butil*(dimetil)silil)oxi)-*N*-(2-(1,1-dioxido-4-tiomorfolinil)etil)etanamina y 2-((2-(1,1-dioxido-4-tiomorfolinil)etil)amino)etanol obtenidos en la siguiente Etapa 3 como la amina reactiva. La etapa de formación de urea produjo el material desililado directamente como el principal producto de reacción, por lo cual no fue necesaria la etapa de desililación. Después de la hidrólisis del éster, el producto salino de mono-TFA se aisló mediante purificación por HPLC preparativa de fase inversa como un sólido blanco (96 mg, 57 % de rendimiento). LCMS: m/z 778 ($M+H^+$), tiempo de retención 2.43 min (método 11). ^1H NMR (400 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.94 (br. s., 3 H) 0.94 (s, 3 H) 1.01 (br. s., 3 H) 1.02 (s, 3 H) 1.06-1.16 (m, 5 H) 1.20-1.45 (m, 6 H) 1.45-1.64 (m, 6 H) 1.64-1.79 (m, 6 H) 1.81-

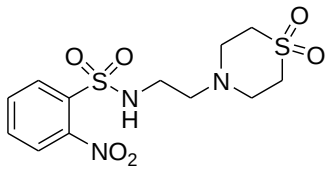
2.00 (m, 2 H) 2.12 (dd, *J*= 17.07, 6.27 Hz, 1 H) 2.38 (dd, *J*= 11.80, 8.03 Hz, 1 H) 2.48-2.63 (m, 2 H) 3.16 (br. s., 2 H) 3.30 (br. s., 1 H) 3.37 (br. s., 4 H) 3.43-3.58 (m, 3 H) 3.60 (br. s., 4 H) 3.76 (br. s., 2 H) 4.61 (d, *J*= 1.51 Hz, 1 H) 4.73 (d, *J*= 1.25 Hz, 1 H) 5.29 (d, *J*= 4.77 Hz, 1 H) 7.20 (m, *J*= 8.28 Hz, 2 H) 7.92 (m, *J*= 8.28 Hz, 2 H).

Síntesis de amina usada para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((2-(1,1-dioxido-4-tiomorfolinil)etil)(2-hidroxietil)carbamoil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico:



Etapa 1. Preparación de *N*-(2-(1,1-dioxido-4-

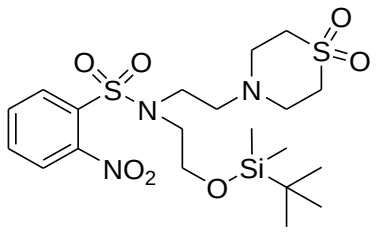
tiomorfolinil)etil)-2-nitrobencensulfonamida.



Una mezcla de 1,1-dióxido de 4-(2-aminoetil)tiomorfolina (2.00 g, 11.2 mmol) y trietilamina (1.42 g, 14.0 mmol) en DCM (100 mL) se enfrió en un baño de hielo y se trató lentamente con cloruro de 2-nitrobencen-1-sulfonilo (2.49 g, 11.2 mmol). Se retiró la mezcla del baño de hielo y se agitó a temperatura ambiente durante 18 h. La mezcla resultante se lavó con agua (2 x 50 mL), y los lavados acuosos combinados se extrajeron con DCM (50 mL). Las fases orgánicas se combinaron, se secaron en sulfato de sodio anhidro, se filtraron y se concentraron al vacío para obtener un sólido amarillo. La purificación mediante cromatografía en gel de sílice (gradiente lineal 100 % DCM a 100:1 DCM:MeOH) produjo el compuesto del título como un sólido amarillo pálido (3.47 g, 85 % de rendimiento). LCMS: m/z 364 ($M+H^+$), tiempo de retención 0.98 min (método 11). ^{1}H NMR (500 MHz, CLOROFORMO-*d*) δ ppm 2.71 (t, *J*= 5.49 Hz, 2 H) 2.96 (br. s., 4 H) 3.05 (br. s., 4 H) 3.20 (q, *J*= 5.49 Hz, 2 H) 5.93 (br. s., 1 H) 7.73-7.84 (m, 2 H) 7.84-7.93 (m, 1 H) 8.11-8.23 (m, 1 H).

Etapa 2. Preparación de *N*-(2-((*terc-butil*(dimetil)silil)oxi)etil)-*N*-(2-(1,1-dioxido-4-

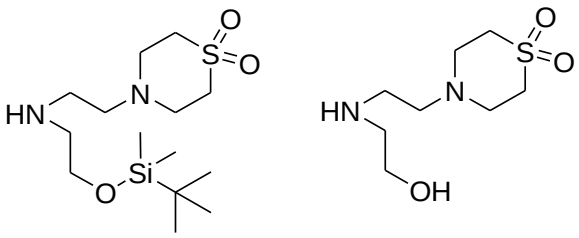
tiomorfolinil)etil)-2-nitrobencensulfonamida.



Se combinó *N*-(2-(1,1-dioxido-4-tiomorfolinil)etil)-2-nitrobencensulfonamida (0.400 g, 1.10 mmol) con carbonato de cesio (0.538 g, 1.65 mmol) en DMF (5 mL). La suspensión se agitó a temperatura ambiente durante 30 min, luego se le agregó (2-bromoetoxi)(*terc-butil*)dimetilsilano (0.527 g, 2.20 mmol). La mezcla resultante se agitó a temperatura ambiente durante 18 h. La dilución con acetato de etilo (60 mL) y agua (40 mL) seguido de agitación produjo la separación de fases. La fase orgánica se aisló, se lavó con agua (2 x 30 mL) y salmuera (25 mL), se secó en sulfato de magnesio anhidro, se filtró y se concentró al vacío hasta obtener un residuo. La purificación mediante cromatografía en gel de sílice (gradiente 100 % DCM a 100:1 DCM:MeOH) produjo el compuesto del título como un sólido amarillo (0.560 g, 98 % de rendimiento). LCMS: m/z 522 ($M+H^+$), tiempo de retención 2.22 min (método 11). ^{1}H NMR (500 MHz, CLOROFORMO-*d*) δ ppm 0.01 (s, 6 H) 0.86 (s, 9 H) 2.75 (t, *J*= 5.95 Hz, 2 H) 3.05 (s, 8 H) 3.44 (t, *J*= 5.49 Hz, 2 H) 3.57 (t, *J*= 6.41 Hz, 2 H) 3.70 (t, *J*= 5.49 Hz, 2 H) 7.63-

7.78 (m, 3 H) 8.02-8.11 (m, 1 H).

Etapa 3. Preparación de una mezcla de 2-((*terc*-*butil*(dimetil)silil)oxi)-*N*-(2-(1,1-dioxido-4-tiomorfolinil)etil)etanamina y 2-((2-(1,1-dioxido-4-tiomorfolinil)etil)amino)etanol

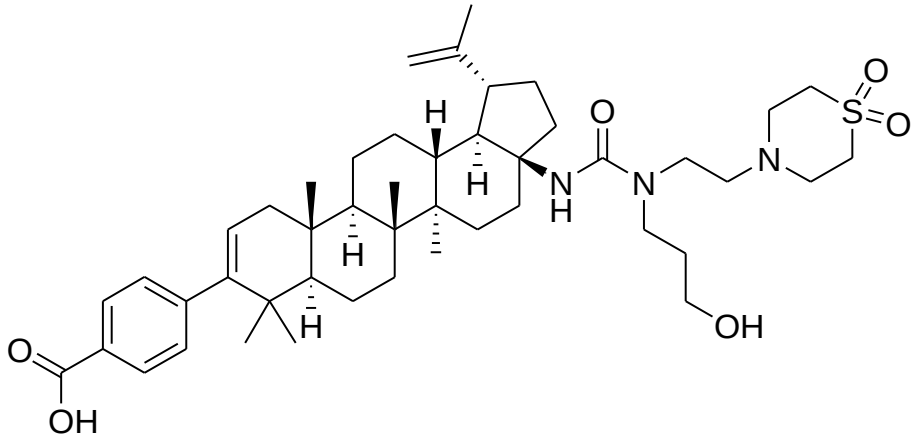


Se combinaron *N*-(2-((*terc*-*butil*(dimetil)silil)oxi)etil)-*N*-(2-(1,1-dioxido-4-tiomorfolinil)etil)-2-nitrobencensulfonamida (0.550 g, 1.05 mmol) y tiofenol (0.348 g, 3.16 mmol) en acetonitrilo seco (10 mL). Se agregó carbonato de potasio (0.583 g, 4.22 mmol), y la mezcla se agitó a temperatura ambiente durante 18 h. La mezcla se diluyó con acetato de etilo y se filtró para retirar los sólidos no deseados. El filtrado crudo se concentró al vacío, se volvió a disolver en metanol y se cargó en un cartucho de resina de intercambio catiónico fuerte, a fin de capturar el producto deseado. Los materiales no deseados se eluyeron del cartucho con metanol, y luego el material deseado se liberó de la resina mediante elución con amoníaco 2 M en metanol. La concentración al vacío produjo un sólido amarillo (0.300 g, 85 % de rendimiento). ^{1}H NMR reveló que

el material recolectado fue aproximadamente una mezcla 2:3 de producto deseado y material deseado desililado. No se realizó purificación adicional, y la mezcla se usó en la siguiente etapa.

Ejemplo 66

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((2-(1,1-dioxido-4-tiomorfolinil)etil)(3-hidroxipropil)carbamoil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

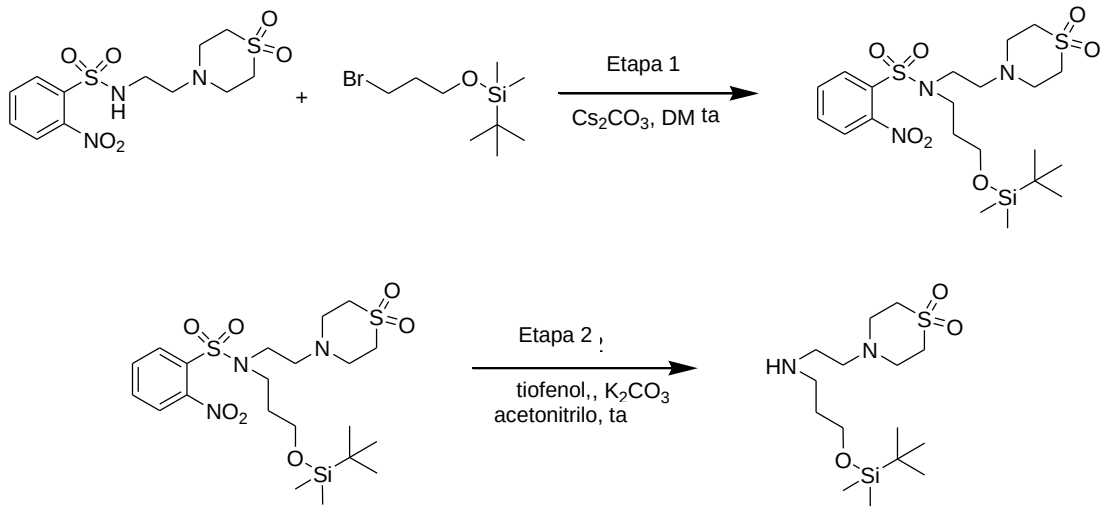


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos para la formación de urea C-17 y la posterior hidrólisis de éster usando 3-((*terc-butil*(dimetil)silil)oxi)-*N*-(2-(1,1-dioxido-4-tiomorfolinil)etil)-1-propanamina como la amina reactiva (preparada como se describe más adelante). La etapa de

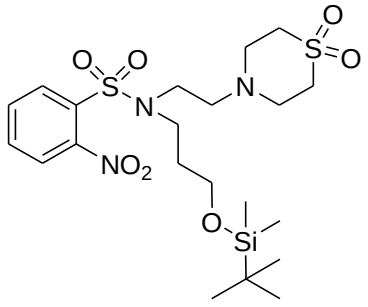
formación de urea produjo el material desililado directamente como el principal producto de reacción, por lo cual no fue necesaria la etapa de desililación. Después de la hidrólisis del éster, el producto salino de mono-TFA se aisló mediante purificación por HPLC preparativa de fase inversa como un sólido blanco (86 mg, 53 % de rendimiento). LCMS: m/z 792 ($M+H^+$), tiempo de retención 2.45 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.93 (br. s., 3 H) 0.94 (br. s., 3 H) 1.00 (s, 3 H) 1.02 (s, 3 H) 1.07-1.17 (m, 5 H) 1.25 (d, *J*= 7.02 Hz, 1 H) 1.28-1.45 (m, 5 H) 1.45-1.65 (m, 7 H) 1.65-1.75 (m, 6 H) 1.75-1.85 (m, 2 H) 1.85-1.99 (m, 2 H) 2.12 (dd, *J*= 17.09, 6.41 Hz, 1 H) 2.41 (dd, *J*= 12.05, 8.09 Hz, 1 H) 2.58 (d, *J*= 13.43 Hz, 1 H) 2.66 (td, *J*= 10.91, 4.73 Hz, 1 H) 3.09 (br. s., 2 H) 3.39-3.52 (m, 2 H) 3.54 (br. s., 4 H) 3.55-3.63 (m, 2 H) 3.67 (ddd, *J*= 10.76, 5.26, 5.04 Hz, 1 H) 4.62 (s, 1 H) 4.75 (s, 1 H) 5.29 (d, *J*= 4.58 Hz, 1 H) 7.20 (m, *J*= 8.24 Hz, 2 H) 7.92 (m, *J*= 8.24 Hz, 2 H).

Síntesis de amina usada en la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((2-(1,1-dioxido-4-tiomorfolinil)etil)(3-hidroxipropil)carbamoil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico:



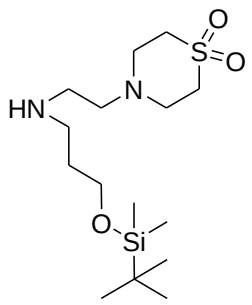
Etapa 1. Preparación de *N*-(3-((*terc-butil*(dimetil)silil)oxi)propil)-*N*-(2-(1,1-dioxido-4-tiomorfolinil)etil)-2-nitrobencensulfonamida.



Se combinó *N*-(2-(1,1-dioxido-4-tiomorfolinil)etil)-2-nitrobencensulfonamida (0.400 g, 1.10 mmol) con carbonato de cesio (0.538 g, 1.65 mmol) en DMF (5 mL). La suspensión se agitó a temperatura ambiente durante 30 min, luego se le agregó (3-bromopropoxi)(*terc-butil*)dimetilsilano (0.558 g, 2.20 mmol). La mezcla resultante se agitó a temperatura ambiente durante 18 h. La LCMS indicó conversión incompleta; por lo tanto, se agregaron (3-bromopropoxi)(*terc-*

butil)dimetilsilano (0.558 g, 2.20 mmol) y carbonato de cesio (0.538 g, 1.65 mmol) adicionales, y la mezcla se calentó a 70 °C durante 1 h. La dilución con acetato de etilo (60 mL) y agua (40 mL), seguido de agitación, produjeron la separación de fases. La fase orgánica se aisló, se lavó con agua (2 x 30 mL) y salmuera (25 mL), se secó en sulfato de magnesio anhidro, se filtró y se concentró al vacío hasta obtener un residuo. La purificación mediante cromatografía en gel de sílice (gradiente 100 % DCM a 100:1 DCM:MeOH) produjo el compuesto del título como un material amarillo pegajoso, parcialmente cristalino (0.548 g, 93 % de rendimiento). LCMS: m/z 536 ($M+H^+$), tiempo de retención 2.26 min (método 11). ^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 0.02 (s, 6 H) 0.87 (s, 9 H) 1.63-1.75 (m, 2 H) 2.72 (t, *J*= 6.40 Hz, 2 H) 3.07 (s, 8 H) 3.32-3.40 (m, 2 H) 3.47 (t, *J*= 6.40 Hz, 2 H) 3.56 (t, *J*= 5.90 Hz, 2 H) 7.63-7.76 (m, 3 H) 8.08 (dd, *J*= 7.53, 1.76 Hz, 1 H).

Etapa 2. Preparación de 3-((*terc-butil*(dimetil)silil)oxi)-*N*-(2-(1,1-dioxido-4-tiomorfolinil)etil)-1-propanamina.



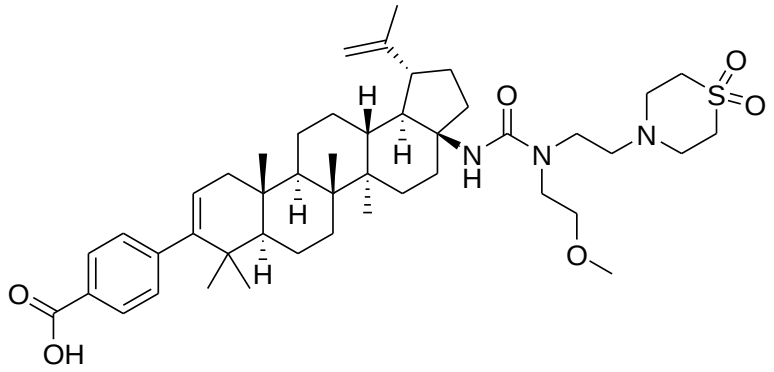
Se combinaron *N*-(3-((*terc-*

butil(dimetil)silil)oxi)propil)-*N*-(2-(1,1-dioxido-4-tiomorfolinil)etil)-2-nitrobencensulfonamida (0.540 g, 1.01 mmol) y tiofenol (0.333 g, 3.02 mmol) en acetonitrilo seco (10 mL). Se agregó carbonato de potasio (0.557 g, 4.03 mmol), y la mezcla se agitó a temperatura ambiente durante 18 h. La mezcla se diluyó con acetato de etilo y se filtró para retirar los sólidos no deseados. El filtrado crudo se concentró al vacío, se volvió a disolver en metanol y se cargó en un cartucho de resina de intercambio catiónico fuerte, a fin de capturar el producto deseado. Los materiales no deseados se eluyeron del cartucho con metanol, y luego el material deseado se liberó de la resina mediante elución con amoníaco 2 M en metanol. La concentración al vacío produjo el compuesto del título como un aceite amarillo (0.294 g, 83 % rendimiento). No se realizó purificación adicional, y la mezcla se usó en la siguiente etapa. LCMS: m/z 351 ($M+H^+$), ^1H NMR (400 MHz, CLOROFORMO-*d*) δ ppm 0.06 (s, 6 H) 0.90 (s, 9 H) 1.75 (quin, *J*= 6.46 Hz, 2 H) 2.69-2.72 (m, 2 H) 2.72-2.80 (m, 4 H) 3.00-3.11 (m, 8 H) 3.70 (t, *J*= 6.02 Hz, 2 H).

Ejemplo 67

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-tiomorfolinil)etil)(2-metoxietil)carbamoil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-

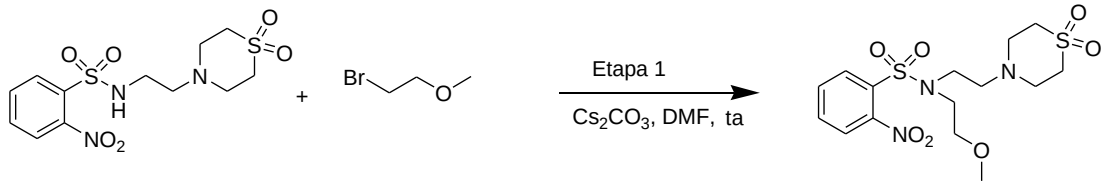
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

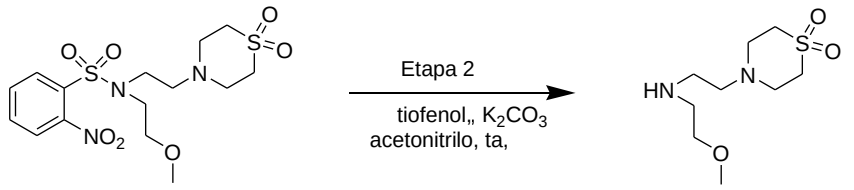


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos para la formación de urea C-17 y la posterior hidrólisis del éster usando 2-(1,1-dioxido-4-tiomorfolinil)-*N*-(2-metoxietil)etanamina (preparada como se describe a continuación) como la amina reactiva. Después de la hidrólisis del éster, el producto salino de mono-TFA se aisló por purificación mediante HPLC preparativa de fase inversa como un sólido blanco (89 mg, 57 % de rendimiento). LCMS: m/z 792 ($M+H^+$), tiempo de retención 2.48 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.94 (br. s., 3 H) 0.95 (s, 3 H) 1.01 (s, 3 H) 1.02 (s, 3 H) 1.06-1.17 (m, 5 H) 1.24-1.29 (m, 1 H) 1.30-1.42 (m, 4 H) 1.44-1.55 (m, 6 H) 1.55-1.65 (m, 2 H) 1.65-1.77 (m, 6 H) 1.82 (td, *J*= 12.13, 3.20 Hz, 1 H) 1.86-1.98 (m, 1 H) 2.13 (dd, *J*= 17.09, 6.41 Hz, 1 H) 2.38 (dd, *J*= 12.36, 8.09 Hz, 1 H) 2.47 (td, *J*= 10.99, 5.19 Hz, 1 H) 2.51-2.61 (m, 1 H) 3.03-

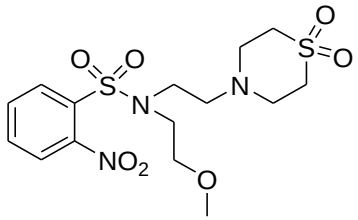
3.19 (m, 2 H) 3.34-3.44 (m, 5 H) 3.51 (s, 3 H) 3.52-3.69 (m, 8 H) 4.64 (s, 1 H) 4.73 (s, 1 H) 5.29 (d, *J*= 4.58 Hz, 1 H) 7.20 (m, *J*= 8.24 Hz, 2 H) 7.92 (m, *J*= 8.24 Hz, 2 H).

Síntesis de amina usada en la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-tiomorfolinil)etil)(2-metoxietil)carbamoil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.





Etapa 1. Preparación de *N*-(2-(1,1-dioxido-4-tiomorfolinil)etil)-*N*-(2-metoxietil)-2-nitrobencensulfonamida.

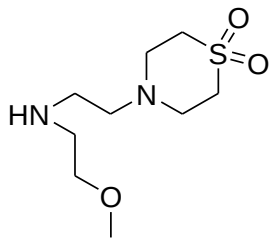


Se combinó *N*-(2-(1,1-dioxido-4-

tiomorfolinil)etil)-2-nitrobencensulfonamida (0.400 g, 1.10 mmol) con carbonato de cesio (0.538 g, 1.65 mmol) en DMF (5 mL). La suspensión se agitó a temperatura ambiente durante 30 min; luego, se agregó 1-bromo-2-metoxietano (0.306 g, 2.20 mmol). La mezcla resultante se agitó a temperatura ambiente durante 72 h. La LCMS indicó la conversión incompleta; por lo tanto, se agregaron 1-bromo-2-metoxietano (0.306 g, 2.20 mmol) y carbonato de cesio (0.538 g, 1.65 mmol) adicionales, y la mezcla se calentó a 70 °C durante 1 h. La dilución con acetato de etilo (60 mL) y agua (40 mL), y luego la agitación produjeron la separación de fases. La fase orgánica se aisló, se lavó con agua (2 x 30 mL) y salmuera (25 mL), se secó en sulfato de magnesio anhidro, se filtró y se concentró al vacío para obtener un residuo. La purificación por cromatografía de gel de sílice (gradiente de 100 % de DCM a 60:1 DCM:MeOH) produjo el compuesto del título como un aceite amarillo (0.486 g, 105 % de rendimiento). LCMS: m/z 422 ($M+H^+$), tiempo de retención 1.35 min (método 11). ^{1}H NMR (500 MHz, CLOROFORMO-*d*) δ ppm 2.72 (t, *J*= 6.41 Hz, 2 H) 3.01 (s, 8 H) 3.21 (s, 3 H) 3.39-3.52 (m, 6 H) 7.62-7.66 (m, 1 H) 7.66-7.74 (m, *J*= 7.48, 7.32, 7.32, 7.32, 1.68 Hz, 2 H) 8.01 (dd, *J*= 7.78, 1.68 Hz, 1 H).

Etapa 2. Preparación de 2-(1,1-dioxido-4-

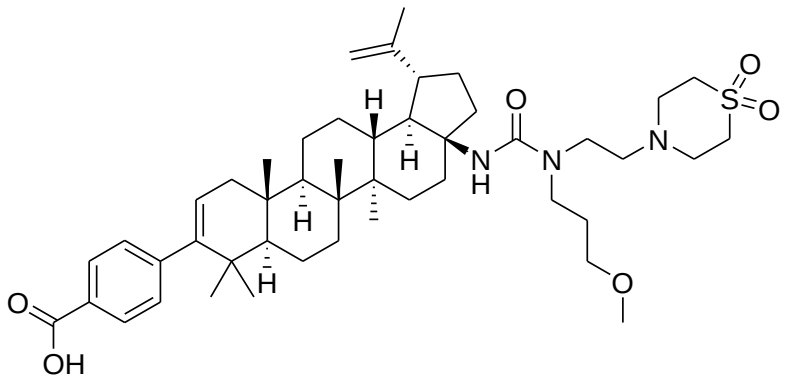
tiomorfolinil)-*N*-(2-metoxietil)etanamina.



Se combinaron *N*-(2-(1,1-dioxido-4-tiomorfolinil)etil)-*N*-(2-metoxietil)-2-nitrobencensulfonamida (0.470 g, 1.12 mmol) y tiofenol (0.369 g, 3.35 mmol) en acetonitrilo seco (10 mL). Se agregó carbonato de potasio (0.616 g, 4.46 mmol), y la mezcla se agitó a temperatura ambiente durante 18 h. La mezcla se diluyó con acetato de etilo y se filtró para retirar los sólidos no deseados. El filtrado crudo se concentró al vacío, se volvió a disolver en metanol y se cargó en un cartucho de resina de intercambio catiónico fuerte, a fin de capturar el producto deseado. Los materiales no deseados se eluyeron del cartucho con metanol, y luego el material deseado se liberó de la resina mediante elución con amoníaco 2M en metanol. La concentración al vacío produjo el compuesto del título como un sólido amarillo (0.222 g, 84 % rendimiento). No se realizó purificación adicional, y la mezcla se usó en la siguiente etapa. LCMS: m/z 237 ($M+H^+$), ^{1}H NMR (500 MHz, CLOROFORMO-*d*) δ ppm 2.15 (br. s., 1 H) 2.66-2.71 (m, 2 H) 2.71-2.77 (m, 2 H) 2.82 (t, *J*= 5.04 Hz, 2 H) 2.97-3.05 (m, 4 H) 3.05-3.10 (m, 4 H) 3.37 (s, 3 H) 3.51 (t, *J*= 5.04 Hz, 2 H).

Ejemplo 68

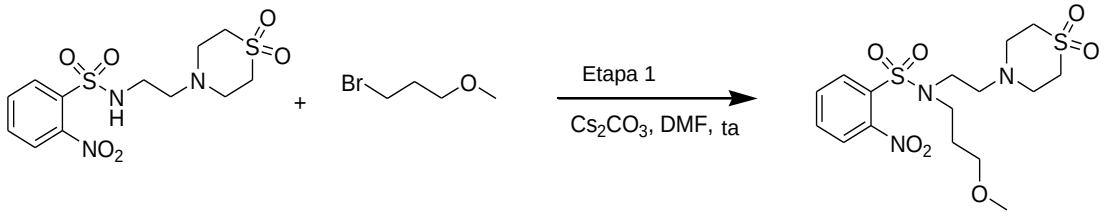
Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-tiomorfolinil)etil)(3-metoxipropil)carbamoil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

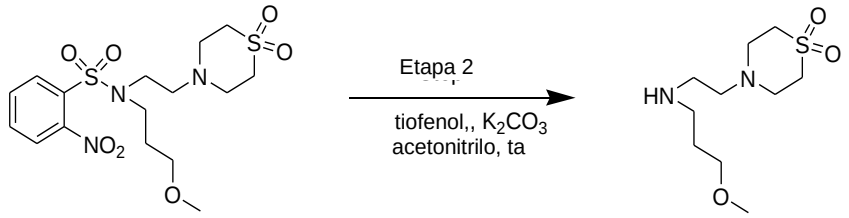


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos para la formación de urea C-17 y la posterior hidrólisis del éster usando *N*-(2-(1,1-dioxido-4-tiomorfolinil)etil)-3-metoxi-1-propanamina (preparada como se describe a continuación) como la amina reactiva. Después de la hidrólisis del éster, el producto salino de mono-TFA se aisló por purificación mediante HPLC preparativa de fase inversa como un sólido blanco (132 mg, 82% de rendimiento). LCMS: m/z 806 ($M+H^+$), tiempo de retención 2.52 min (método 11). ^{1}H NMR (400 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.94 (br. s., 3

H) 0.95 (s, 3 H) 1.01 (s, 3 H) 1.03 (s, 3 H) 1.10 (s, 3 H) 1.11-1.21 (m, 2 H) 1.21-1.42 (m, 5 H) 1.43-1.65 (m, 8 H) 1.65-1.77 (m, 6 H) 1.77-1.98 (m, 5 H) 2.12 (dd, *J*= 17.07, 6.27 Hz, 1 H) 2.40 (dd, *J*= 12.17, 8.16 Hz, 1 H) 2.55-2.67 (m, 2 H) 3.01 (t, *J*= 6.15 Hz, 2 H) 3.29 (d, *J*= 5.02 Hz, 4 H) 3.34-3.42 (m, 1 H) 3.42-3.59 (m, 11 H) 4.74 (d, *J*= 1.51 Hz, 1 H) 5.24-5.34 (m, 1 H) 7.20 (m, *J*= 8.28 Hz, 2 H) 7.92 (m, *J*= 8.28 Hz, 2 H).

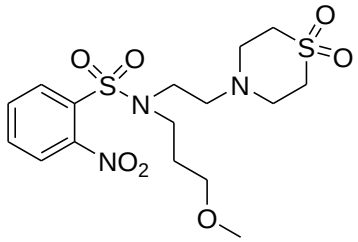
Síntesis de amina usada en la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-tiomorfolinil)etil)(3-metoxipropil)carbamoil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.





Etapa 1. Preparación de *N*-(2-(1,1-dioxido-4-

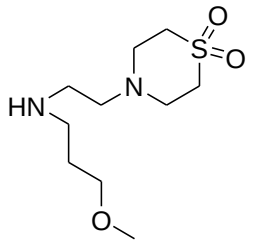
tiomorfolinil)etil)-*N*-(3-metoxipropil)-2-nitrobencensulfonamida.



Se combinó *N*-(2-(1,1-dioxido-4-tiomorfolinil)etil)-2-nitrobencensulfonamida (0.400 g, 1.10 mmol) con carbonato de cesio (0.538 g, 1.65 mmol) en DMF (5 mL). La suspensión se agitó a temperatura ambiente durante 30 min; luego, se agregó 1-bromo-3-metoxipropano (0.337 g, 2.20 mmol). La mezcla resultante se agitó a temperatura ambiente durante 72 h. La LCMS indicó la conversión incompleta; por lo tanto, se agregaron 1-bromo-3-metoxipropano (0.337 g, 2.20 mmol) y carbonato de cesio (0.538 g, 1.65 mmol), y la mezcla se agitó a 70 °C durante 1 hora. La dilución con acetato de etilo (60 mL) y agua (40 mL), y luego la agitación produjo la separación de fases. La fase orgánica se aisló, se lavó con agua (2 x 30 mL) y salmuera (25 mL), se secó en sulfato de magnesio anhidro, se filtró y se concentró al vacío para obtener un residuo. La purificación por cromatografía de gel de sílice (gradiente de 100 % de DCM a 60:1 de DCM:MeOH) produjo el compuesto del título como un aceite amarillo (0.522 g, 109 % de rendimiento). LCMS: m/z 436 ($M+H^+$), tiempo de retención 1.50 min (método 11). ^1H NMR (500 MHz,

CLOROFORMO-*d*) δ ppm 1.68-1.77 (m, 2 H) 2.67 (t, *J*= 6.26 Hz, 2 H) 3.02 (br. s., 8 H) 3.16 (s, 3 H) 3.27 (t, *J*= 5.80 Hz, 2 H) 3.31-3.37 (m, 2 H) 3.41 (t, *J*= 6.26 Hz, 2 H) 7.61-7.65 (m, 1 H) 7.66-7.74 (m, 2 H) 7.99-8.03 (m, 1 H).

Etapa 2. Preparación de *N*-(2-(1,1-dioxido-4-tiomorfolinil)etil)-3-metoxi-1-propanamina.

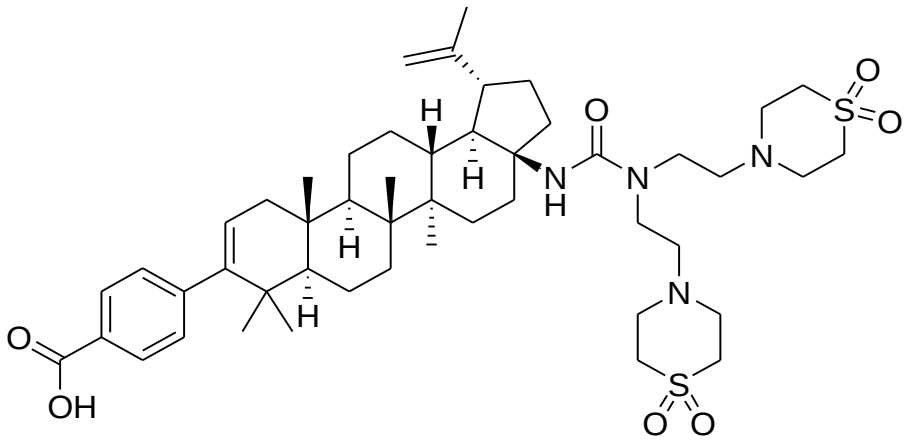


Se combinaron *N*-(2-(1,1-dioxido-4-tiomorfolinil)etil)-*N*-(3-metoxipropil)-2-nitrobencensulfonamida (0.510 g, 1.17 mmol) y tiofenol (0.387 g, 3.51 mmol) en acetonitrilo seco (10 mL). Se agregó carbonato de potasio (0.647 g, 4.68 mmol), y la mezcla se agitó a temperatura ambiente durante 18 h. La mezcla se diluyó con acetato de etilo y se filtró para retirar los sólidos no deseados. El filtrado crudo se concentró al vacío, se volvió a disolver en metanol y se cargó en un cartucho de resina de intercambio catiónico fuerte, a fin de capturar el producto deseado. Los materiales no deseados se eluyeron del cartucho con metanol, y luego el material deseado se liberó de la resina mediante elución con amoníaco 2 M en metanol. La concentración al vacío produjo un aceite amarillo (0.255 g, 87 % de rendimiento). No se realizó purificación adicional, y

la mezcla se pasó a la siguiente etapa. LCMS: m/z 251 ($M+H^+$), ^{1}H NMR (400 MHz, Cloroformo-*d*) δ ppm 1.77 (quin, *J*= 6.53 Hz, 2 H) 2.13 (br. s., 2 H) 2.62-2.68 (m, 2 H) 2.68-2.75 (m, 4 H) 2.93-3.11 (m, 8 H) 3.32 (s, 3 H) 3.44 (t, *J*= 6.15 Hz, 2 H).

Ejemplo 69

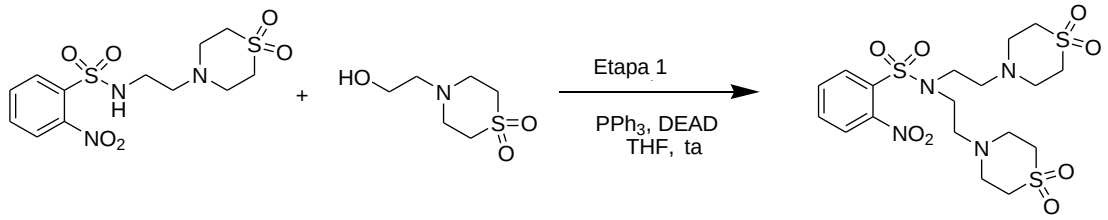
Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((bis(2-(1,1-dioxido-4-tiomorfolinil)etil)carbamoil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

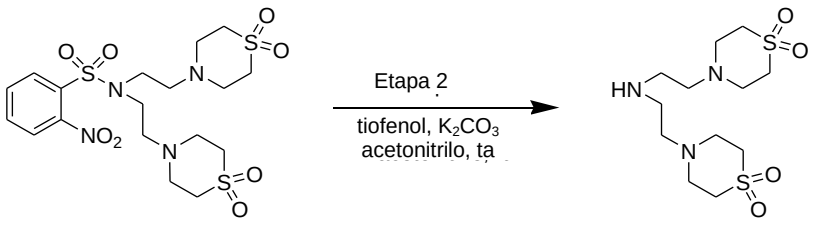


El compuesto del título se preparó de acuerdo con los procedimientos generales descritos para la formación de urea C-17 y la posterior hidrólisis del éster usando 2-(1,1-dioxido-4-tiomorfolinil)-N-(2-(1,1-dioxido-4-tiomorfolinil)etil)etanamina (preparada como se describe a continuación) como la amina reactiva. Después de la hidrólisis del éster, el producto salino de bis-TFA se

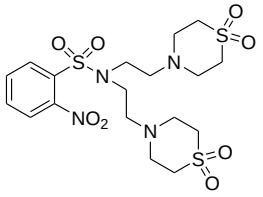
aisló por purificación mediante HPLC preparativa de fase inversa como un sólido ligeramente amarillo (109 mg, 64 % de rendimiento). LCMS: m/z 895 ($M+H^+$), tiempo de retención 2.42 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 0.94 (br. s., 3 H) 0.95 (br. s., 3 H) 1.01 (s, 3 H) 1.04 (s, 3 H) 1.12 (s, 3 H) 1.13-1.22 (m, 2 H) 1.23-1.32 (m, 2 H) 1.33-1.43 (m, 2 H) 1.43-1.63 (m, 8 H) 1.64-1.81 (m, 7 H) 1.84-1.96 (m, 1 H) 2.13 (dd, *J*= 17.24, 6.26 Hz, 1 H) 2.38 (td, *J*= 10.61, 5.04 Hz, 1 H) 2.47 (dd, *J*= 12.51, 8.24 Hz, 1 H) 2.50-2.59 (m, 1 H) 3.01 (br. s., 4 H) 3.26 (br. s., 8 H) 3.35-3.50 (m, 10 H) 3.50-3.62 (m, 2 H) 4.67 (s, 1 H) 4.80 (s, 1 H) 5.29 (dd, *J*= 6.10, 1.53 Hz, 1 H) 7.20 (d, *J*= 8.24 Hz, 2 H) 7.92 (d, *J*= 8.55 Hz, 2 H).

Síntesis de amina usada en la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((bis(2-(1,1-dioxido-4-tiomorfolinil)etil)carbamoil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.





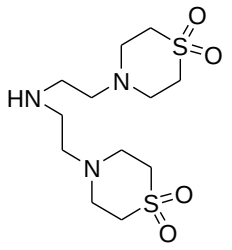
Etapa 1. Preparación de *N*,*N*-bis(2-(1,1-dioxido-4-tiomorfolinil)etil)-2-nitrobencensulfonamida.



Se combinó *N*-(2-(1,1-dioxido-4-tiomorfolinil)etil)-2-nitrobencensulfonamida (0.500 g, 1.38 mmol) con 1,1-dioxido de 4-(2-hidroxietil)tiomorfolina (0.296 g, 1.65 mmol) en THF (10 mL). A esta mezcla, se agregó trifenilfosfina (0.541 g, 2.06 mmol) y azodicarboxilato de dietilo (0.359 g, 2.06 mmol). La mezcla resultante se agitó a temperatura ambiente durante 72 h. La

mezcla se concentró al vacío y, luego, se volvió a disolver en acetonitrilo. La purificación mediante HPLC preparativa de fase inversa produjo el compuesto del título como una sal de bis-TFA sólida amarilla pálida (0.863 g, 83 % de rendimiento). LCMS: m/z 525 ($M+H^+$), tiempo de retención 1.25 min (método 11). ^{1}H NMR (500 MHz, MeOD) δ ppm 2.85 (t, *J*= 6.71 Hz, 4 H) 3.14 (d, *J*= 5.49 Hz, 8 H) 3.18 (d, *J*= 5.80 Hz, 8 H) 3.51 (t, *J*= 6.71 Hz, 4 H) 7.71-7.75 (m, 1 H) 7.75-7.84 (m, 2 H) 8.05 (d, *J*= 7.63 Hz, 1 H).

Etapa 2. Preparación de 2-(1,1-dioxido-4-tiomorfolinil)-*N*-(2-(1,1-dioxido-4-tiomorfolinil)etil)etanamina.

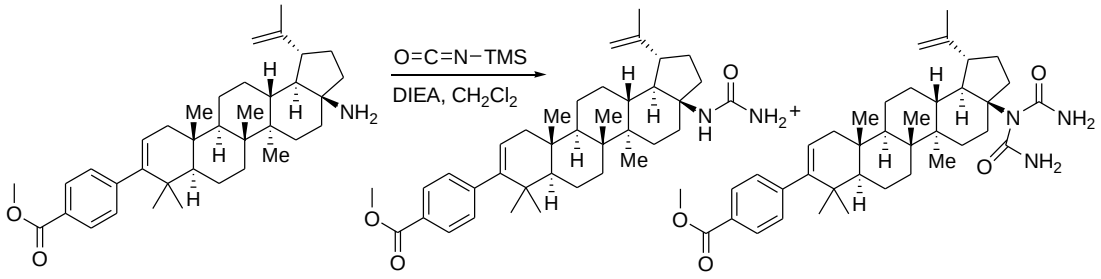


Se combinaron *N*,*N*-bis(2-(1,1-dioxido-4-tiomorfolinil)etil)-2-nitrobencenesulfonamida (0.85 g, 1.13 mmol) y tiofenol (0.373 g, 3.39 mmol) en acetonitrilo seco (10 mL). Se agregó carbonato de potasio (0.936 g, 6.78 mmol), y la mezcla se agitó a temperatura ambiente durante 18 h. La mezcla se diluyó con acetato de etilo y se filtró para eliminar los sólidos no deseados. El filtrado crudo se concentró al vacío, se volvió a disolver en metanol y se cargó en un cartucho de resina de intercambio catiónico fuerte, a fin de capturar el producto deseado. Los materiales no deseados se eluyeron del

cartucho con metanol, y luego el material deseado se liberó de la resina mediante elución con amoníaco 2 M en metanol. La concentración al vacío produjo un aceite amarillo pegajoso (0.381 g, 100 % de rendimiento). No se realizó purificación adicional, y la mezcla se pasó a la siguiente etapa.

Ejemplo 69-1

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-ureido-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico y ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(1-carbamoilureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



Ejemplo 69-1

Etapa 1. A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (50 mg, 0.092 mmol) en DCM (1 mL) se agregaron diisopropiletilamina (0.016 mL, 0.092 mmol) e isocianatotrimetilsilano (15.89 mg, 0.138 mmol). La mezcla resultante se agitó a temperatura ambiente durante 48 horas. La LC-MS mostró el producto deseado a M+1= 587.48 (2.87 min, método 13) y un subproducto M+1= 630.48 (2.97 min, método 13). Los volátiles se eliminaron al vacío. Los productos crudos se obtuvieron como un aceite amarillo y se usaron en la siguiente etapa de esa manera.

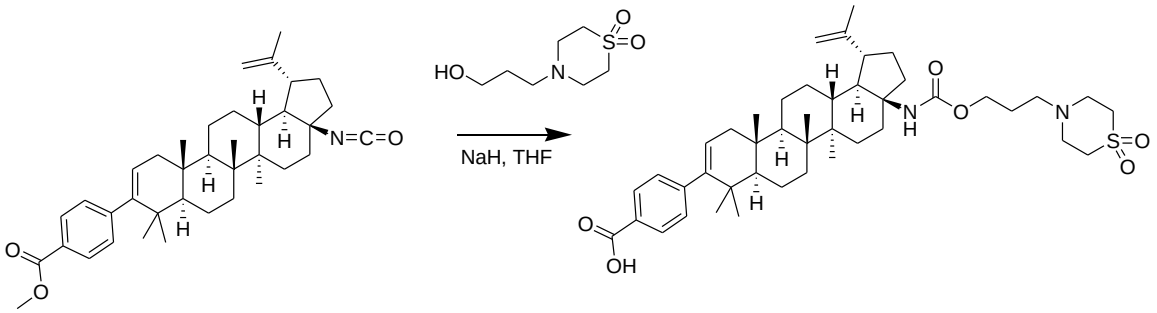
Etapa 2. Se preparó ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-ureido-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimetilamino)-2-oxoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, etapa 2.

El producto se aisló como un sólido blanco (15 mg, 28 %). **Ejemplo 69-1:** LCMS: m/e 573.45 $(M+H)^+$, 2.67 min (método 13). ^{1}H NMR (400MHz, METANOL-d_4) δ 7.94 (d, *J*= 8.5 Hz, 2H), 7.24 (d, *J*= 8.5 Hz, 2H), 5.32 (dd, *J*= 6.1, 1.6 Hz, 1H), 4.78 (d, *J*= 1.8 Hz, 1H), 4.67-4.63 (m, 1H), 2.69-2.59 (m, 2H), 2.40 (dd, *J*= 12.2, 8.2 Hz, 1H), 2.17 (dd, *J*= 17.2, 6.4 Hz, 1H), 2.04-1.84 (m, 2H), 1.74 (s, 3H), 1.82-1.67 (m, 3H), 1.63-1.48 (m, 6H), 1.46-1.26 (m, 6H), 1.16 (s, 3H), 1.22-1.08 (m, 2H), 1.06 (s, 3H), 1.06 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H).

Sección 2. Carbamatos

Ejemplo 70

Preparación de ácido benzoico, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[[3-(1,1-dioxido-4-tiomorfolinil)propoxi]carbonil]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-1H-ciclopenta[a]crisen-9-il].



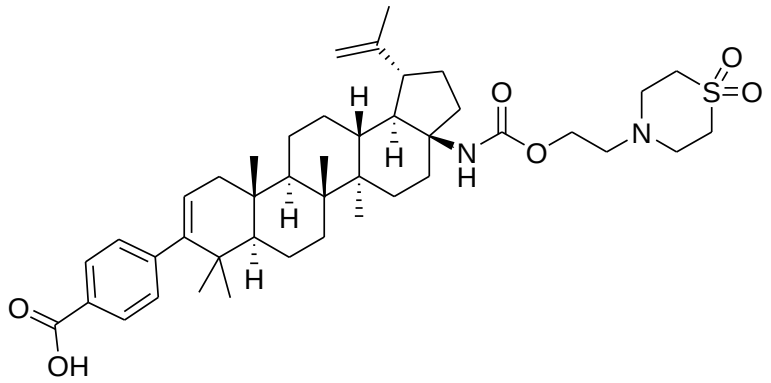
A una solución turbia de 1,1-dióxido de 4-(3-hidroxipropil)tiomorfolina (407 mg, 2.106 mmol) en tetrahidrofurano (5 mL), se agregó hidruro de sodio (84 mg,

2.106 mmol). La suspensión blanca resultante se agitó a temperatura ambiente. Después de 40 min, la pasta resultante se diluyó con tetrahidrofurano (5 mL) y se trató con 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocianato-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (200 mg, 0.351 mmol) en una porción. La suspensión blanca resultante se agitó a temperatura ambiente durante la noche. Después de 16 h, la reacción se vertió en HCl 0.1 N (20 mL) y se extrajo con 2 x 50 mL de EtOAc. La capa orgánica combinada se lavó con salmuera, se secó en $MgSO_4$, se filtró y se concentró para obtener un producto de espuma blanca. El material crudo se disolvió en 2 mL de THF, se filtró y se purificó mediante HPLC preparativa de fase inversa usando el método 1 de HPLC para obtener la sal de mono-TFA del compuesto del título (123.1 mg, 0.143 mmol, 40.6 % de rendimiento) como un sólido blanco. LCMS: m/e 749.5 $(M+H)^+$, 2.10 min (método 6). ^{1}H NMR (500MHz, 1:1 *MeOD:CDCl$_3$*) δ = 7.92 (d, *J* = 8.5 Hz, 2 H), 7.20 (d, *J* = 8.5 Hz, 2 H), 5.29 (dd, *J* = 1.8, 6.1 Hz, 1 H), 4.75 (d, *J* = 1.5 Hz, 1 H), 4.63 (d, *J* = 1.2 Hz, 1 H), 4.09 (t, *J* = 5.8 Hz, 2 H), 3.42 (br. s., 3 H), 2.98 (t, *J* = 7.0 Hz, 2 H), 2.57 (dt, *J* = 5.3, 10.9 Hz, 1 H), 2.51 (d, *J* = 12.8 Hz, 1 H), 2.35-2.28 (m, 1 H), 2.12 (dd, *J* = 6.4, 17.1 Hz, 1 H), 2.02-1.88 (m, 3 H), 1.82-

1.65 (m, 7 H), 1.65-1.45 (m, 6 H), 1.45-1.19 (m, 6 H), 1.15-1.10 (m, 2 H), 1.09 (s, 3 H), 1.02 (s, 3 H), 1.01 (s, 3 H), 0.95 (s, 3 H), 0.94 (s, 3 H). ^{13}C NMR (*1:1 MeOD:CDCl$_3$*) δ ppm 15.2, 16.5, 17.2, 19.9, 20.7, 21.8, 22.3, 26.2, 26.5, 28.2, 29.9, 30.2, 30.5, 34.5, 37.2, 38.4, 38.6, 41.6, 42.7, 43.0, 48.2, 50.1, 50.5, 50.6, 51.9, 53.9, 54.6, 62.4, 64.9, 78.8, 111.0, 124.9, 129.3, 129.7, 131.0, 147.4, 149.8, 150.4, 156.3, 170.1.

Ejemplo 71

Preparación de ácido benzoico, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[[2-(1,1-dioxido-4-tiomorfolinil)etoxi]carbonil]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-1H-ciclopenta[a]crisen-9-il].



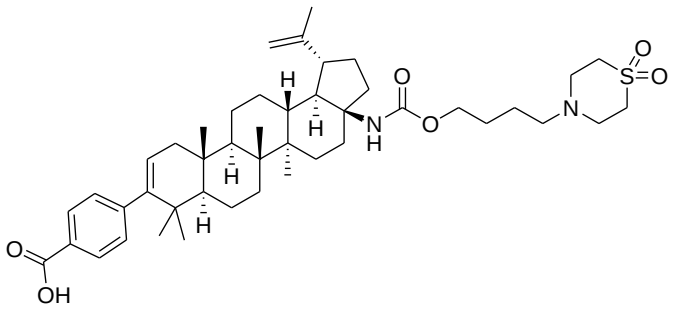
El compuesto del título se preparó en 24 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocianato-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido benzoico, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[[3-(1,1-dioxido-4-tiomorfolinil)propoxi]carbonil]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-1H-ciclopenta[a]crisen-9-il], excepto que se usó 1,1-dióxido de 4-(2-hidroxietil)tiomorfolina en lugar de 1,1-dióxido de 4-(3-hidroxipropil)tiomorfolina. LCMS: m/e 735.3 $(M+H)^+$, 2.63 min (método 6). ^{1}H NMR (500MHz, *METANOL-d_4*) δ = 7.95 (d, *J* = 8.5 Hz, 2 H), 7.25 (d, *J* = 8.5 Hz, 2 H), 5.33 (dd, *J* = 1.7, 6.3 Hz, 1 H), 4.79 (d, *J* = 1.8 Hz, 1 H), 4.66 (s, 1 H), 4.38-4.28 (m, 1 H), 4.27-4.19 (m, 1 H), 3.56-3.43 (m, 3 H), 3.31 (br. s., 2 H), 3.17 (br. s., 2 H), 2.71 (dt, *J* = 5.3, 11.1 Hz, 1 H), 2.57 (d, *J* = 13.4 Hz, 1 H), 2.33 (dd, *J* = 8.4, 12.1 Hz, 1 H), 2.18 (dd, *J* = 6.4, 17.1 Hz, 1 H), 2.00-1.89 (m, 2 H), 1.84-1.76 (m, 2 H), 1.75 (s, 3 H), 1.73 (d, *J* = 4.3 Hz, 1 H), 1.71-1.64 (m, 1 H), 1.62-1.56 (m, 2 H), 1.56-1.48 (m, 4 H), 1.47-1.35 (m, 4 H), 1.31 (dt, *J* = 4.0, 9.3 Hz, 2 H), 1.15 (s, 3 H), 1.12 (d, *J* = 3.1 Hz, 1 H), 1.07 (s, 6 H), 0.99 (s, 3 H), 0.97 (s, 3 H).

Ejemplo 72

Preparación de ácido benzoico, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[[4-(1,1-

dioxido-4-tiomorfolinil)butoxi]carbonil]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-1H-ciclopenta[a]crisen-9-il].



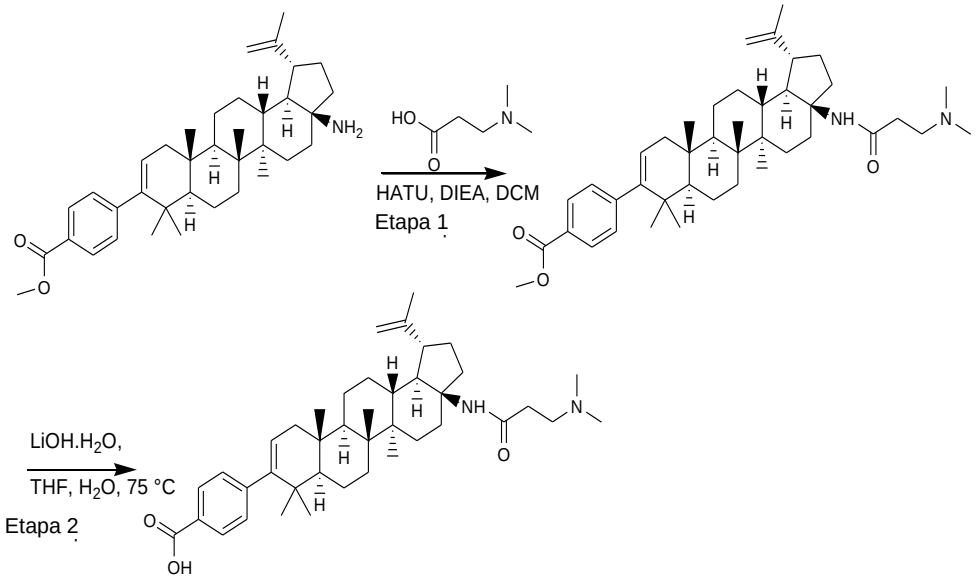
El compuesto del título se preparó en 55 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocianato-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido benzoico, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[[3-(1,1-dioxido-4-tiomorfolinil)propoxi]carbonil]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-1H-ciclopenta[a]crisen-9-il], excepto que se usó 1,1-dióxido de 4-(4-hidroxibutil)tiomorfolina en lugar de 1,1-dióxido de 4-(3-hidroxipropil)tiomorfolina. LCMS: m/e 763.5 $(M+H)^+$, 2.14 min (método 6). ^{1}H NMR (500MHz, *METANOL-d_4*) δ = 7.95 (d, *J* = 8.2 Hz, 2 H), 7.24 (d, *J* = 8.2 Hz, 2 H), 5.32 (dd, *J* = 1.5, 6.1

Hz, 1 H), 4.78 (d, *J* = 1.5 Hz, 1 H), 4.65 (s, 1 H), 4.14-4.04 (m, 2 H), 3.87-3.79 (m, 4 H), 3.62-3.51 (m, 4 H), 2.69 (dt, *J* = 5.0, 11.1 Hz, 1 H), 2.56 (d, *J* = 13.4 Hz, 1 H), 2.32 (dd, *J* = 8.9, 11.3 Hz, 1 H), 2.18 (dd, *J* = 6.3, 17.2 Hz, 1 H), 2.00-1.91 (m, 2 H), 1.91-1.82 (m, 2 H), 1.82-1.75 (m, 3 H), 1.74 (s, 4 H), 1.70-1.56 (m, 3 H), 1.51 (d, *J* = 11.0 Hz, 4 H), 1.46-1.34 (m, 4 H), 1.33-1.26 (m, 2 H), 1.14 (s, 3 H), 1.13-1.09 (m, 2 H), 1.08-1.06 (m, 3 H), 1.06 (s, 3 H), 0.99 (s, 3 H), 0.97 (s, 3 H).

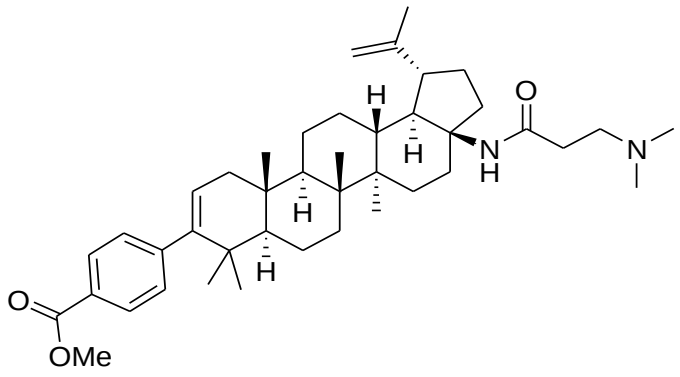
Sección 3. Amidas

Ejemplo 73

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

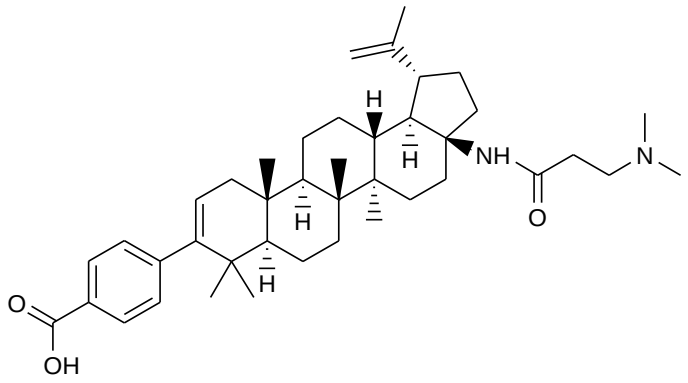


A una solución turbia de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (0.240 g, 0.441 mmol) en THF (5 mL), se agregó *N,N*-diisopropiletilamina (0.461 mL, 2.65 mmol), hexafluorofosfato(V) de 2-(3H-[1,2,3]triazolo[4,5-b]piridin-3-il)-1,1,3,3-tetrametilisouronio (0.369 g, 0.971 mmol) y clorhidrato de ácido 3-(dimetilamino)propiónico (0.136 g, 0.883 mmol). La mezcla de reacción se agitó a temperatura ambiente. Después de 16 h, la mezcla de reacción se diluyó con EtOAc (50 mL), se lavó con HCl 1N (5 mL), 5 % de $NaHCO_3$,

salmuera, se secó en $MgSO_4$, se filtró y se concentró para obtener un producto de aceite viscoso. El material crudo se disolvió en THF (1 mL) y MeOH (1.5 mL), se filtró y se purificó mediante HPLC preparativa de fase inversa usando el método 4 de HPLC para obtener 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo, TFA (93.8 mg, 0.116 mmol, 26.4 % de rendimiento) como un sólido blanco. LCMS: m/e 643.3 $(M+H)^+$, 4.17 min (método 8). ^1H NMR (500MHz, 1:1 *MeOD:CDCl*$_3$) δ = 7.97-7.85 (m, 2 H), 7.29-7.23 (m, 2 H), 7.21 (br. s., 1 H), 5.32 (d, *J* = 4.0 Hz, 1 H), 4.80 (br. s., 1 H), 4.67 (br. s., 1 H), 3.97-3.88 (m, 3 H), 3.43-3.37 (m, 2 H), 2.92 (br. s., 6 H), 2.84-2.77 (m, 2 H), 2.77-2.68 (m, 2 H), 2.46-2.38 (m, 1 H), 2.22-2.13 (m, 1 H), 2.05-1.88 (m, 2 H), 1.83 (d, *J* = 13.4 Hz, 1 H), 1.75 (br. s., 5 H), 1.66-1.49 (m, 7 H), 1.48-1.34 (m, 4 H), 1.32 (br. s., 1 H), 1.16 (br. s., 4 H), 1.07 (br. s., 6 H), 0.98 (br. s., 3 H), 0.96 (br. s., 3 H). ^{13}C NMR (1:1 *MeOD:CDCl*$_3$) δ ppm 13.8, 15.4, 16.0, 18.4, 19.9, 20.6, 21.4, 25.6, 27.5, 28.7, 29.0, 29.5, 29.7, 33.8, 34.8, 36.4, 37.5, 37.5, 40.8, 41.8, 42.1, 47.0, 49.5, 49.8, 51.5, 53.3, 54.5, 65.8, 102.7, 109.7, 124.3, 128.2, 128.5, 130.3, 146.7, 149.2, 150.1,

167.6, 170.3.

Etapa 2. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



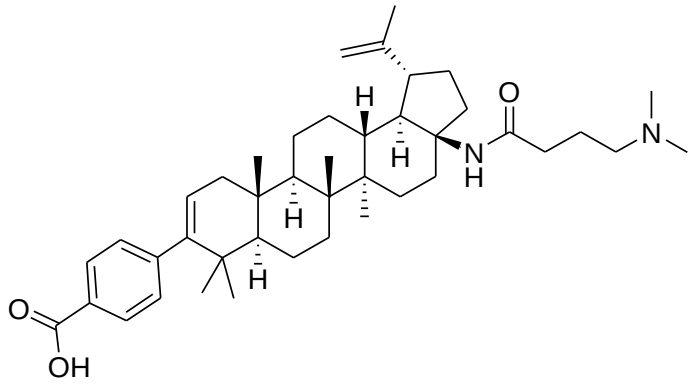
A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo, TFA (87,9 mg, 0.116 mmol) en THF (5 mL) se agregó una solución de hidróxido de litio monohidrato (19.49 mg, 0.464 mmol) en agua (1.00 mL). La reacción se agitó a 75 °C. Después de 8 h, la reacción se concentró hasta secarse. El material crudo se disolvió en THF (1 mL) y

MeOH (1.5 mL), se filtró y se purificó mediante HPLC preparativa de fase inversa usando el método 1 de HPLC para obtener el compuesto del título (59.5 mg, 0.078 mmol, 67.6 % de rendimiento) como un sólido blanco. LCMS: m/e 629.4 $(M+H)^+$, 4.17 min (método 8). ^{1}H NMR (500MHz, *METANOL-d_4*) δ = 7.95 (d, *J* = 8.2 Hz, 2 H), 7.24 (d, *J* = 8.2 Hz, 3 H), 5.33 (dd, *J* = 1.5, 6.1 Hz, 1 H), 4.80 (d, *J* = 1.5 Hz, 1 H), 4.67 (s, 1 H), 3.40 (t, *J* = 6.6 Hz, 2 H), 2.92 (s, 6 H), 2.88-2.69 (m, 4 H), 2.42 (dd, *J* = 8.4, 12.4 Hz, 1 H), 2.18 (dd, *J* = 6.4, 17.1 Hz, 1 H), 2.05-1.89 (m, 2 H), 1.83 (d, *J* = 11.3 Hz, 1 H), 1.79-1.76 (m, 1 H), 1.75 (s, 3 H), 1.74-1.71 (m, 1 H), 1.66-1.56 (m, 3 H), 1.56-1.49 (m, 4 H), 1.47-1.28 (m, 5 H), 1.22-1.17 (m, 1 H), 1.16 (s, 3 H), 1.15-1.10 (m, 1 H), 1.07 (s, 6 H), 0.99 (s, 3 H), 0.97 (s, 3 H). ^{13}C NMR (*MeOD*) δ ppm 14.5, 16.1, 16.8, 19.1, 20.6, 21.3, 22.1, 26.2, 28.2, 29.4, 29.7, 30.4, 34.5, 35.5, 37.1, 38.1, 38.2, 41.5, 42.5, 42.8, 43.2, 47.6, 49.3, 50.1, 50.5, 54.0, 55.1, 66.4, 110.4, 124.9, 129.5, 130.9, 147.4, 149.6, 150.8, 169.6, 171.0.

Ejemplo 74

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-(dimetilamino)butanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

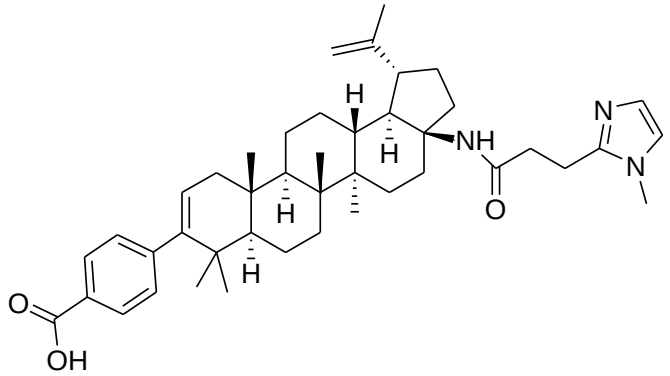


El compuesto del título se preparó en 26 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó clorhidrato de ácido 4-(dimetilamino)butírico en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 643.4 $(M+H)^+$, 4.19 min (método 8). ^{1}H NMR (500MHz, *METANOL-d_4*) δ = 7.95 (d, *J* = 8.2 Hz, 2 H), 7.24 (d, *J* = 8.5 Hz, 2 H), 5.33 (dd, *J* = 1.7, 6.3 Hz, 1 H), 4.80 (d, *J* = 1.5 Hz, 1 H), 4.67 (s, 1 H), 3.21-3.14 (m, 2

H), 2.93 (s, 6 H), 2.82-2.67 (m, 2 H), 2.49 (t, *J* = 6.9 Hz, 2 H), 2.41 (dd, *J* = 8.2, 12.2 Hz, 1 H), 2.18 (dd, *J* = 6.4, 17.1 Hz, 1 H), 2.06-1.96 (m, 3 H), 1.96-1.86 (m, 1 H), 1.85-1.79 (m, 1 H), 1.77 (br. s., 1 H), 1.75 (s, 3 H), 1.73-1.69 (m, 1 H), 1.64-1.56 (m, 3 H), 1.55-1.48 (m, 4 H), 1.47-1.38 (m, 3 H), 1.35 (d, *J* = 12.2 Hz, 1 H), 1.33-1.27 (m, 1 H), 1.21-1.17 (m, 1 H), 1.15 (s, 3 H), 1.12 (d, *J* = 3.4 Hz, 1 H), 1.07 (s, 6 H), 0.99 (s, 3 H), 0.97 (s, 3 H).

Ejemplo 75

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(3-(1-metil-1H-imidazol-2-il)propanamido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



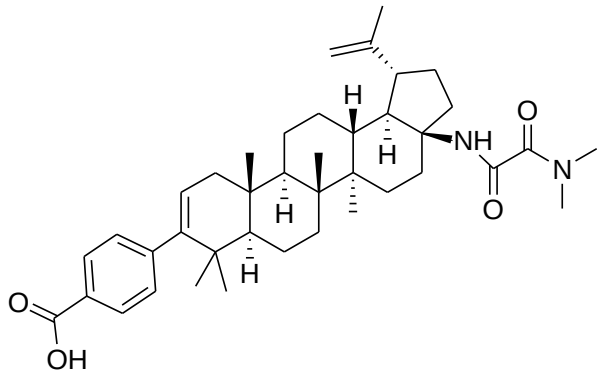
El compuesto del título se preparó en 29 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido 3-(1-metil-1H-imidazol-2-il)propanoico en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 666.4 $(M+H)^+$, 4.15 min (método 8). ^{1}H NMR (500MHz, *METANOL-d_4*) δ = 7.95 (d, *J* = 8.5 Hz, 2 H), 7.53-7.46 (m, 2 H), 7.25 (d, *J* = 8.2 Hz, 2 H), 5.33 (dd, *J* = 1.8, 6.1 Hz, 1 H), 4.79 (d, *J* = 1.5 Hz, 1 H), 4.66 (s, 1 H), 3.91 (s, 3 H), 3.30-3.18 (m, 2 H), 2.84-2.79 (m, 2 H), 2.73 (dt, *J* = 5.2, 11.1 Hz, 1 H), 2.64 (d, *J* = 12.5 Hz, 1 H), 2.35 (dd, *J* = 8.2, 12.2 Hz, 1 H), 2.18 (dd, *J* = 6.4, 17.4 Hz, 1 H), 1.96 (dt, *J* = 3.2, 12.1 Hz, 1 H), 1.91-1.78 (m, 2 H), 1.77 (s, 1 H), 1.74 (s, 3 H), 1.71-1.66 (m, 1 H), 1.60 (br. s., 2 H), 1.46-1.26 (m, 7 H), 1.22-1.13 (m, 1 H), 1.11 (s, 3 H), 1.07 (s, 3 H), 1.05 (s, 4 H), 0.99 (s, 3 H), 0.97 (s, 3 H).

Ejemplo 76

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-

(dimetilamino)-2-oxoacetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

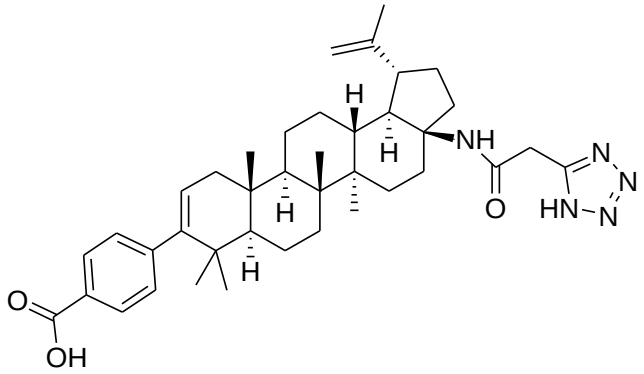


El compuesto del título se preparó en 13 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido *N,N*-dimetiloxámico en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 627.6 $(M-H)^-$, 1.91 min (método 5). ^{1}H NMR (500MHz, 2:1

MeOD:CDCl$_3$) δ = 7.93 (d, *J* = 8.2 Hz, 2 H), 7.55 (s, 1 H), 7.21 (d, *J* = 8.2 Hz, 2 H), 5.30 (dd, *J* = 1.7, 6.3 Hz, 1 H), 4.77 (d, *J* = 1.2 Hz, 1 H), 4.65 (s, 1 H), 3.22 (s, 3 H), 3.01 (s, 3 H), 2.71-2.59 (m, 2 H), 2.46 (dd, *J* = 8.2, 11.9 Hz, 1 H), 2.14 (dd, *J* = 6.3, 17.2 Hz, 1 H), 2.02-1.93 (m, 1 H), 1.89 (dt, *J* = 3.4, 12.2 Hz, 1 H), 1.79 (d, *J* = 13.1 Hz, 1 H), 1.75 (d, *J* = 3.7 Hz, 1 H), 1.71 (br. s., 1 H), 1.66 (dt, *J* = 3.5, 13.5 Hz, 1 H), 1.61-1.54 (m, 2 H), 1.54-1.48 (m, 4 H), 1.46 (br. s., 1 H), 1.45-1.40 (m, 3 H), 1.40-1.34 (m, 1 H), 1.28 (br. s., 2 H), 1.20-1.14 (m, 2 H), 1.13 (s, 3 H), 1.05 (s, 3 H), 1.03 (s, 3 H), 0.96 (s, 3 H), 0.95 (s, 3 H).

Ejemplo 77

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(1H-tetrazol-5-il)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

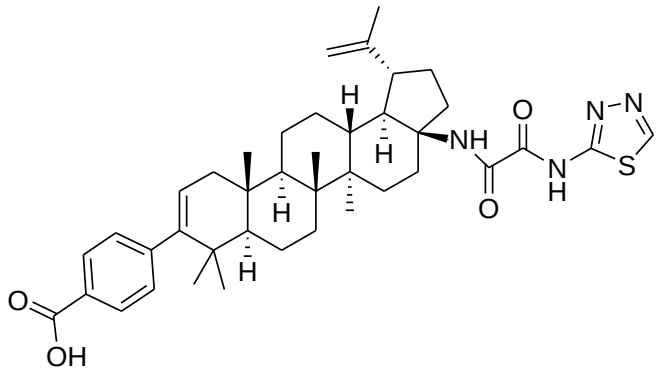


El compuesto del título se preparó en 8 % de

rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido (1H-tetrazol-5-il)-acético en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 640.5 $(M+H)^+$, 1.58 min (método 6). ^{1}H NMR (500MHz, *METANOL-d_4*) δ = 7.95 (d, *J* = 8.2 Hz, 2 H), 7.48 (s, 1 H), 7.25 (d, *J* = 8.2 Hz, 2 H), 5.33 (dd, *J* = 1.5, 6.1 Hz, 1 H), 4.82 (d, *J* = 1.8 Hz, 1 H), 4.68 (s, 1 H), 4.12-4.00 (m, 2 H), 2.79 (dt, *J* = 5.0, 11.2 Hz, 1 H), 2.72-2.62 (m, 1 H), 2.45-2.35 (m, 1 H), 2.19 (dd, *J* = 6.4, 17.1 Hz, 1 H), 2.07-1.92 (m, 2 H), 1.84 (d, *J* = 11.6 Hz, 1 H), 1.77 (br. s., 1 H), 1.76 (s, 3 H), 1.73 (d, *J* = 7.3 Hz, 1 H), 1.66-1.56 (m, 3 H), 1.56-1.49 (m, 4 H), 1.48-1.27 (m, 6 H), 1.23-1.15 (m, 1 H), 1.12 (s, 3 H), 1.08 (s, 3 H), 1.07 (s, 3 H), 1.00 (s, 3 H), 0.97 (s, 3 H).

Ejemplo 78

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(1,3,4-tiadiazol-2-ilamino)-2-oxoacetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

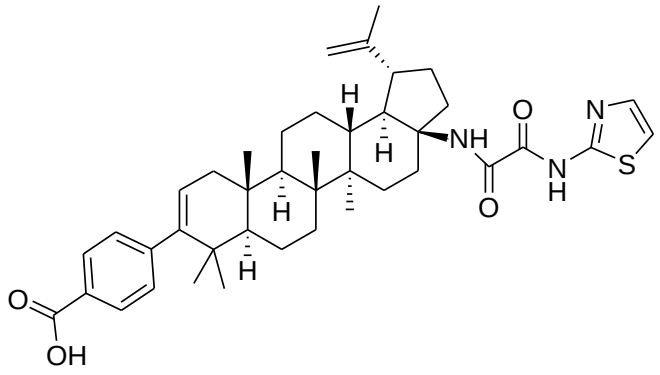


El compuesto del título se preparó en 21 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto

que se usó ácido 2-(1,3,4-tiadiazol-2-ilamino)-2-oxoacético en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 683.6 $(M-H)^-$, 1.77 min (método 9). ^{1}H NMR (500MHz, 2:1 *MeOD:CDCl$_3$*) δ = 9.13 (s, 1 H), 7.92 (d, *J* = 8.5 Hz, 2 H), 7.45 (s, 1 H), 7.21 (d, *J* = 8.2 Hz, 2 H), 5.37-5.24 (m, 1 H), 4.81-4.78 (m, 1 H), 4.67 (s, 1 H), 2.67-2.56 (m, 2 H), 2.55-2.47 (m, 1 H), 2.15 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.99-1.90 (m, 1 H), 1.82 (dd, *J* = 10.5, 16.3 Hz, 3 H), 1.74 (s, 3 H), 1.71 (br. s., 1 H), 1.59-1.44 (m, 9 H), 1.44-1.39 (m, 1 H), 1.30-1.24 (m, 1 H), 1.22-1.14 (m, 2 H), 1.10 (s, 3 H), 1.07 (s, 3 H), 1.03 (s, 3 H), 0.95 (s, 3 H), 0.94 (s, 3 H).

Ejemplo 79

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-oxo-2-(tiazol-2-ilamino)acetamido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

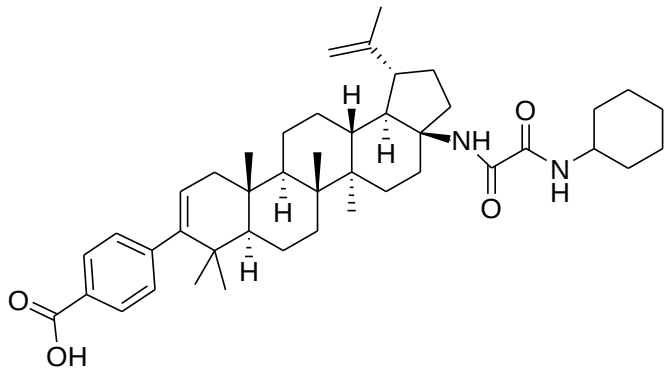


El compuesto del título se preparó en 23 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido 2-oxo-2-(tiazol-2-ilamino)acético en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 684.5 $(M+H)^+$, 2.04 min (método 9). ^{1}H NMR (500MHz, 1:1 *MeOD:CDCl$_3$*) δ = 7.92 (d, *J* = 8.5 Hz, 2 H), 7.54 (d, *J* = 3.7 Hz, 1 H), 7.49 (s, 1 H), 7.22-7.19 (m, 3 H), 5.30 (dd, *J* = 1.8, 6.1 Hz, 1 H), 4.79 (d, *J* = 1.2 Hz, 1 H), 2.65-2.55 (m, 2 H), 2.53-2.46 (m, 1 H), 2.14 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.98-1.89 (m, 1 H), 1.88-1.76 (m, 3 H), 1.73 (s, 3 H), 1.70 (s, 1 H), 1.61-1.36 (m, 11 H), 1.29-1.22 (m, 1 H), 1.21-1.14 (m, 2 H), 1.09 (s, 3 H), 1.06 (s, 3 H), 1.02 (s, 3 H), 0.95-0.94 (m, 3 H), 0.93 (s, 3 H).

Ejemplo 80

Preparación de ácido 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(ciclohexilamino)-2-oxoacetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

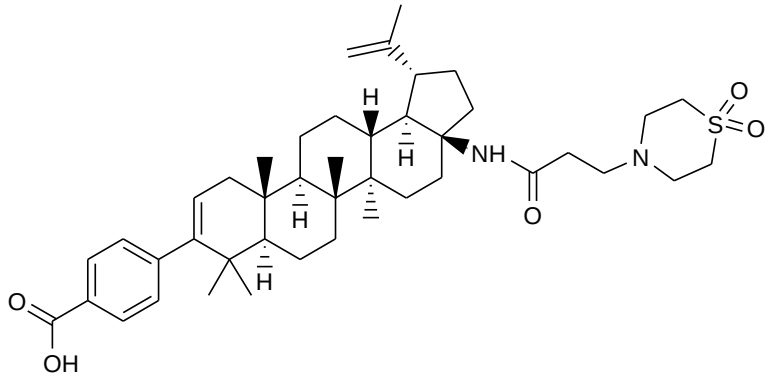


El compuesto del título se preparó en 40 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido 2-(ciclohexilamino)-2-oxoacético en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa

1. LCMS: m/e 681.7 $(M-H)^-$, 2.42 min (método 9). ^{1}H NMR (500MHz, *CLOROFORMO-d*) δ = 8.03 (d, *J* = 8.5 Hz, 2 H), 7.61 (s, 1 H), 7.52 (d, *J* = 8.5 Hz, 1 H), 7.25 (d, *J* = 8.2 Hz, 2 H), 6.51 (br. s., 1 H), 5.33 (d, *J* = 4.6 Hz, 1 H), 4.79 (d, *J* = 1.2 Hz, 1 H), 4.67 (s, 1 H), 3.83-3.72 (m, 1 H), 2.62-2.54 (m, 2 H), 2.50 (dd, *J* = 8.5, 11.6 Hz, 1 H), 2.14 (dd, *J* = 6.3, 17.2 Hz, 1 H), 2.00-1.89 (m, 3 H), 1.86-1.75 (m, 4 H), 1.71-1.62 (m, 2 H), 1.61-1.36 (m, 13 H), 1.35-1.20 (m, 5 H), 1.18-1.11 (m, 2 H), 1.08 (s, 3 H), 1.05-1.02 (m, 3 H), 1.00 (s, 3 H), 0.96 (s, 6 H).

Ejemplo 81

Preparación de ácido benzoico, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-tiomorfolinil)-1-oxopropil]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-1H-ciclopenta[a]crisen-9-il].



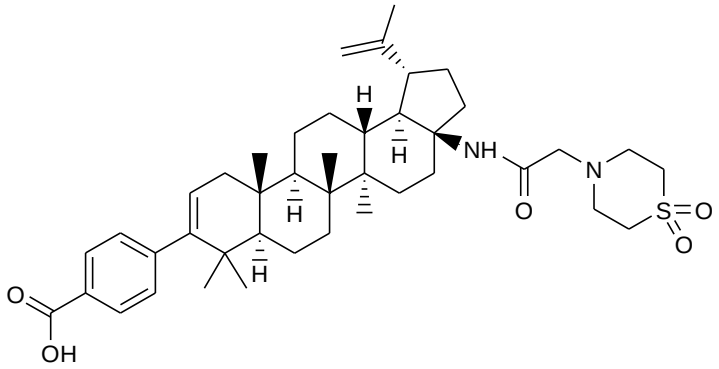
El compuesto del título se preparó en 70 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-

3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido 3-(1,1-dioxo-1lamda-6,4-tiazinan-4-il)propanoico en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 719.5 $(M+H)^+$, 1.88 min (método 6). ^{1}H NMR (500MHz, 2:1 *MeOD:CDCl$_3$*) δ = 7.93 (d, *J* = 7.9 Hz, 2 H), 7.25 (br. s., 1 H), 7.21 (d, *J* = 7.9 Hz, 2 H), 5.30 (d, *J* = 6.1 Hz, 1 H), 4.78 (s, 1 H), 4.66 (s, 1 H), 3.47 (br. s., 4 H), 3.36 (br. s., 4 H), 3.19 (br. s., 2 H), 2.72-2.59 (m, 4 H), 2.40 (dd, *J* = 8.9, 11.9 Hz, 1 H), 2.15 (dd, *J* = 6.3, 17.2 Hz, 1 H), 1.98-1.86 (m, 2 H), 1.80 (d, *J* = 13.1 Hz, 1 H), 1.73 (s, 3 H), 1.71-1.66 (m, 1 H), 1.63-1.43 (m, 8 H), 1.42-1.23 (m, 5 H), 1.22-1.13 (m, 2 H), 1.12 (s, 3 H), 1.05 (br. s., 3 H), 1.04 (br. s., 3 H), 0.97 (br. s., 3 H), 0.95 (br. s., 3 H).

Ejemplo 82

Preparación de ácido benzoico, 4-

[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[(1,1-dioxido-4-tiomorfolinil)acetil]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-1H-ciclopenta[a]crisen-9-il].

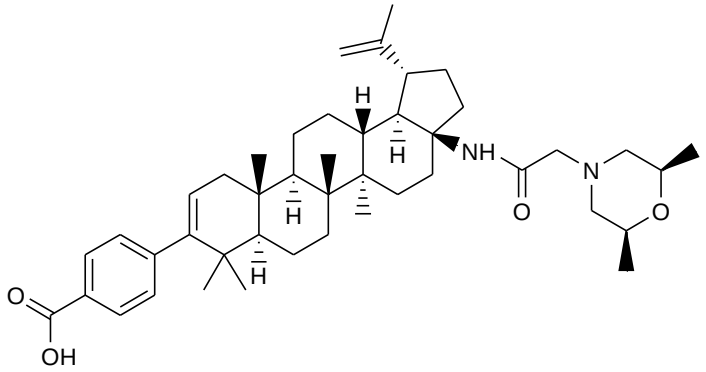


El compuesto del título se preparó en 61 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó 1,1-dióxido de ácido 4-tiomorfolineacético en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en

la Etapa 1. LCMS: m/e 704.5 $(M+H)^+$, 1.90 min (método 6). ^1H NMR (500MHz, 2:1 *MeOD:CDCl$_3$*) δ = 7.93 (d, *J* = 8.2 Hz, 2 H), 7.23 (br. s., 1 H), 7.21 (s, 2 H), 5.31 (dd, *J* = 1.7, 6.0 Hz, 1 H), 4.78 (d, *J* = 1.2 Hz, 1 H), 4.67 (s, 1 H), 3.29 (d, *J* = 5.2 Hz, 4 H), 3.24 (d, *J* = 5.2 Hz, 4 H), 2.67-2.60 (m, 1 H), 2.53 (dt, *J* = 5.5, 10.8 Hz, 1 H), 2.47 (dd, *J* = 8.1, 12.7 Hz, 1 H), 2.16 (dd, *J* = 6.3, 17.2 Hz, 1 H), 1.94-1.78 (m, 3 H), 1.76 (d, *J* = 2.1 Hz, 1 H), 1.74 (s, 3 H), 1.62-1.49 (m, 7 H), 1.47-1.33 (m, 4 H), 1.31-1.25 (m, 1 H), 1.21-1.13 (m, 2 H), 1.12 (s, 3 H), 1.07 (s, 3 H), 1.05 (s, 3 H), 0.97 (s, 3 H), 0.96 (s, 3 H).

Ejemplo 83

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((2S,6R)-2,6-dimetilmorfolino)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



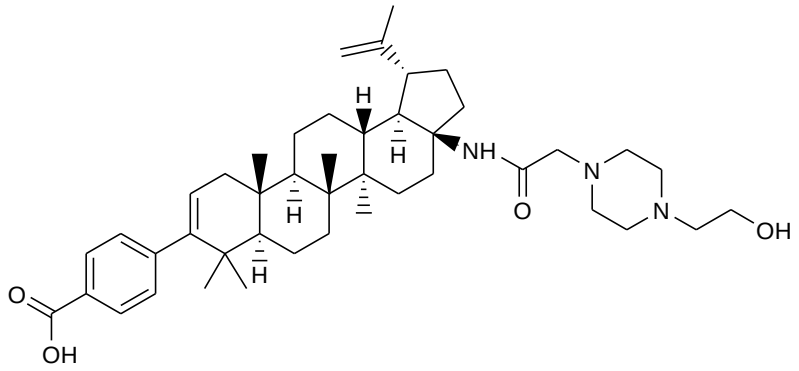
El compuesto del título se preparó en 43 % de

rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido [(2R,6S)-2,6-dimetilmorfolin-4-il]acético en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 685.6 $(M+H)^+$, 2.48 min (método 6). ^{1}H NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 5.29 (dd, *J* = 1.5, 6.1 Hz, 1 H), 4.75 (d, *J* = 1.2 Hz, 1 H), 3.89 (dd, *J* = 6.3, 9.0 Hz, 2 H), 3.64 (br. s., 1 H), 3.24 (br. s., 2 H), 2.69-2.49 (m, 4 H), 2.39 (dd, *J* = 8.1, 12.4 Hz, 1 H), 2.13 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.93-1.76 (m, 3 H), 1.74 (br. s., 1 H), 1.72 (s, 3 H), 1.70-1.66 (m, 1 H), 1.60-1.42 (m, 8 H), 1.42-1.30 (m, 3 H), 1.25 (d, *J* = 3.1 Hz, 3 H), 1.24 (d, *J* = 2.7 Hz, 3 H), 1.18-1.11 (m, 2 H), 1.08 (s, 3 H), 1.03

(s, 3 H), 1.01 (s, 3 H), 0.95 (s, 3 H), 0.94 (s, 3 H).

Ejemplo 84

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4-(2-hidroxietil)piperazin-1-il)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



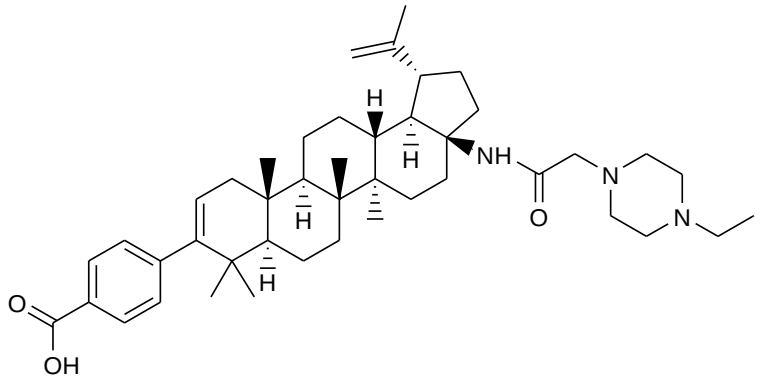
El compuesto del título se preparó en 23 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó clorhidrato de ácido [4-(2-hidroxi-etil)-piperazin-1-il]-acético en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 700.6 $(M+H)^+$, 2.03 min (método 6). ^{1}H NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.5 Hz, 2 H), 7.20 (d, *J* = 8.5 Hz, 2 H), 6.96 (s, 1 H), 5.30 (dd, *J* = 1.7, 6.0 Hz, 1 H), 4.76 (s, 1 H), 4.66 (s, 1 H), 3.93-3.89 (m, 2 H), 3.42 (br. s., 2 H), 3.30-3.25 (m, 2 H), 3.22 (d, *J* = 4.6 Hz, 2 H), 2.97 (br. s., 3 H), 2.68-2.60 (m, 1 H), 2.55-2.47 (m, 1 H), 2.44 (dd, *J* = 8.2, 12.5 Hz, 1 H), 2.13 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.91-1.77 (m, 2 H), 1.75 (br. s., 1 H), 1.72 (s, 3 H), 1.72-1.68 (m, 1 H), 1.62-1.31 (m, 11 H), 1.30-1.24 (m, 1 H), 1.15 (d, *J* = 13.1 Hz, 2 H), 1.08 (s, 3 H), 1.05 (s, 3 H), 1.02 (s, 3 H), 0.95 (s, 3 H), 0.94 (s, 3 H).

Ejemplo 85

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4-etilpiperazin-1-il)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-

il)benzoico.

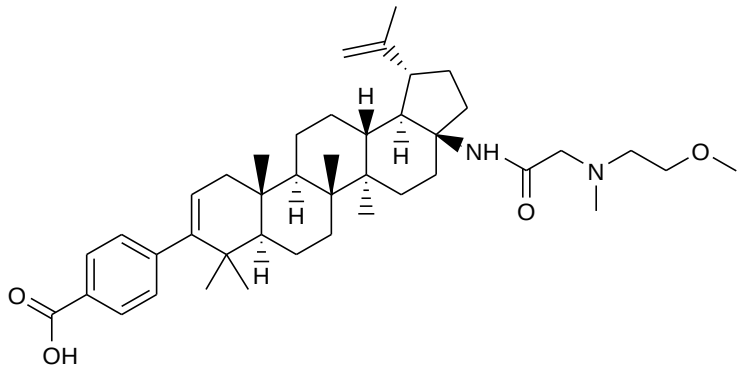


El compuesto del título se preparó en 34 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido 2-(4-etilpiperazin-1-il)acético en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 684.6 $(M+H)^+$, 2.35 min (método 6). ^{1}H NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 6.90 (s, 1 H), 5.29 (d, *J* = 6.1 Hz, 1 H), 4.75 (d, *J* = 1.2 Hz, 1 H), 3.27-3.14 (m, 5 H),

2.96 (br. s., 3 H), 2.64 (d, *J* = 13.4 Hz, 1 H), 2.55-2.38 (m, 2 H), 2.13 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.92-1.76 (m, 2 H), 1.74 (br. s., 1 H), 1.72 (s, 3 H), 1.70-1.67 (m, 1 H), 1.61-1.41 (m, 9 H), 1.37 (t, *J* = 7.3 Hz, 4 H), 1.35-1.31 (m, 1 H), 1.29-1.23 (m, 1 H), 1.18-1.12 (m, 2 H), 1.06 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 2 H), 0.94 (s, 3 H), 0.94 (s, 3 H).

Ejemplo 86

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((2-metoxietil)(metil)amino)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



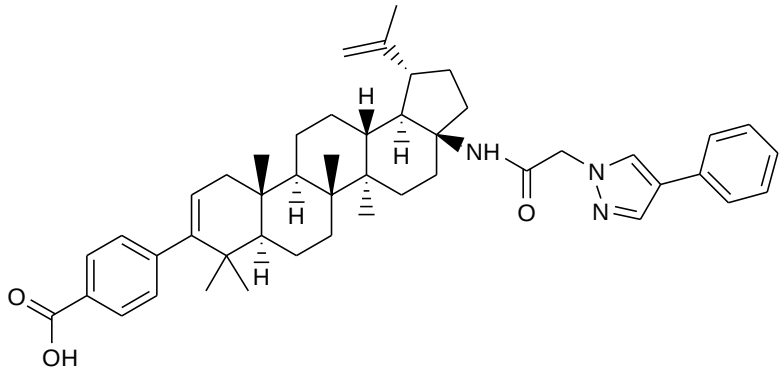
El compuesto del título se preparó en 38 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la

preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó *N*-(2-metoxietil)-*N*-metilglicina en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 659.6 $(M+H)^+$, 2.41 min (método 6). ^{1}H NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 7.9 Hz, 2 H), 7.43 (s, 1 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 5.29 (d, *J* = 5.8 Hz, 1 H), 4.75 (s, 1 H), 3.96 (br. s., 2 H), 3.73 (t, *J* = 4.7 Hz, 2 H), 3.42 (s, 3 H), 3.40 (br. s., 2 H), 2.94 (s, 3 H), 2.73-2.61 (m, 2 H), 2.36 (dd, *J* = 8.4, 12.1 Hz, 1 H), 2.12 (dd, *J* = 6.1, 17.1 Hz, 1 H), 1.88 (t, *J* = 11.6 Hz, 2 H), 1.77 (d, *J* = 11.6 Hz, 1 H), 1.73 (br. s., 1 H), 1.71 (s, 3 H), 1.70-1.65 (m, 1 H), 1.58-1.30 (m, 11 H), 1.25 (d, *J* = 6.1 Hz, 1 H), 1.18-1.10 (m, 2 H), 1.09 (s, 3 H), 1.02 (s, 3 H), 1.01 (s, 3 H), 0.94 (br. s., 3 H), 0.93 (br. s., 3 H).

Ejemplo 87

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(4-fenil-1H-pirazol-1-il)acetamido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

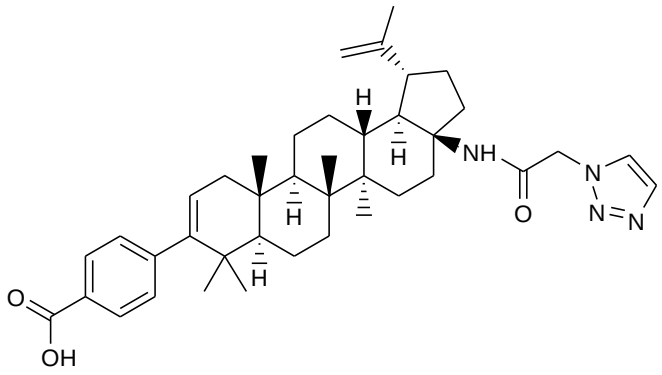


El compuesto del título se preparó en 22 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido 2-(3-fenil-1H-pirazol-1-il)acético en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 714.6 $(M+H)^+$, 2.59 min (método 6). ^{1}H NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ = 7.91 (d, *J* = 8.2 Hz, 4 H), 7.67 (d, *J* = 2.1 Hz, 1 H), 7.42 (d, *J* = 7.3 Hz, 2 H), 7.40 (s, 1 H), 7.37-7.31 (m, 1 H), 7.18 (d, *J* = 7.9 Hz, 2 H),

5.24 (d, *J* = 4.6 Hz, 1 H), 4.86-4.75 (m, 2 H), 4.59 (s, 1 H), 3.37 (s, 3 H), 2.50 (dd, *J* = 2.4, 9.2 Hz, 1 H), 2.47-2.38 (m, 2 H), 1.97 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.93-1.83 (m, 1 H), 1.64 (s, 3 H), 1.60-1.52 (m, 2 H), 1.50-1.37 (m, 4 H), 1.37-1.27 (m, 7 H), 1.26-1.19 (m, 1 H), 1.16-1.11 (m, 1 H), 1.00 (dd, *J* = 2.4, 9.2 Hz, 1 H), 0.90 (s, 3 H), 0.89 (s, 6 H), 0.79 (s, 3 H), 0.61 (s, 3 H), 0.49 (dd, *J* = 4.3, 13.1 Hz, 1 H).

Ejemplo 88

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(1H-1,2,3-triazol-1-il)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



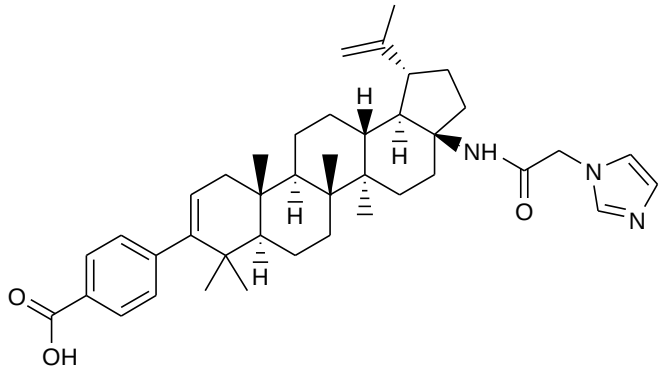
El compuesto del título se preparó en 36 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo

de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó clorhidrato de ácido 1H-1,2,3-triazol-1-acético en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 639.5 $(M+H)^+$, 2.04 min (método 6). ^{1}H NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ = 7.94 (d, *J* = 0.9 Hz, 1 H), 7.92 (d, *J* = 8.5 Hz, 2 H), 7.77 (d, *J* = 0.9 Hz, 1 H), 7.20 (d, *J* = 8.5 Hz, 2 H), 6.93 (s, 1 H), 5.29 (dd, *J* = 1.7, 6.3 Hz, 1 H), 5.15 (s, 2 H), 4.75 (d, *J* = 1.5 Hz, 1 H), 4.64 (br. s., 1 H), 2.63-2.57 (m, 1 H), 2.57-2.50 (m, 1 H), 2.37 (dd, *J* = 8.1, 12.7 Hz, 1 H), 2.12 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.94-1.83 (m, 1 H), 1.78-1.72 (m, 3 H), 1.70 (s, 3 H), 1.69-1.64 (m, 1 H), 1.58-1.39 (m, 8 H), 1.38-1.29 (m, 3 H), 1.24 (dd, *J* = 3.7, 10.4 Hz, 1 H), 1.15-1.06 (m, 2 H), 1.02 (s, 3 H), 1.01 (s, 3 H), 1.00 (s, 3 H), 0.94 (s, 3 H), 0.93 (s, 3 H).

Ejemplo 89

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(1H-imidazol-1-il)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

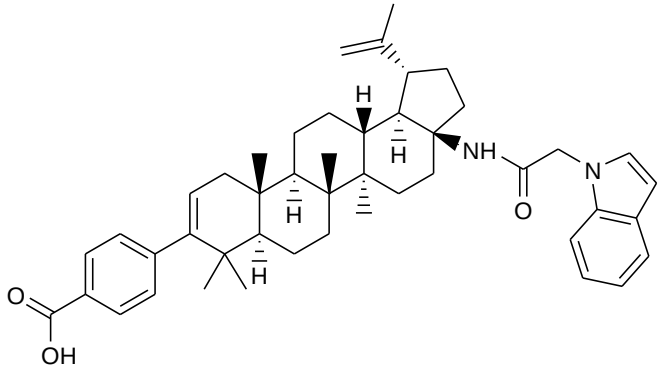


El compuesto del título se preparó en 60 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido imidazol-1-ilacético en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 638.5 $(M+H)^+$, 2.05 min (método 6). ^1H NMR (400MHz, 1:1 *$CDCl_3$:MeOD*) δ = 8.88 (s, 1 H), 7.92 (d, *J* = 8.3 Hz, 2 H), 7.47 (ddd, *J* = 1.6, 1.8, 9.7 Hz, 2 H), 7.42 (s, 1 H), 7.20

(d, *J* = 8.5 Hz, 2 H), 5.33-5.25 (m, 1 H), 5.02 (d, *J* = 5.0 Hz, 2 H), 4.78 (d, *J* = 1.3 Hz, 1 H), 4.65 (d, *J* = 1.8 Hz, 2 H), 2.72 (dt, *J* = 5.3, 11.0 Hz, 1 H), 2.66-2.57 (m, 1 H), 2.33 (dd, *J* = 8.2, 12.7 Hz, 1 H), 2.13 (dd, *J* = 6.3, 17.1 Hz, 1 H), 2.00-1.88 (m, 2 H), 1.80 (d, *J* = 14.6 Hz, 1 H), 1.74 (br. s., 1 H), 1.72 (s, 3 H), 1.71-1.67 (m, 1 H), 1.60-1.32 (m, 11 H), 1.30-1.22 (m, 1 H), 1.19-1.13 (m, 1 H), 1.12 (s, 3 H), 1.03 (s, 3 H), 1.02 (s, 2 H), 0.95 (s, 3 H), 0.94 (br. s., 3 H).

Ejemplo 90

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-1H-indol-1-il)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



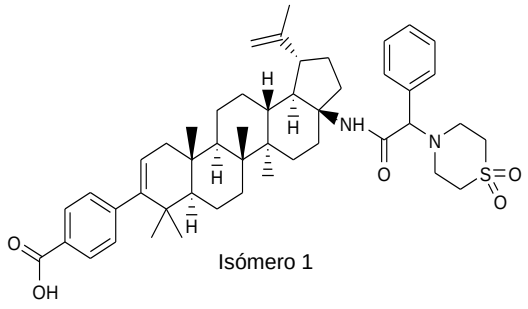
El compuesto del título se preparó en 31 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido 2-(1H-indol-1-il)acético en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 687.6 $(M+H)^+$, 2.60 min (método 6). ^{1}H NMR (400MHz, 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.5 Hz, 2 H), 7.72 (d, *J* = 7.8 Hz, 1 H), 7.40-7.35 (m, 1 H), 7.32-7.25 (m, 1 H), 7.24-7.16 (m, 4 H), 6.71 (dd, *J* = 0.8, 3.3 Hz, 1 H), 5.27 (dd, *J* = 1.6, 6.1 Hz, 1 H), 4.90 (s, 1 H), 4.83 (s, 2 H), 4.44 (s, 1 H), 4.33 (d, *J* = 1.8 Hz, 1 H), 2.48 (d, *J* = 12.5 Hz, 1 H), 2.39-2.31 (m, 1 H), 2.08 (dd, *J* = 6.4, 17.2 Hz, 1 H), 1.64 (d, *J* = 16.6 Hz, 1 H), 1.54 (d, *J* = 8.0 Hz, 2 H), 1.50 (s, 3 H), 1.39 (br. s., 3 H), 1.37-1.23 (m, 6 H), 1.23-1.13 (m, 4 H), 1.04 (br. s., 1 H), 1.00 (s, 4 H), 0.95 (s, 3 H), 0.92 (s, 3 H), 0.87 (s, 3 H), 0.82 (s, 3 H).

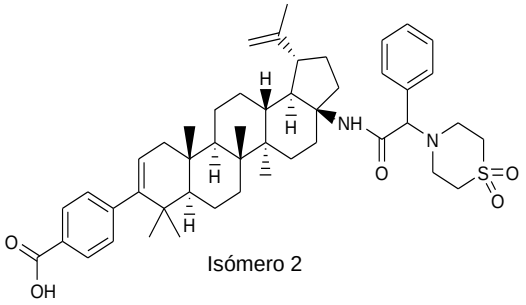
Ejemplo 91 (Isómero 1) y Ejemplo 92 (Isómero 2)

Preparación de ácido benzoico, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[(1,1-dioxido-4-tiomorfolinil)fenilacetil]amino]-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-1H-ciclopenta[a]crisen-9-il].



Isómero 1



Isómero 2

Los compuestos del título se prepararon en 21 % y 11 % de rendimiento, respectivamente, de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido 2-(1,1-dioxo-1-lamda-6-4-tiazinan-4-il)-2-fenilacético en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. Los dos isómeros formados en la reacción se separaron mediante HPLC

preparativa de fase inversa.

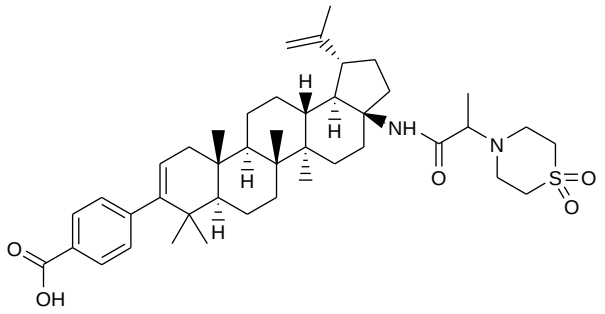
Isómero 1: LCMS: m/e 781.6 $(M+H)^+$, 2.21 min (método 6). ^{1}H NMR (400MHz, 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.5 Hz, 2 H), 7.49-7.44 (m, 2 H), 7.43-7.36 (m, 3 H), 7.20 (d, *J* = 8.3 Hz, 2 H), 6.62 (s, 1 H), 5.29 (dd, *J* = 1.6, 6.1 Hz, 1 H), 4.76 (d, *J* = 1.3 Hz, 1 H), 4.64 (br. s., 1 H), 4.26 (s, 1 H), 3.19-3.13 (m, 4 H), 3.12-3.01 (m, 4 H), 2.57-2.48 (m, 2 H), 2.40 (dd, *J* = 8.0, 11.8 Hz, 1 H), 2.12 (dd, *J* = 6.3, 17.1 Hz, 1 H), 1.76 (d, *J* = 14.6 Hz, 1 H), 1.71 (br. s., 1 H), 1.70 (s, 3 H), 1.66 (d, *J* = 11.0 Hz, 3 H), 1.50 (d, *J* = 16.3 Hz, 3 H), 1.46-1.38 (m, 3 H), 1.38-1.09 (m, 9 H), 1.00 (s, 3 H), 0.97 (s, 3 H), 0.94 (s, 3 H), 0.92 (s, 3 H), 0.84 (s, 3 H).

Isómero 2: LCMS: m/e 781.6 (M+H)+, 2.22 min (método 6). ^{1}H NMR (400MHz,1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.3 Hz, 2 H), 7.49-7.44 (m, 2 H), 7.43-7.34 (m, 3 H), 7.21 (d, *J* = 8.3 Hz, 2 H), 6.64 (s, 1 H), 5.30 (dd, *J* = 1.6, 6.1 Hz, 1 H), 4.75 (s, 1 H), 4.65 (s, 1 H), 4.16 (s, 1 H), 3.25-2.99 (m, 8 H), 2.65-2.57 (m, 1 H), 2.42 (dt, *J* = 5.6, 10.9 Hz, 1 H), 2.32 (dd, *J* = 8.3, 12.5 Hz, 1 H), 2.15 (dd, *J* = 6.4, 16.9 Hz, 1 H), 1.85-1.72 (m, 3 H), 1.70 (s, 3 H), 1.61-1.23 (m, 14 H), 1.10 (s, 3 H), 1.05 (s, 3 H), 1.01 (s, 3 H), 0.96 (s, 3 H), 0.94 (s, 3 H).

Ejemplo 93

Preparación de ácido benzoico, 4-

[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxido-4-tiomorfolinil)-1-oxopropil]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-1H-ciclopenta[a]crisen-9-il].

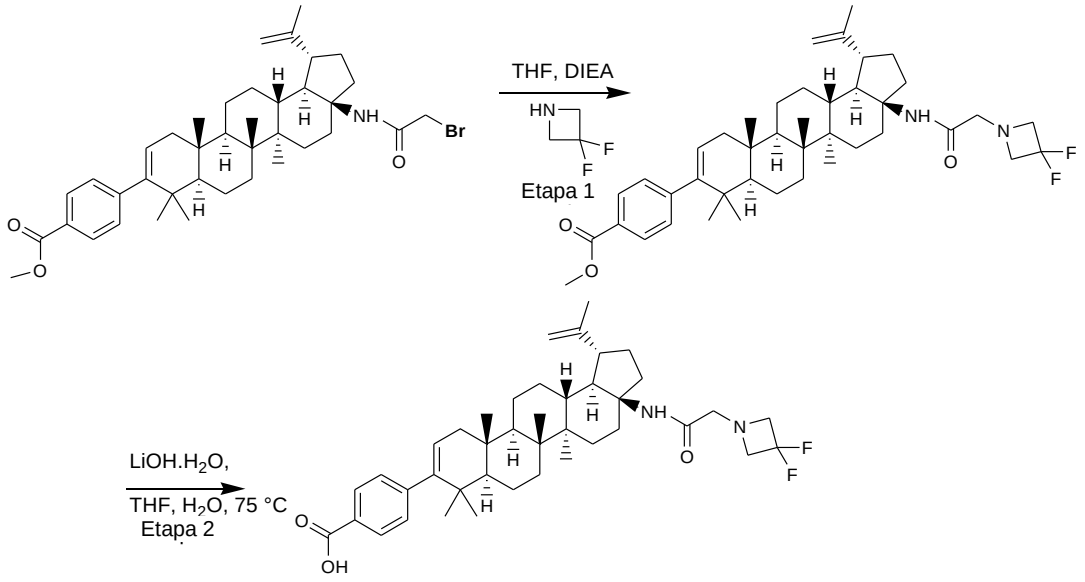


El compuesto del título se preparó en 44 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido 2-(1,1-dioxidotiomorfolin-4-il)-propiónico en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 719.5 $(M+H)^+$, 2.03 min (método 6). ^1H

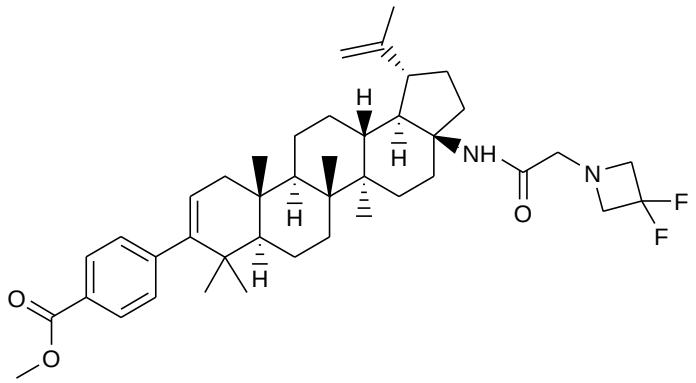
NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.54 (s, 1 H), 7.20 (d, *J* = 7.9 Hz, 2 H), 5.29 (d, *J* = 5.2 Hz, 1 H), 4.75 (d, *J* = 10.4 Hz, 1 H), 4.66 (br. s., 1 H), 3.48-3.39 (m, 1 H), 3.28-3.11 (m, 8 H), 2.69-2.55 (m, 1 H), 2.50-2.34 (m, 2 H), 2.13 (dd, *J* = 6.1, 17.1 Hz, 1 H), 1.80 (d, *J* = 11.6 Hz, 2 H), 1.72 (s, 6 H), 1.59-1.44 (m, 8 H), 1.43-1.36 (m, 2 H), 1.33 (dd, *J* = 6.9, 14.8 Hz, 4 H), 1.25 (d, *J* = 6.7 Hz, 1 H), 1.15 (d, *J* = 11.0 Hz, 2 H), 1.08 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.94 (br. s., 6 H).

Ejemplo 94

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3,3-difluoroazetidin-1-il)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



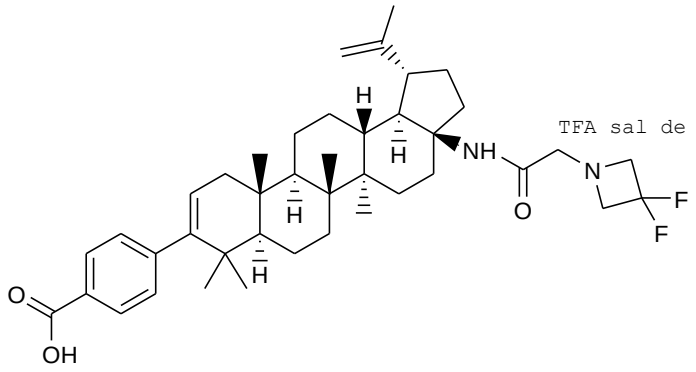
Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3,3-difluoroazetidin-1-il)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.



A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-bromoacetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (129 mg, 0.194 mmol) en THF (3 mL), se agregó *N,N*-diisopropiletilamina (0.338 mL, 1.941 mmol) y 3,3-difluoroazetidina, HCl (126 mg, 0.970 mmol). La mezcla de reacción se agita a 160 °C durante 5 h. La mezcla se concentra, y el residuo crudo se disolvió en THF (1.5 mL), se filtró y se purificó mediante HPLC preparativa de fase inversa usando el método 3 de HPLC Prep para obtener 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3,3-

difluoroazetidin-1-il)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (28.8 mg, 0.043 mmol, 21.9 % de rendimiento) como un sólido marrón. LC/MS: m/e 677.5 $(M+H)^+$, 2.93 min (método 6).

Etapa 2. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3,3-difluoroazetidin-1-il)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, TFA.



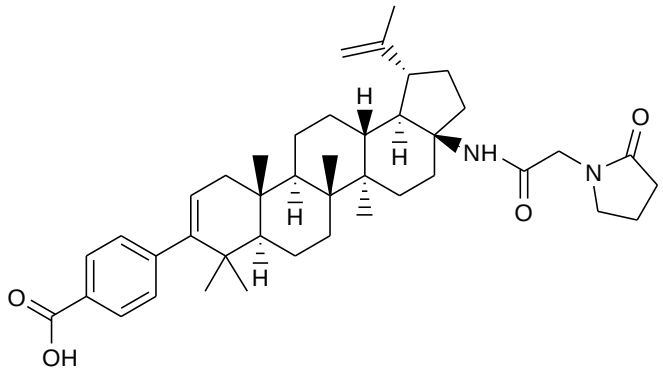
A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3,3-difluoroazetidin-1-il)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (28.8 mg, 0.043 mmol) en THF (Volumen: 3 mL) se agregó una

solución de Li. H O.0.753 molar H_2O (0.340 mL, 0.170 mmol) en H_2O. La reacción se calentó a 75 °C durante 6 h y, luego, se concentró para obtener un aceite viscoso marrón. El residuo crudo se disolvió en THF (1,3 mL) y 0.2 mL de HCl 1N, se filtró y se purificó mediante HPLC preparativa de fase inversa usando el método 3 de HPLC preparativa para obtener ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3,3-difluoroazetidin-1-il)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, TFA (17.6 mg, 0.022 mmol, 52.7 % de rendimiento) como un sólido amarillo claro. LCMS: m/e 663.7 $(M+H)^+$, 2.22 min (método 2). ^{1}H NMR (500MHz, *1:1 $CDCl_3$:METANOL-d_4*) δ 7.90 (d, *J*= 8.2 Hz, 2H), 7.18 (d, *J*= 8.2 Hz, 2H), 5.27 (d, *J*= 4.6 Hz, 1H), 4.73 (s, 1H), 3.88 (t, *J*= 12.5 Hz, 2H), 3.69-3.59 (m, 1H), 3.55-3.39 (m, 3H), 2.64-2.53 (m, 2H), 2.39 (dd, *J*= 12.2, 8.2 Hz, 1H), 2.10 (dd, *J*= 17.1, 6.4 Hz, 1H), 1.93-1.73 (m, 3H), 1.69 (s, 3H), 1.67 (d, *J*= 4.6 Hz, 1H), 1.58-1.39 (m, 8H), 1.39-1.29 (m, 3H), 1.23 (d, *J*= 10.1 Hz, 1H), 1.11 (d, *J*= 13.7 Hz, 2H), 1.06 (s, 3H), 1.00 (s, 3H), 0.99 (s, 3H), 0.92 (br. s., 3H), 0.91 (br. s., 3H).

Ejemplo 95

Preparación del ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-

pentametil-3a-(2-(2-oxopirrolidin-1-il)acetamido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

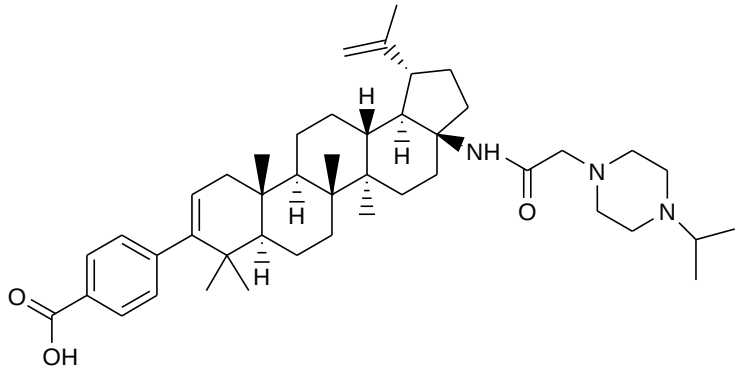


El compuesto del título se preparó en 14 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido 2-(2-oxopirrolidin-1-il)acético en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 655.5 $(M+H)^+$, 1.99 min (método 6). ^1H NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 7.9 Hz, 2 H),

7.20 (d, *J* = 7.9 Hz, 2 H), 6.77 (s, 1 H), 5.29 (d, *J* = 4.7 Hz, 1 H), 4.75 (d, *J* = 1.3 Hz, 1 H), 4.63 (s, 1 H), 3.97-3.85 (m, 2 H), 3.58-3.51 (m, 2 H), 2.65-2.54 (m, 2 H), 2.47 (t, *J* = 8.0 Hz, 2 H), 2.38 (dd, *J* = 8.4, 12.5 Hz, 1 H), 2.17-2.07 (m, 3 H), 1.95-1.85 (m, 1 H), 1.83-1.74 (m, 2 H), 1.73 (br. s., 1 H), 1.70 (s, 3 H), 1.68-1.62 (m, 1 H), 1.60-1.43 (m, 8 H), 1.42-1.22 (m, 6 H), 1.13 (br. s., 1 H), 1.09 (s, 3 H), 1.01 (s, 6 H), 0.94 (s, 3 H), 0.93 (s, 3 H).

Ejemplo 96

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4-isopropilpiperazin-1-il)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



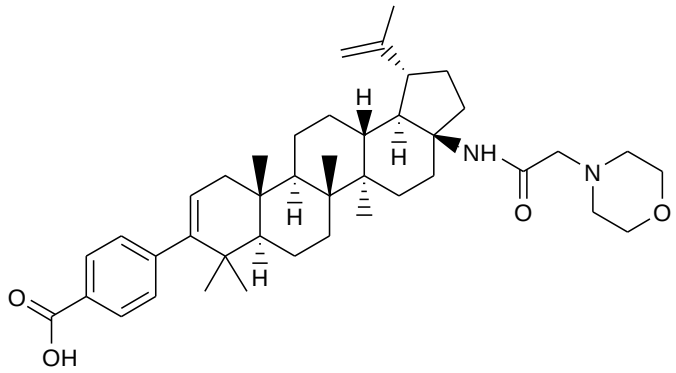
El compuesto del título se preparó en 22 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido (4-isopropil-piperazin-1-il)-acético en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 698.6 $(M+H)^+$, 2.64 min (método 6). ^1H NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.37 (br. s., 1 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 6.34-6.03 (m, 1 H), 5.29 (d, *J* = 4.6 Hz, 1 H), 4.76 (br. s., 1 H), 4.70 (br. s., 1 H), 3.95 (br. s., 1 H), 3.84-3.55 (m, 8 H), 3.17 (q, *J* = 7.2 Hz, 2 H), 2.64 (d, *J* = 13.1 Hz, 2 H), 2.39 (dd, *J* = 8.1, 11.4 Hz, 1 H), 2.12 (dd, *J* = 6.3, 17.2 Hz, 1 H), 1.96-1.84 (m, 2 H), 1.79 (d, *J* = 12.5 Hz, 1 H), 1.76-1.65 (m, 5 H), 1.59-1.40 (m, 14 H), 1.35 (t, *J* = 7.2 Hz, 4 H), 1.29-1.21 (m, 1 H), 1.15 (d, *J* = 6.1 Hz, 1 H), 1.10 (br. s., 3 H), 1.02 (s, 3 H), 1.01 (br. s., 2 H), 0.94 (br. s., 3 H), 0.93 (br. s., 3 H).

Ejemplo 97

Preparación del ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-

pentametil-3a-(2-morfolinoacetamido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

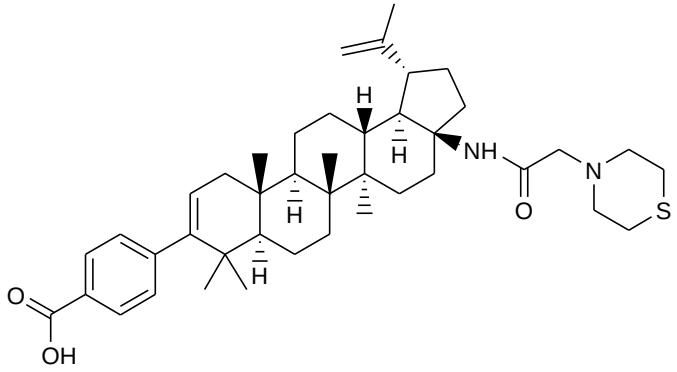


El compuesto del título se preparó en 40 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido morfolin-4-il-acético en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 657.6 $(M+H)^+$, 2.20 min (método 6). ^1H NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ = 7.91 (d, *J* = 7.9 Hz, 2 H),

7.48 (br. s., 1 H), 7.19 (d, *J* = 8.2 Hz, 2 H), 5.28 (d, *J* = 4.9 Hz, 1 H), 4.77 (br. s., 1 H), 4.12-3.79 (m, 6 H), 3.57-3.40 (m, 2 H), 3.22-3.11 (m, 1 H), 2.74 (br. s., 1 H), 2.65 (d, *J* = 12.8 Hz, 1 H), 2.42-2.29 (m, 1 H), 2.12 (dd, *J* = 6.1, 17.1 Hz, 1 H), 2.03-1.85 (m, 2 H), 1.79 (d, *J* = 12.8 Hz, 1 H), 1.72 (br. s., 1 H), 1.71 (s, 3 H), 1.69 (br. s., 1 H), 1.60-1.30 (m, 12 H), 1.24 (d, *J* = 5.8 Hz, 1 H), 1.14 (br. s., 1 H), 1.10 (br. s., 4 H), 1.02 (br. s., 3 H), 1.00 (br. s., 3 H), 0.93 (br. s., 3 H), 0.92 (br. s., 3 H).

Ejemplo 98

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(2-tiomorfolinoacetamido)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



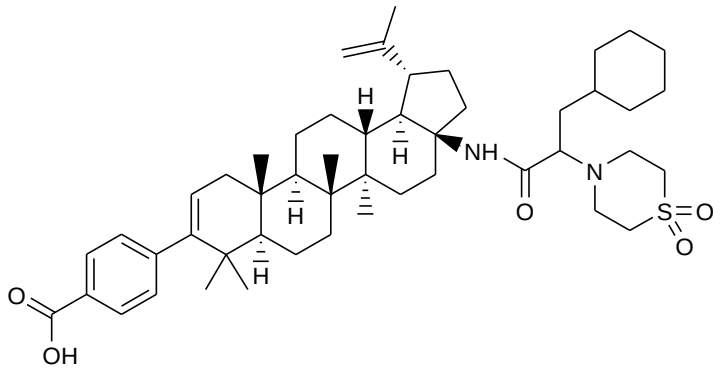
El compuesto del título se preparó en 44 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido 2-tiomorfolinoacético en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 671.8 $(M-H)^-$, 2.37 min (método 6). ^{1}H NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.47 (s, 1 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 5.29 (d, *J* = 4.3 Hz, 1 H), 4.75 (s, 1 H), 3.79-3.63 (m, 2 H), 3.58 (td, *J* = 6.5, 12.9 Hz, 1 H), 3.47-3.35 (m, 3 H), 2.95 (br. s., 4 H), 2.68-2.57 (m, 2 H), 2.37 (dd, *J* = 8.4, 12.4 Hz, 1 H), 2.13 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.92-1.82 (m, 2 H), 1.81-1.76 (m, 1 H), 1.73 (br. s., 1 H), 1.71 (s, 3 H), 1.69-1.64 (m, 1 H), 1.60-1.31 (m, 12 H), 1.30-1.22 (m, 1 H), 1.19-1.11 (m, 2 H), 1.09 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.94 (br. s., 3 H), 0.93 (br. s., 3 H).

Ejemplo 99

Preparación de ácido benzoico, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-ciclohexilo-2-(1,1-dioxido-4-tiomorfolinil)-1-oxopropil]amino]-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-1H-ciclopenta[a]crisen-9-il].

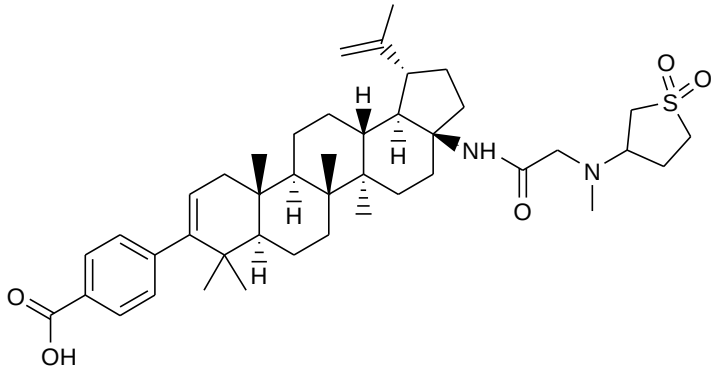


El compuesto del título se preparó en 23 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido 3-ciclohexil-2-(1,1-dioxo-1lambda6, -4,tiazinan-4-il)propanoico en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 801.6 $(M+H)^+$, 2.43 min (método 6). ^1H NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ

= 7.92 (d, *J* = 8.2 Hz, 2 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 6.56 (s, 1 H), 5.29 (d, *J* = 4.6 Hz, 1 H), 4.76 (s, 1 H), 3.58 (td, *J* = 6.6, 13.4 Hz, 1 H), 3.44 (dd, *J* = 5.0, 9.6 Hz, 1 H), 3.30-3.25 (m, 3 H), 3.24-3.15 (m, 2 H), 3.14-3.06 (m, 2 H), 2.68 (d, *J* = 13.4 Hz, 1 H), 2.56 (dt, *J* = 5.6, 11.1 Hz, 1 H), 2.41 (dd, *J* = 8.4, 12.7 Hz, 1 H), 2.13 (dd, *J* = 6.3, 17.2 Hz, 1 H), 1.92-1.75 (m, 5 H), 1.73 (br. s., 1 H), 1.72 (s, 3 H), 1.70-1.64 (m, 4 H), 1.61-1.40 (m, 10 H), 1.40-1.29 (m, 3 H), 1.28-1.11 (m, 7 H), 1.09 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.97 (d, *J* = 3.1 Hz, 1 H), 0.94 (br. s., 3 H), 0.93 (br. s., 3 H).

Ejemplo 100

Preparación de ácido benzoico, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-3a-[[[metil(tetrahidro-1,1-dioxido-3-tienil)amino]acetil]amino]-1H-ciclopenta[a]crisen-9-il].

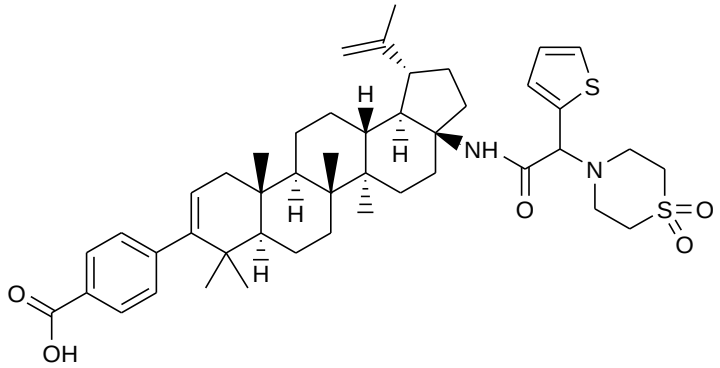


El compuesto del título se preparó en 17 % de

rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó *N*-(1,1-dioxidotetrahidro-3-tienil)-*N*-metilglicina en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 719.5 $(M+H)^+$, 2.00 min (método 6). ^{1}H NMR (500MHz, *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.30 (d, *J* = 7.6 Hz, 1 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 5.29 (d, *J* = 4.9 Hz, 1 H), 3.80 (br. s., 1 H), 3.40 (dd, *J* = 7.6, 13.4 Hz, 1 H), 3.30-3.05 (m, 4 H), 2.60 (br. s., 1 H), 2.57 (d, *J* = 1.5 Hz, 3 H), 2.55-2.41 (m, 3 H), 2.23 (quin, *J* = 10.6 Hz, 1 H), 2.13 (dd, *J* = 6.1, 17.1 Hz, 1 H), 1.91-1.76 (m, 2 H), 1.73 (br. s., 1 H), 1.71 (s, 3 H), 1.70 (br. s., 1 H), 1.60-1.29 (m, 12 H), 1.25 (d, *J* = 7.0 Hz, 1 H), 1.21-1.11 (m, 3 H), 1.09 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.94 (s, 3 H), 0.93 (br. s., 3 H).

Ejemplo 101

Preparación de ácido benzoico, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-tiomorfolinil)-1-oxo-3-(2-tienil)propil]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-1H-ciclopenta[a]crisen-9-il].



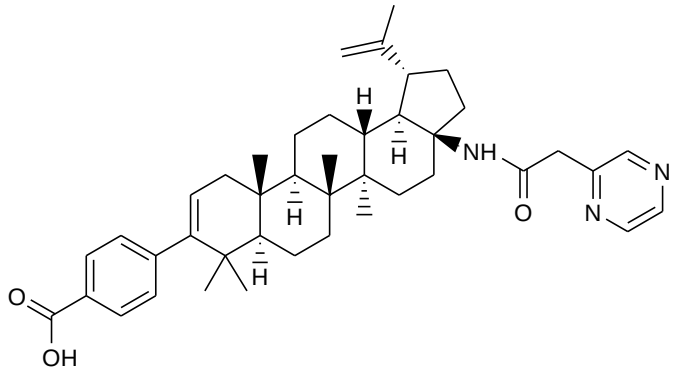
El compuesto del título se preparó en 39 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido 3-(1,1-dioxo-1lambda6,4-tiazinan-4-il)-3-(2-tienil)propanoico en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 801.6 $(M+H)^+$, 2.16 min (método 6). ^{1}H NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.36-7.28 (m, 1 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 7.05-6.91 (m, 2 H), 6.59 (s, 1 H), 5.29 (d, *J* = 4.9 Hz, 1 H), 4.74 (d, *J* = 7.6 Hz, 1 H), 4.60-4.52 (m, 2 H), 3.18-3.05 (m, 6 H), 3.04-2.93 (m, 2 H), 2.91-2.72 (m, 2 H), 2.68-2.49 (m, 2 H), 2.48-2.40 (m, 1 H), 2.27 (dd, *J* = 8.5, 11.9 Hz, 1 H), 2.12 (dd, *J* = 4.9, 17.1 Hz, 1 H), 1.93-1.72 (m, 3 H), 1.69 (d, *J* = 7.9 Hz, 3 H), 1.64 (d, *J* = 11.6 Hz, 1 H), 1.61-1.38 (m, 8 H), 1.37-1.19 (m, 5 H), 1.13 (br. s., 1 H), 1.11 (br. s., 15 H), 1.10 (br. s., 2 H), 1.02 (br. s., 1 H), 1.01 (br. s., 2 H), 1.01 (br. s., 1 H), 1.00 (br. s., 2 H), 0.95 (br. s., 1 H), 0.95 (br. s., 2 H), 0.93 (s, 3 H).

Ejemplo 102

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(2-(pirazin-2-il)acetamido)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

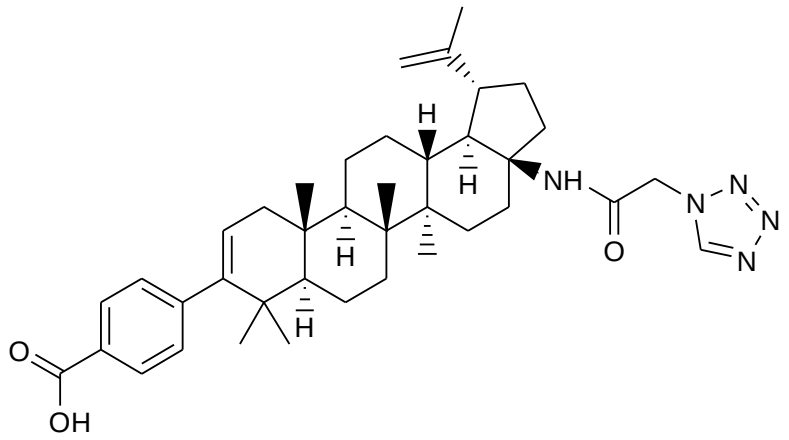


El compuesto del título se preparó en 14 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido 2-pirazinacético en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 650.6 $(M+H)^+$, 2.12 min (método 6). ^1H NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ = 8.68-8.50 (m, 3 H), 7.92 (d, *J* = 8.2 Hz, 2 H), 7.20 (d, *J* = 8.2 Hz, 3 H), 5.29 (dd, *J* = 1.7, 6.0 Hz, 1 H), 4.76 (s, 1 H), 3.79 (q, *J* = 14.3 Hz, 2 H), 2.66-2.53 (m,

2 H), 2.42-2.31 (m, 1 H), 2.12 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.91-1.74 (m, 3 H), 1.72 (br. s., 1 H), 1.71 (s, 2 H), 1.67 (d, *J* = 11.9 Hz, 2 H), 1.57-1.18 (m, 13 H), 1.17-1.02 (m, 3 H), 1.00 (br. s., 3 H), 1.00 (br. s., 3 H), 0.94 (s, 3 H), 0.92 (br. s., 3 H), 0.92 (br. s., 3 H).

Ejemplo 103

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(1H-tetrazol-1-il)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



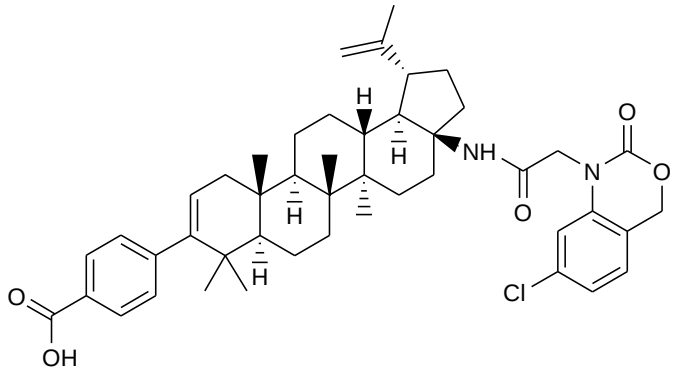
El compuesto del título se preparó en 33 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido 1-H-tetrazol-1-acético en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 638.7 $(M-H)^-$, 1.98 min (método 6). ^{1}H NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ = 9.10 (s, 1 H), 7.93 (d, *J* = 8.2 Hz, 2 H), 7.39 (s, 1 H), 7.21 (d, *J* = 8.2 Hz, 2 H), 5.30 (dd, *J* = 1.5, 6.1 Hz, 1 H), 5.27 (d, *J* = 1.5 Hz, 2 H), 4.78 (d, *J* = 1.2 Hz, 1 H), 4.65 (s, 1 H), 2.71 (dt, *J* = 5.2, 11.1 Hz, 1 H), 2.64-2.56 (m, 1 H), 2.34 (dd, *J* = 8.1, 12.7 Hz, 1 H), 2.13 (dd, *J* = 6.4, 17.1 Hz, 1 H), 2.00-1.86 (m, 2 H), 1.80 (d, *J* = 11.0 Hz, 1 H), 1.74 (br. s., 1 H), 1.72 (s, 3 H), 1.71-1.66 (m, 1 H), 1.62-1.30 (m, 11 H), 1.29-1.22 (m, 1 H), 1.20-1.14 (m, 1 H), 1.12 (s, 3 H), 1.10 (d, *J* = 4.3 Hz, 1 H), 1.03 (s, 6 H), 0.95 (s, 3 H), 0.94 (s, 3 H).

Ejemplo 104

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(7-cloro-2-oxo-2.4-dihidro-1H-benzo[d][1,3]oxazin-1-il)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

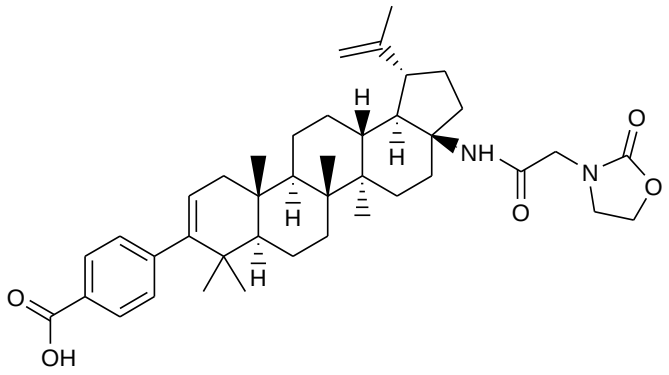


El compuesto del título se preparó en 36 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido 2-(6-cloro-3-oxo-2H-benzo[b][1.4]oxazin-4(3H)-il)acético en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 653.5 $(M+H)^+$, 2.29 min (método 6). ^{1}H NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.5 Hz, 2 H), 7.21 (d, *J* = 8.5 Hz, 2 H), 7.05-7.01 (m, 1 H), 7.01-6.97 (m, 2 H), 6.83 (s, 1 H), 5.29

(dd, *J* = 1.7, 6.3 Hz, 1 H), 4.73 (d, *J* = 1.8 Hz, 1 H), 4.70 (d, *J* = 1.2 Hz, 2 H), 4.66 (br. s., 1 H), 4.63 (s, 1 H), 4.57-4.50 (m, 1 H), 2.65-2.57 (m, 1 H), 2.51-2.34 (m, 2 H), 2.13 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.96-1.85 (m, 1 H), 1.83-1.72 (m, 3 H), 1.70 (s, 3 H), 1.69-1.64 (m, 1 H), 1.63-1.55 (m, 2 H), 1.54-1.45 (m, 4 H), 1.45-1.30 (m, 5 H), 1.30-1.23 (m, 1 H), 1.18-1.12 (m, 2 H), 1.10 (s, 3 H), 1.02 (s, 6 H), 0.95 (s, 3 H), 0.94 (s, 3 H).

Ejemplo 105

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(2-oxooxazolidin-3-il)acetamido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



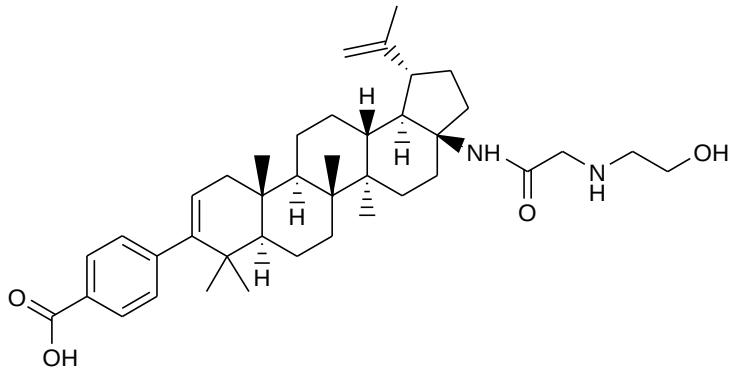
El compuesto del título se preparó en 29 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo

de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido 2-(2-oxooxazolidin-3-il)acético en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 657.5 $(M+H)^+$, 1.97 min (método 6). ^{1}H NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.20 (d, *J* = 8.5 Hz, 2 H), 6.82 (s, 1 H), 5.29 (dd, *J* = 1.7, 6.3 Hz, 1 H), 4.76 (d, *J* = 1.5 Hz, 1 H), 4.64 (s, 2 H), 4.43 (dt, *J* = 1.7, 8.2 Hz, 2 H), 3.98-3.84 (m, 2 H), 3.74 (t, *J* = 8.1 Hz, 2 H), 2.69-2.56 (m, 2 H), 2.40 (dd, *J* = 8.1, 12.4 Hz, 1 H), 2.13 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.98-1.81 (m, 2 H), 1.81-1.75 (m, 1 H), 1.73 (br. s., 1 H), 1.71 (s, 3 H), 1.70-1.65 (m, 1 H), 1.61-1.43 (m, 7 H), 1.42-1.29 (m, 4 H), 1.29-1.21 (m, 2 H), 1.16-1.12 (m, 1 H), 1.10 (s, 3 H), 1.02 (s, 3 H), 1.02 (s, 3 H), 0.95 (s, 3 H), 0.94 (s, 3 H).

Ejemplo 106

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-hidroxietilamino)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-

1-en-2-il)-
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

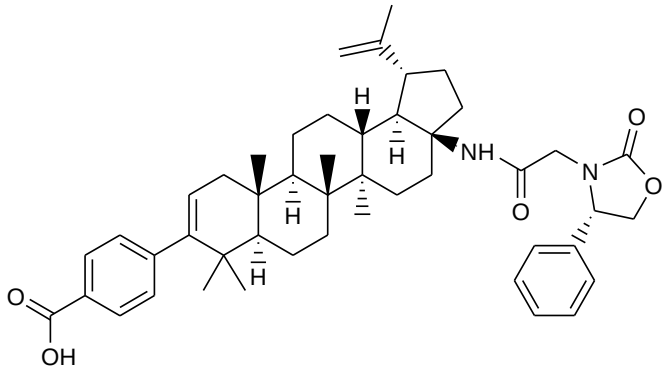


El compuesto del título se preparó en 14 % de rendimiento como un subproducto durante la preparación descrita anteriormente de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(2-oxooxazolidin-3-il)acetamido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico. LCMS: m/e 631.5 $(M+H)^+$, 1.94 min (método 6). ^1H NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 5.29 (d, *J* = 4.6 Hz, 1 H), 4.76 (s, 1 H), 4.65 (s, 1 H), 3.87-3.75 (m, 4 H), 3.17-3.12 (m, 2 H), 2.73-2.62 (m, 2 H), 2.37 (dd, *J* = 8.4, 12.1 Hz, 1 H), 2.13 (dd, *J* = 6.3, 17.2 Hz, 1 H), 2.16-2.09 (m, 1 H), 1.95-1.85 (m, 2 H), 1.79 (d, *J* = 11.0 Hz, 1 H), 1.74 (br. s., 1 H), 1.72 (s, 3 H), 1.71-1.66 (m, 1 H), 1.58-1.47 (m, 6 H), 1.47-1.32 (m, 5 H), 1.30-1.23 (m, 1 H), 1.16-1.11 (m, 2 H), 1.10 (s, 3 H),

1.03 (s, 3 H), 1.02 (s, 3 H), 0.95 (s, 3 H), 0.94 (br. s., 3 H).

Ejemplo 107

Preparación del ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-((S)-2-oxo-4-feniloxazolidin-3-il)acetamido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



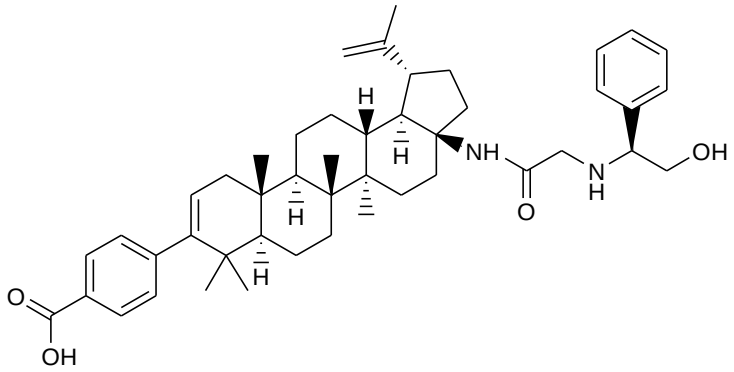
El compuesto del título se preparó en 30 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-

(prop-1-en-2-il)-
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido (S)-(+)-2-oxo-4-fenil-3-oxazolidinacético en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 733.5 $(M+H)^+$, 2.25 min (método 6). ^{1}H NMR (400MHz, 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.3 Hz, 2 H), 7.47-7.39 (m, 3 H), 7.37-7.32 (m, 2 H), 7.20 (d, *J* = 8.3 Hz, 2 H), 6.60 (s, 1 H), 5.28 (d, *J* = 4.5 Hz, 1 H), 5.04 (t, *J* = 8.3 Hz, 1 H), 4.75 (t, *J* = 8.9 Hz, 1 H), 4.71 (s, 1 H), 4.61 (br. s., 1 H), 4.25-4.19 (m, 1 H), 4.04 (d, *J* = 16.3 Hz, 1 H), 3.40 (d, *J* = 16.3 Hz, 1 H), 2.65-2.59 (m, 1 H), 2.47 (dt, *J* = 4.8, 11.0 Hz, 1 H), 2.37 (dd, *J* = 8.2, 11.7 Hz, 1 H), 2.11 (dd, *J* = 6.3, 17.1 Hz, 1 H), 1.84-1.70 (m, 4 H), 1.69 (s, 3 H), 1.66-1.59 (m, 1 H), 1.58-1.40 (m, 7 H), 1.39-1.22 (m, 6 H), 1.09 (br. s., 1 H), 1.07 (s, 3 H), 1.00 (s, 6 H), 0.95 (s, 3 H), 0.94 (br. s., 3 H).

Ejemplo 108

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((S)-2-hidroxi-1-feniletilamino)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-

il)benzoico.

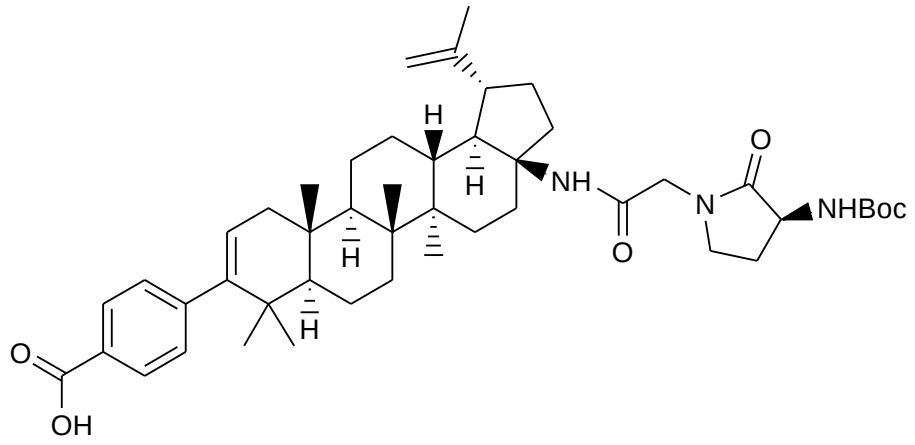


El compuesto del título se preparó en 8 % de rendimiento como un subproducto durante la preparación descrita anteriormente de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-((S)-2-oxo-4-feniloxazolidin-3-il)acetamido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico. LCMS: m/e 707.5 $(M+H)^+$, 2.18 min (método 6). ^1H NMR (400MHz, 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.3 Hz, 2 H), 7.49-7.45 (m, 3 H), 7.45-7.40 (m, 2 H), 7.19 (d, *J* = 8.3 Hz, 2 H), 5.28 (d, *J* = 4.8 Hz, 1 H), 4.71 (s, 1 H), 4.62 (br. s., 2 H), 4.35 (dd, *J* = 4.9, 7.7 Hz, 1 H), 4.04-3.90 (m, 2 H), 3.72-3.55 (m, 2 H), 2.60-2.50 (m, 2 H), 2.36 (dd, *J* = 8.5, 12.0 Hz, 1 H), 2.10 (dd, *J* = 6.4, 17.2 Hz, 1 H), 1.91-1.75 (m, 2 H), 1.73 (d, *J* = 7.3 Hz, 2 H), 1.69 (s, 3 H), 1.65-1.60 (m, 1 H), 1.50-1.37 (m, 6 H), 1.37-1.19 (m, 7 H), 1.07 (d, *J* = 18.6 Hz, 3 H), 0.99 (s, 6 H), 0.97 (s, 3 H), 0.94 (br. s., 3

H), 0.94 (br. s., 3 H).

Ejemplo 109

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-((S)-3-(terc-butoxicarbonilamino)-2-oxopirrolidin-1-il)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



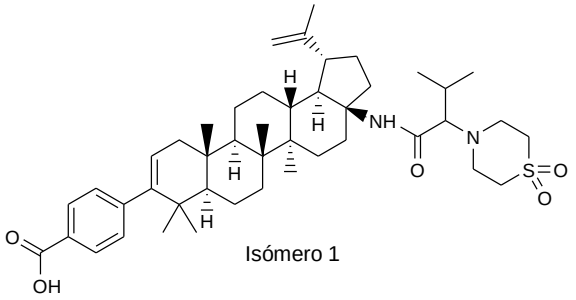
El compuesto del título se preparó en 34 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-

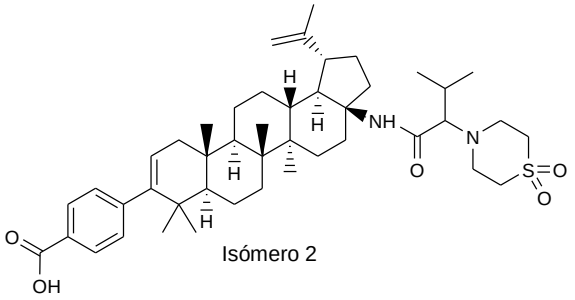
(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido (S)-2-(3-(terc-butoxicarbonilamino)-2-oxopirrolidin-1-il)acético en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 770.6 (M+H)+, 2.07 min (método 6). ^{1}H NMR (400MHz, 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.0 Hz, 2 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 6.83-6.60 (m, 1 H), 5.29 (d, *J* = 4.8 Hz, 1 H), 4.76 (s, 1 H), 4.63 (br. s., 1 H), 4.32-4.16 (m, 1 H), 4.07-3.84 (m, 2 H), 3.44 (d, *J* = 7.0 Hz, 2 H), 2.70-2.56 (m, 2 H), 2.55-2.44 (m, 1 H), 2.43-2.31 (m, 1 H), 2.13 (dd, *J* = 6.3, 17.1 Hz, 1 H), 2.08-1.95 (m, 1 H), 1.94-1.82 (m, 2 H), 1.81-1.73 (m, 2 H), 1.71 (s, 3 H), 1.68-1.62 (m, 1 H), 1.61-1.48 (m, 6 H), 1.46 (s, 9 H), 1.43-1.22 (m, 6 H), 1.13 (br. s., 1 H), 1.10 (d, *J* = 3.8 Hz, 3 H), 1.02 (s, 6 H), 0.95 (br. s., 3 H), 0.94 (br. s., 3 H).

Ejemplo 110 (Isómero 1) y Ejemplo 111 (Isómero 2)

Preparación de ácido benzoico, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxido-4-tiomorfolinil)-3-metil-1-oxobutil]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-1H-

ciclopenta[a]crisen-9-il].





Los compuestos del título se prepararon en 9 % de rendimiento cada uno de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido 2-(1,1-dioxo-1-lamda-6,4-tiazinan-4-il)3-metilbutanoico (91 mg, 0.388 mmol) en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. Los dos isómeros formados en la reacción se separaron mediante HPLC preparativa de fase inversa.

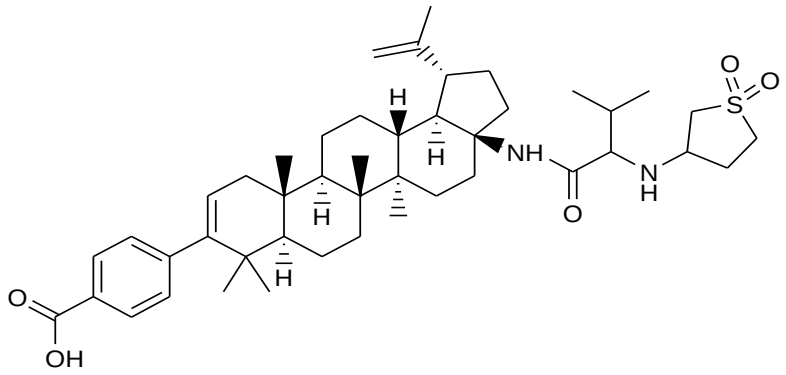
Isómero 1: LCMS: m/e 747.5 $(M+H)^+$, 2.23 min (método 6). ^{1}H NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.20 (d, *J* = 8.5 Hz, 2 H), 6.42 (s, 1 H), 5.29 (dd, *J* = 1.5, 6.1 Hz, 1 H), 4.75 (d, *J* = 1.5 Hz, 1 H), 4.64 (br. s., 1 H), 3.31-3.23 (m, 2 H), 3.16-3.07 (m, 4 H), 3.06-2.97 (m, 2 H), 2.84 (d, *J* = 10.4 Hz, 1 H), 2.77-2.71 (m, 1 H), 2.63 (dt, *J* = 5.5, 11.1 Hz, 1 H), 2.42 (dd, *J* = 8.2, 12.5 Hz, 1 H), 2.12 (dd, *J* = 6.4, 17.1 Hz, 1 H), 2.03 (qd, *J* = 6.5, 16.9 Hz, 1 H), 1.91-1.81 (m, 2 H), 1.78 (d, *J* = 12.2 Hz, 1 H), 1.73 (br. s., 1 H), 1.71 (s, 3 H), 1.68 (d, *J* = 11.3 Hz, 1 H), 1.62 (dd, *J* = 3.4, 13.4 Hz, 1 H), 1.57 (d, *J* = 4.9 Hz, 1 H), 1.51 (br. s., 3 H), 1.47 (d, *J* = 12.5 Hz, 1 H), 1.44-1.28 (m, 5 H), 1.28-1.23 (m, 2 H), 1.18 (d, *J* = 13.7 Hz, 1 H), 1.11 (dd, *J* = 4.0, 12.8 Hz, 1 H), 1.08 (s, 3 H), 1.02 (s, 3 H), 1.01 (s, 4 H), 0.99 (s, 2 H), 0.94 (s, 3 H), 0.94 (br. s., 3 H), 0.90 (d, *J* = 6.4 Hz, 3 H).

Isómero 2: LCMS: m/e 747.5 (M+H)+, 2.29 min (método 6). ^{1}H NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.5 Hz, 2 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 6.40 (s, 1 H), 5.29 (dd, *J* = 1.5, 6.1 Hz, 1 H), 4.76 (d, *J* = 1.5 Hz, 1 H), 4.64 (s, 1 H), 3.77-3.72 (m, 1 H), 3.23-3.14 (m, 2 H), 3.13-3.06 (m, 4 H), 3.05-2.99 (m, 2 H), 2.80 (d, *J* = 10.4 Hz, 1 H), 2.74-2.67 (m, 1 H), 2.61 (dt, *J* = 5.3, 11.1 Hz, 1 H), 2.49 (dd, *J* = 8.4, 12.7 Hz, 1 H), 2.12 (dd, *J* = 6.4, 17.1 Hz, 1 H), 2.08-2.01 (m, 1 H), 1.99-1.91 (m, 1 H), 1.88 (ddd, *J* = 3.1,

3.3, 6.8 Hz, 1 H), 1.86-1.82 (m, 1 H), 1.78 (d, *J* = 11.0 Hz, 1 H), 1.72 (br. s., 1 H), 1.71 (s, 3 H), 1.69 (d, *J* = 4.6 Hz, 1 H), 1.67-1.63 (m, 1 H), 1.61-1.53 (m, 2 H), 1.51 (br. s., 1 H), 1.48 (br. s., 2 H), 1.47-1.41 (m, 2 H), 1.12 (dd, *J* = 3.4, 13.4 Hz, 2 H), 1.07 (s, 3 H), 1.01 (br. s., 3 H), 1.00 (s, 3 H), 0.99 (s, 3 H), 0.97 (d, *J* = 6.7 Hz, 3 H), 0.93 (s, 3 H), 0.93 (s, 3 H).

Ejemplo 112

Preparación de ácido benzoico, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-3a-[[3-metil-1-oxo-2-[(tetrahidro-1,1-dioxido-3-tienil)amino]butil]amino]-1H-ciclopenta[a]crisen-9-il].

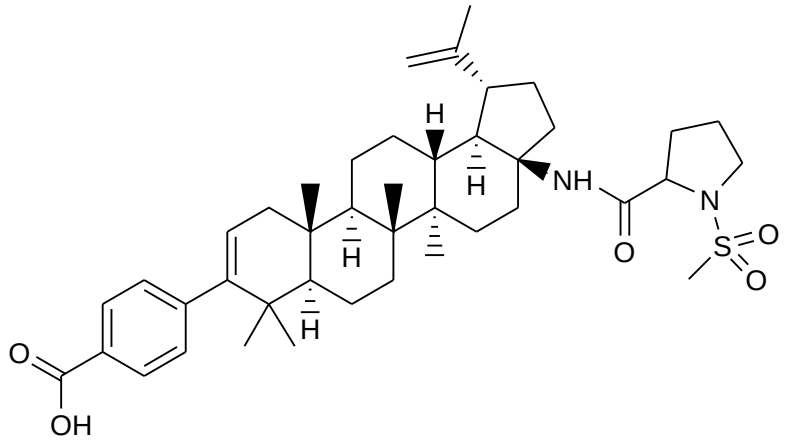


El compuesto del título se preparó en 30 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo

de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido 2-(1,1-dioxo-tetrahidro-1lambda6-tiofen-3-il-amino)-3-metilbutírico en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 747.5 $(M+H)^+$, 2.09 min (método 6). ^{1}H NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.25 (br. s., 1 H), 7.19 (d, *J* = 8.2 Hz, 2 H), 5.28 (d, *J* = 4.9 Hz, 1 H), 4.78 (s, 1 H), 4.65 (br. s., 1 H), 3.73 (ddd, *J* = 6.6, 6.7, 9.3 Hz, 1 H), 3.47 (dd, *J* = 7.2, 13.3 Hz, 1 H), 3.41 (dt, *J* = 4.1, 8.6 Hz, 1 H), 3.27 (br. s., 1 H), 3.17-3.07 (m, 1 H), 2.75-2.63 (m, 2 H), 2.59 (dd, *J* = 7.2, 13.0 Hz, 1 H), 2.43 (dd, *J* = 8.5, 12.2 Hz, 1 H), 2.35 (dd, *J* = 8.9, 12.8 Hz, 1 H), 2.25-2.16 (m, 1 H), 2.12 (dd, *J* = 6.3, 17.2 Hz, 1 H), 1.91-1.76 (m, 3 H), 1.74 (br. s., 1 H), 1.71 (s, 3 H), 1.69 (br. s., 1 H), 1.58-1.47 (m, 6 H), 1.46-1.35 (m, 4 H), 1.35-1.28 (m, 1 H), 1.25 (d, *J* = 9.8 Hz, 1 H), 1.18-1.12 (m, 2 H), 1.10 (d, *J* = 6.7 Hz, 3 H), 1.08 (s, 3 H), 1.06 (d, *J* = 7.3 Hz, 3 H), 1.03 (s, 3 H), 1.00 (s, 3 H), 0.93 (s, 3 H), 0.93 (br. s., 3 H).

Ejemplo 113

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(1-(metilsulfonil)pirrolidin-2-carboxamido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



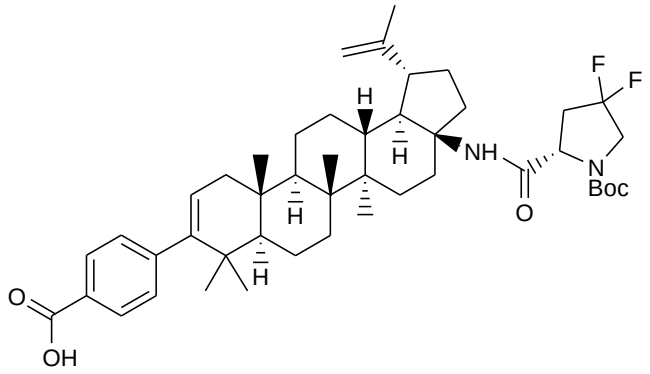
El compuesto del título se preparó en 17 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido 1-(metilsulfonil)pirrolidin-2-carboxílico en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 705.5 $(M+H)^+$, 2.04 min (método 6). ^{1}H NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.5 Hz, 2 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 6.88 (s, 1 H), 5.29 (dd, *J* = 1.5, 6.1 Hz, 1 H), 4.76 (d, *J* = 1.5 Hz, 1 H), 4.10 (dd, *J* = 3.1, 8.8 Hz, 1 H), 3.60 (ddd, *J* = 3.5, 7.0, 10.2 Hz, 1 H), 3.40 (dt, *J* = 6.4, 9.6 Hz, 1 H), 2.96 (s, 3 H), 2.62-2.52 (m, 2 H), 2.42 (dd, *J* = 8.2, 11.6 Hz, 1 H), 2.31 (dddd, *J* = 3.2, 3.4, 6.4, 9.7 Hz, 1 H), 2.21-2.16 (m, 1 H), 2.16-2.10 (m, 1 H), 2.03 (tdd, *J* = 3.2, 6.6, 13.0 Hz, 1 H), 1.99-1.89 (m, 2 H), 1.82-1.75 (m, 1 H), 1.75-1.72 (m, 1 H), 1.70 (s, 3 H), 1.69-1.66 (m, 1 H), 1.58-1.46 (m, 6 H), 1.46-1.29 (m, 5 H), 1.28-1.22 (m, 1 H), 1.14 (d, *J* = 13.1 Hz, 2 H), 1.09 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.93 (s, 6 H).

Ejemplo 114

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((S)-1-(terc-butoxicarbonil)-4,4-difluoropirrolidin-2-carboxamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

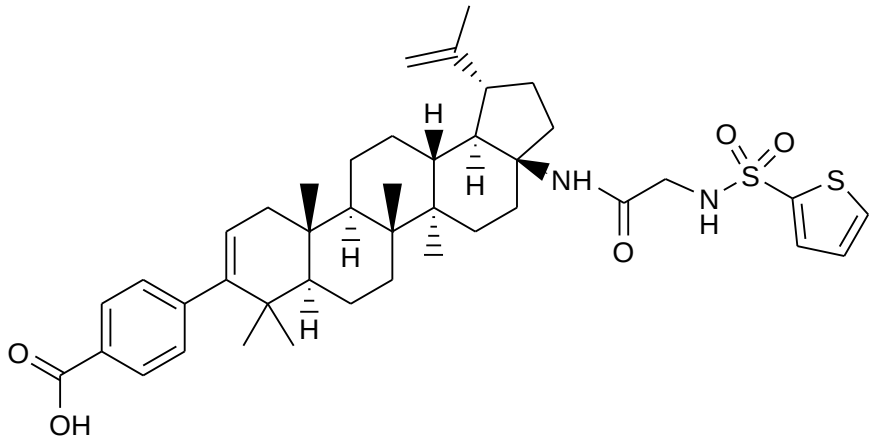


El compuesto del título se preparó en 29 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido (S)-1-(terc-butoxicarbonil)-4,4-difluoropirrolidin-2-carboxílico en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 763.5 $(M+H)^+$, 2.55 min (método 6). ^1H NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.5 Hz, 2 H), 7.20 (d, *J* = 8.5 Hz, 2 H), 6.46 (br. s., 1 H), 5.29 (dd, *J* = 1.7, 6.3 Hz,

1 H), 4.72 (s, 1 H), 4.63 (br. s., 1 H), 4.50 (d, *J* = 9.2 Hz, 1 H), 3.84 (br. s., 1 H), 3.72 (td, *J* = 6.7, 13.4 Hz, 1 H), 2.84 (br. s., 1 H), 2.55 (d, *J* = 13.4 Hz, 1 H), 2.51-2.37 (m, 2 H), 2.12 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.96 (br. s., 1 H), 1.73 (br. s., 1 H), 1.70 (s, 4 H), 1.61 (br. s., 2 H), 1.56 (br. s., 9 H), 1.53-1.45 (m, 5 H), 1.45-1.37 (m, 3 H), 1.36-1.29 (m, 2 H), 1.28-1.23 (m, 1 H), 1.17-1.09 (m, 2 H), 1.08 (s, 3 H), 1.02 (s, 6 H), 0.94 (s, 3 H), 0.93 (s, 3 H).

Ejemplo 115

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(2-(tiofen-2-sulfonamido)acetamido)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

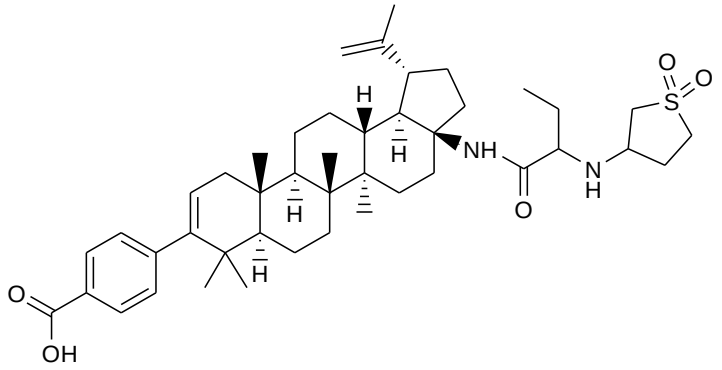


El compuesto del título se preparó en 31 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-

3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido 2-(tiofen-2-sulfonamido)acético en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 733.6 $(M+H)^+$, 2.06 min (método 6). ^{1}H NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.5 Hz, 2 H), 7.73 (dd, *J* = 1.4, 5.0 Hz, 1 H), 7.66 (dd, *J* = 1.2, 3.7 Hz, 1 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 7.16 (dd, *J* = 3.8, 5.0 Hz, 1 H), 6.88 (s, 1 H), 5.32-5.26 (m, 1 H), 4.78 (d, *J* = 1.5 Hz, 1 H), 3.58-3.45 (m, 2 H), 2.63-2.57 (m, 1 H), 2.56-2.50 (m, 1 H), 2.42 (dd, *J* = 8.2, 12.2 Hz, 1 H), 2.13 (dd, *J* = 6.3, 17.2 Hz, 1 H), 1.98-1.88 (m, 1 H), 1.87-1.76 (m, 2 H), 1.73 (br. s., 1 H), 1.72 (s, 3 H), 1.70-1.66 (m, 1 H), 1.63-1.53 (m, 3 H), 1.53-1.46 (m, 4 H), 1.45-1.37 (m, 3 H), 1.37-1.30 (m, 2 H), 1.28-1.22 (m, 1 H), 1.14 (s, 3 H), 1.10 (d, *J* = 3.1 Hz, 1 H), 1.03 (s, 3 H), 1.02 (s, 3 H), 0.94 (s, 3 H), 0.94 (br. s., 3 H).

Ejemplo 116

Preparación de ácido benzoico, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-3a-[[1-oxo-2-[(tetrahidro-1,1-dioxido-3-tienil)amino]butil]amino]-1H-ciclopenta[a]crisen-9-il].



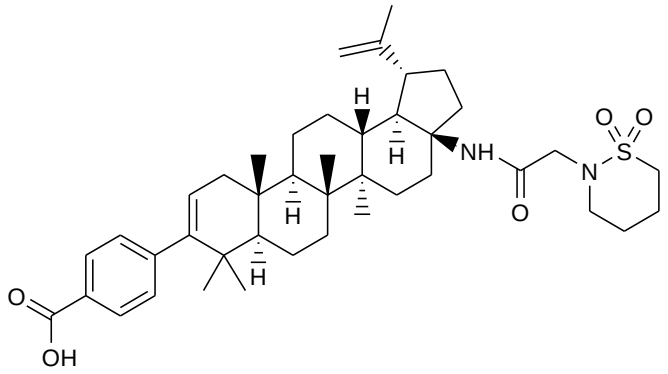
El compuesto del título se preparó en 19 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido 2-(1,1-dioxo-tetrahidro-1lambda6-tiofen-3-il-amino)-butírico en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 733.6 $(M+H)^+$, 2.00 min (método 6). ^1H NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.38 (br. s., 1 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 5.29 (d, *J* = 4.6 Hz, 1 H), 4.77 (d, *J* = 8.5 Hz, 1 H), 3.77 (br. s., 1 H), 3.51-3.36 (m, 2 H), 3.22-3.09 (m, 2 H), 2.65 (d, *J* = 15.9 Hz, 3 H), 2.37 (br. s., 2 H), 2.13 (dd, *J* = 6.4, 17.4 Hz, 1 H), 1.96-1.77 (m, 5 H), 1.73 (br. s., 1 H), 1.73 (s, 3 H), 1.72-1.67 (m, 1 H), 1.61-1.52 (m, 2 H), 1.50 (d, *J* = 2.1 Hz, 3 H), 1.48-1.30 (m, 6 H), 1.29-1.23 (m, 1 H), 1.22-1.14 (m, 2 H), 1.12 (s, 2 H), 1.09 (d, *J* = 1.8 Hz, 2 H), 1.08-1.05 (m, 1 H), 1.04 (d, *J* = 1.8 Hz, 4 H), 1.03 (d, *J* = 4.0 Hz, 4 H), 0.95 (br. s., 3 H), 0.94 (br. s., 3 H).

Ejemplo 117

Preparación de ácido benzoico, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-3a-[[(tetrahidro-1,1-dioxido-2H-1,2-tiazin-2-il)acetil]amino]-1H-ciclopenta[a]crisen-9-

il].

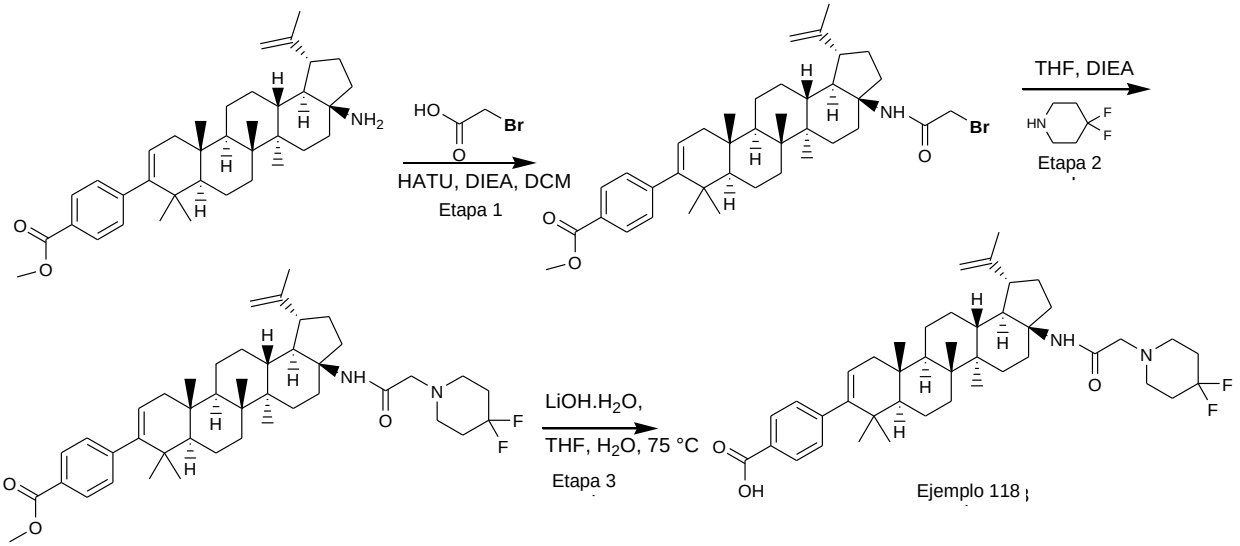


El compuesto del título se preparó en 13 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propanamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó ácido (1,1-dioxo-1,6-[1,2]tiazinan-2-il)acético en lugar de clorhidrato de ácido 3-(dimetilamino)propiónico en la Etapa 1. LCMS: m/e 705.5 $(M+H)^+$, 2.01 min (método 6). ^{1}H NMR (500MHz, *METANOL-d_4*) δ = 7.92 (d, *J* = 8.5 Hz, 2 H), 7.20 (d, *J* = 8.5 Hz, 2 H), 6.83 (s, 1 H), 5.32-5.26 (m, 1 H), 4.77 (d, *J* = 1.5 Hz, 1 H), 4.64 (s, 1 H), 3.83-3.72 (m,

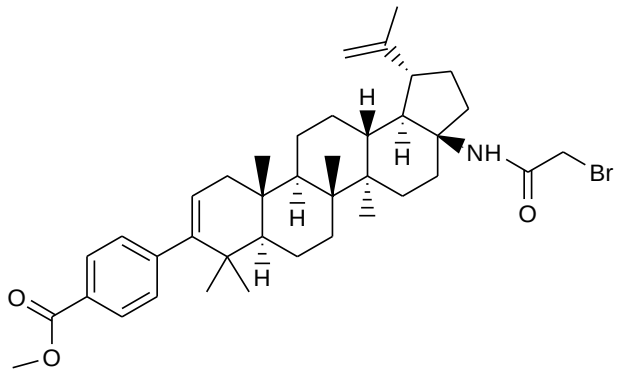
2 H), 3.63-3.46 (m, 2 H), 3.37 (s, 2 H), 3.21-3.11 (m, 2 H), 2.62-2.54 (m, 1 H), 2.53-2.50 (m, 1 H), 2.49-2.41 (m, 1 H), 2.32-2.23 (m, 2 H), 2.13 (dd, *J* = 6.6, 17.2 Hz, 1 H), 1.99-1.87 (m, 1 H), 1.78 (br. s., 1 H), 1.77-1.73 (m, 3 H), 1.72 (s, 3 H), 1.71-1.67 (m, 1 H), 1.62-1.51 (m, 3 H), 1.48 (d, *J* = 5.2 Hz, 3 H), 1.46-1.31 (m, 5 H), 1.28-1.23 (m, 1 H), 1.14 (d, *J* = 13.4 Hz, 2 H), 1.11 (s, 3 H), 1.03 (s, 3 H), 1.02 (s, 3 H), 0.94 (s, 3 H), 0.94 (s, 3 H).

Ejemplo 118

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4,4-difluoropiperidin-1-il)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



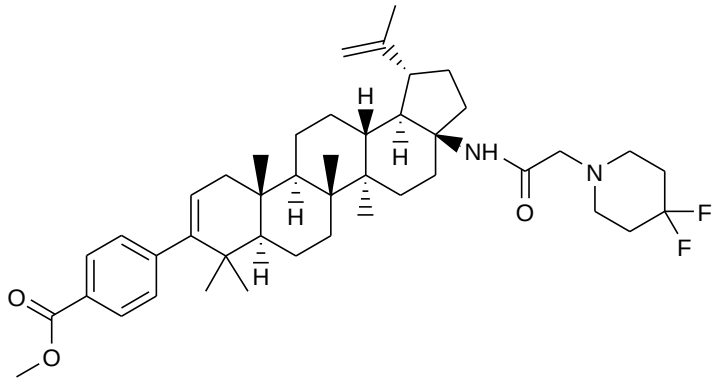
Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-bromoacetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.



A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo, HCl (403 mg, 0.694 mmol) en DCM (10 mL), se agregaron *N,N*-diisopropiletilamina (0.484 mL, 2.78 mmol), ácido bromoacético (106 mg, 0.764 mmol) y hexafluorofosfato(V) 2-(3H-[1,2,3]triazolo[4,5-β]piridin-3-il)-1,1,3,3-tetrametilisouronio (317 mg, 0.833 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 15 h. Luego, la reacción se concentró, y el residuo crudo se disolvió en THF (3.0 mL), se filtró y se purificó mediante HPLC preparativa de fase inversa usando el método 3 de HPLC para

obtener 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-bromoacetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (148.9 mg, 0.224 mmol, 32.3 % de rendimiento) como un sólido blanco. LCMS: m/e 664.6 $(M+H)^+$, 2.41 min (método 6).

Etapa 2. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4,4-difluoropiperidin-1-il)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

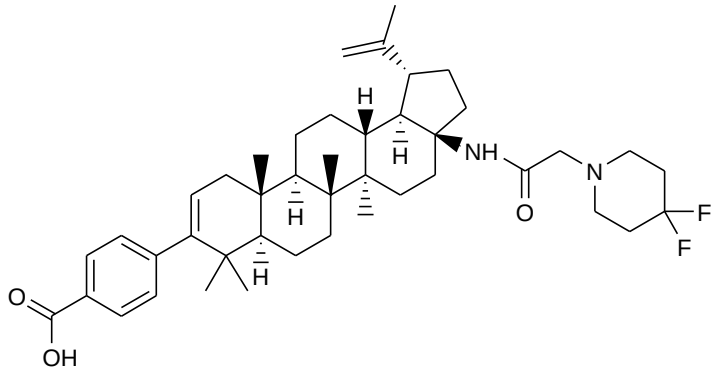


A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-bromoacetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (30 mg, 0.045 mmol) en THF (3 mL), se agregó *N,N*-diisopropiletilamina (0.039 mL, 0.226 mmol) y 4,4-

difluoropiperidina, HCl (21.34 mg, 0.135 mmol). La mezcla de reacción se agitó a 80 °C durante 18 h. Se agregaron *N,N*-diisopropiletilamina (0.078 mL, 0.452 mmol) y 4,4-difluoropiperidina, HCl (40 mg, 0.354 mmol) adicionales, y la mezcla se calentó a 150 °C en un microondas durante 7.5 h. La mezcla se concentró para obtener un aceite viscoso marrón. El residuo crudo se disolvió en THF (1.5 mL), se filtró y se purificó mediante HPLC preparativa de fase inversa usando el método 3 de HPLC para obtener 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4,4-difluoropiperidin-1-il)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo, TFA (13.1 mg, 0.016 mmol, 35.4 % de rendimiento) como un sólido blanco. LCMS: m/e 705.6 $(M+H)^+$, 2.95 min (método 6). ^{1}H NMR (500MHz, *CLOROFORMO-d*) δ = 7.94 (d, *J* = 8.5 Hz, 2 H), 7.90-7.80 (m, 1 H), 7.21 (d, *J* = 8.2 Hz, 2 H), 6.32 (s, 1 H), 5.31 (dd, *J* = 1.4, 6.0 Hz, 1 H), 4.77 (s, 1 H), 4.67 (s, 1 H), 3.93 (s, 3 H), 3.72-3.61 (m, 3 H), 3.51-3.41 (m, 5 H), 2.83 (d, *J* = 2.7 Hz, 2 H), 2.63 (d, *J* = 13.1 Hz, 1 H), 2.56 (dt, *J* = 5.3, 10.9 Hz, 1 H), 2.39 (dd, *J* = 8.2, 12.8 Hz, 1 H), 2.12 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.91-1.81 (m, 1 H), 1.79-1.73 (m, 2 H), 1.72 (s, 3 H), 1.70-1.64 (m, 1 H), 1.54-1.40 (m, 7 H), 1.39-1.26 (m, 3 H), 1.26-1.21 (m, 1 H), 1.18-

1.09 (m, 2 H), 1.04 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H), 0.95 (br. s., 3 H), 0.94 (br. s., 3 H).

Etapa 3. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4,4-difluoropiperidin-1-il)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



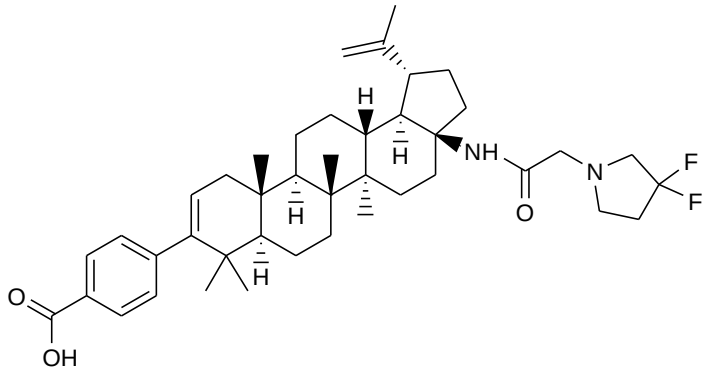
A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4,4-difluoropiperidin-1-il)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (13.1 mg, 0.019 mmol) en THF (3 mL), se agregó una solución acuosa de LiOH 0.753 molar. H_2O (0.149 mL, 0.074 mmol). La reacción se calentó a 75 °C durante 6 h. La reacción se concentró para obtener un aceite viscoso marrón, y el material crudo se purificó mediante HPLC preparativa de fase

inversa usando el método 3 de HPLC para obtener ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4,4-difluoropiperidin-1-il)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, TFA (9.4 mg, 0.012 mmol, 62.8 % de rendimiento) como un sólido blanco. LCMS: m/e 691.6 $(M+H)^+$, 2.34 min (método 6). ^{1}H NMR (500MHz, *METANOL-d$_4$*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.43 (s, 1 H), 7.20 (d, *J* = 8.5 Hz, 2 H), 5.30 (dd, *J* = 1.7, 6.3 Hz, 1 H), 4.75 (d, *J* = 1.2 Hz, 1 H), 4.66 (d, *J* = 1.5 Hz, 1 H), 3.71-3.58 (m, 2 H), 3.24 (br. s., 3 H), 2.67-2.61 (m, 1 H), 2.57 (dt, *J* = 5.3, 11.1 Hz, 1 H), 2.41 (dd, *J* = 8.2, 12.5 Hz, 1 H), 2.33-2.22 (m, 4 H), 2.13 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.95-1.83 (m, 1 H), 1.81 (d, *J* = 9.2 Hz, 2 H), 1.74 (br. s., 1 H), 1.72 (s, 3 H), 1.71-1.67 (m, 1 H), 1.59-1.43 (m, 8 H), 1.42-1.31 (m, 3 H), 1.29-1.23 (m, 1 H), 1.18-1.12 (m, 2 H), 1.09 (s, 3 H), 1.04 (s, 3 H), 1.02 (s, 3 H), 0.95 (s, 3 H), 0.94 (br. s., 3 H).

Ejemplo 119

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3,3-difluoropirrolidin-1-il)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

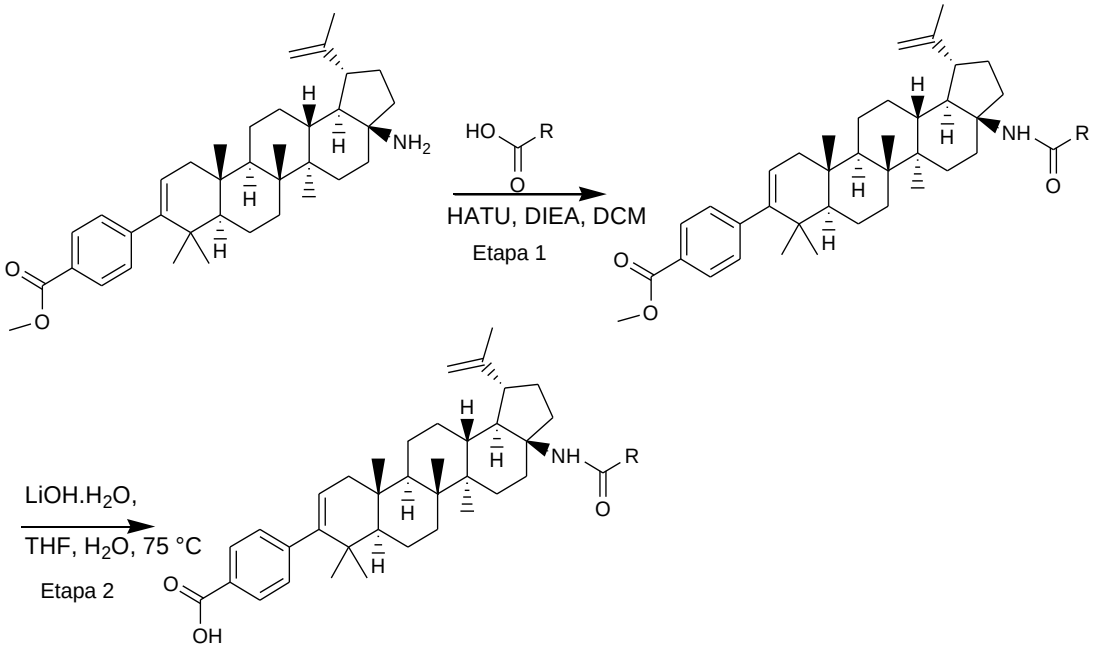
octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



El compuesto del título se preparó en 38 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4,4-difluoropiperidin-1-il)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó 3,3-difluoropirrolidina, HCl en lugar de 4,4-difluoropiperidina, HCl en la Etapa 2. LCMS: m/e 677.5 $(M+H)^+$, 2.26 min (método 6). ^{1}H NMR (500MHz, 1:1 *$CDCl_3$:MeO D*) δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.40 (s, 1 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 5.29 (dd, *J* = 1.7, 6.3 Hz, 1 H), 4.75 (d, *J* = 1.2 Hz, 1 H), 4.65 (s, 1 H), 3.59-3.44 (m, 2 H), 3.43-3.36

(m, 1 H), 3.31-3.20 (m, 2 H), 2.63-2.55 (m, 1 H), 2.55-2.47 (m, 3 H), 2.47-2.39 (m, 1 H), 2.13 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.94-1.83 (m, 1 H), 1.81-1.76 (m, 2 H), 1.76-1.73 (m, 1 H), 1.72 (s, 3 H), 1.70-1.65 (m, 1 H), 1.57-1.46 (m, 6 H), 1.46-1.40 (m, 2 H), 1.39-1.31 (m, 2 H), 1.26 (dd, *J* = 2.7, 10.7 Hz, 1 H), 1.19-1.10 (m, 2 H), 1.09 (s, 3 H), 1.03 (s, 3 H), 1.02 (s, 3 H), 0.95 (s, 3 H), 0.94 (s, 3 H).

Procedimiento general para la síntesis paralela de C-17 amidas:



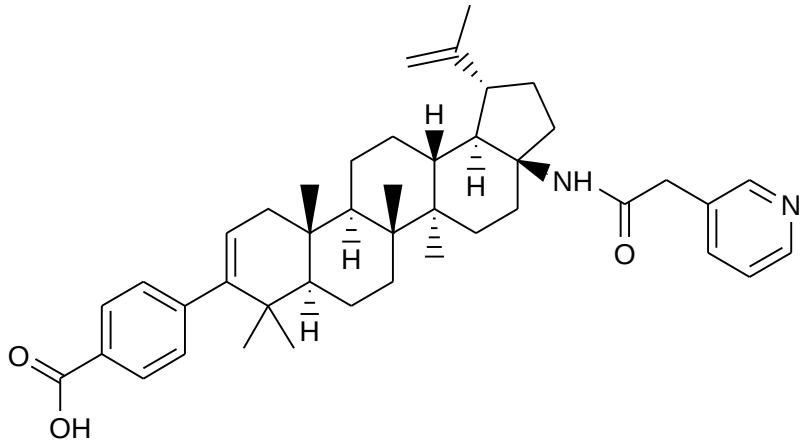
Se preparó una solución de reserva de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo, HCl (0.990 g, 1.7 mmol) y DIPEA (1.10 g, 8.52 mmol) en DCE

(13 mL). Se preparó una solución de reserva de HATU (1.94 g, 5.11 mmol) en DCE (13 mL). A cada uno de los ácidos carboxílicos (0.393 mmol) cargados en viales Wheaton de 16 x 100 mm, se agregó 1 mL de la solución HATU de reserva. Los viales se taparon y se agitaron a temperatura ambiente durante 10 min antes de agregar 1 mL de la solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo, HCl /DIPEA de reserva a cada vial. Los viales se taparon y se agitaron a temperatura ambiente durante 18 h. Las muestras se concentraron. Se preparó una solución de reserva de hidróxido de litio monohidrato (0.286 g, 6.81 mmol) en agua (6.50 mL). A cada uno de los viales de reacción se agregaron 2.5 mL de THF y 0.5 mL de la solución de hidróxido de litio de reserva. Los viales se agitaron, y las reacciones se agitaron a 75 °C durante 18 h. Se agregaron 0.5 mL adicionales de la solución de hidróxido de litio de reserva y se agitaron a 75 °C durante 48 h más. Las muestras se concentraron, se volvieron a disolver en una cantidad pequeña de una mezcla de THF y metanol, se filtraron y se purificaron mediante HPLC preparativa de fase inversa.

Ejemplo 120

Preparación de ácido benzoico, 4-

[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-3a-[(3-piridinilacetil)amino]-1H-ciclopenta[a]crisen-9-il].

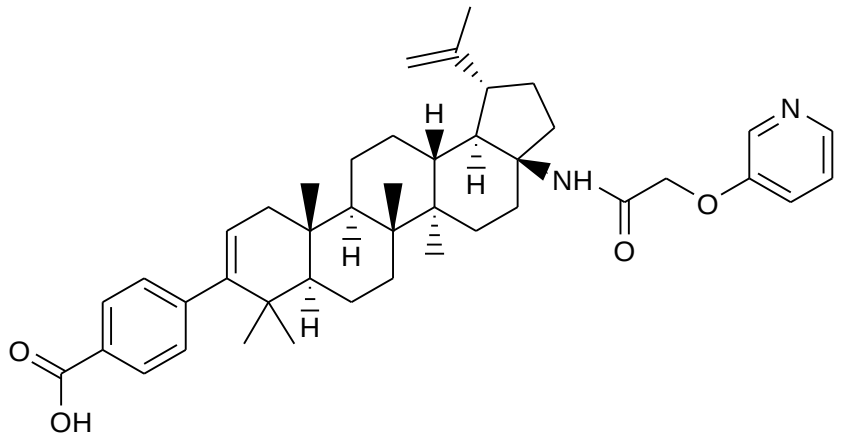


El compuesto del título se preparó de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo siguiendo el procedimiento general descrito para la síntesis paralela de C-17 amidas antes mencionado, usando clorhidrato de ácido piridilacético como el ácido carboxílico de reacción. LCMS: m/e 649.6 $(M+H)^+$, 4.09 min (método 3).

Ejemplo 121

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(2-(piridin-3-

iloxi)acetamido)-
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-
octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

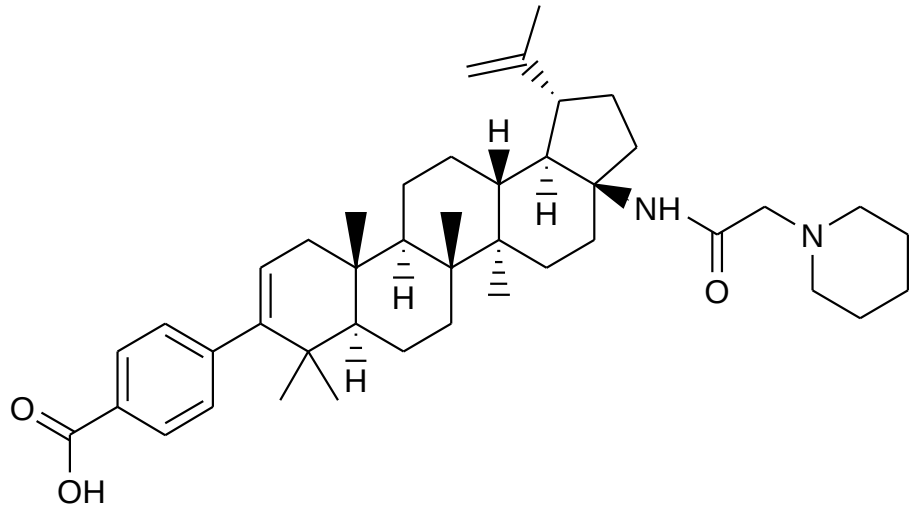


El compuesto del título se preparó de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo siguiendo el procedimiento general descrito para la síntesis paralela de C-17 amidas antes mencionado, usando ácido 3-piridiloxiacético como el ácido carboxílico de reacción. LCMS: m/e 665.6 $(M+H)^+$, 4.37 min (método 3).

Ejemplo 122

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(piperidin-1-il)acetamido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

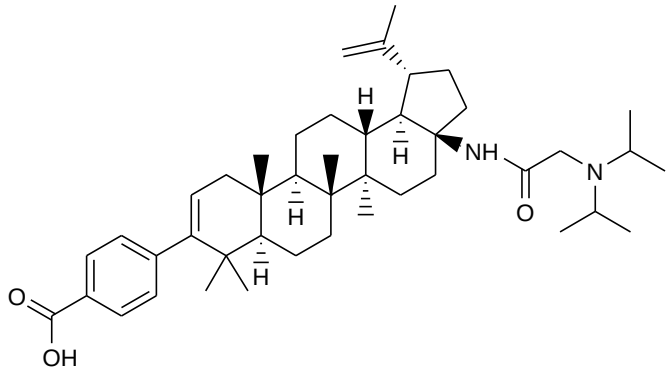


El compuesto del título se preparó de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo siguiendo el procedimiento general descrito para la síntesis paralela de C-17 amidas antes mencionado, usando clorhidrato de ácido piperidin-1-ilacético como el ácido carboxílico de reacción. LCMS: m/e 655.7 $(M+H)^+$, 4.68 min (método 3).

Ejemplo 123

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(diisopropilamino)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

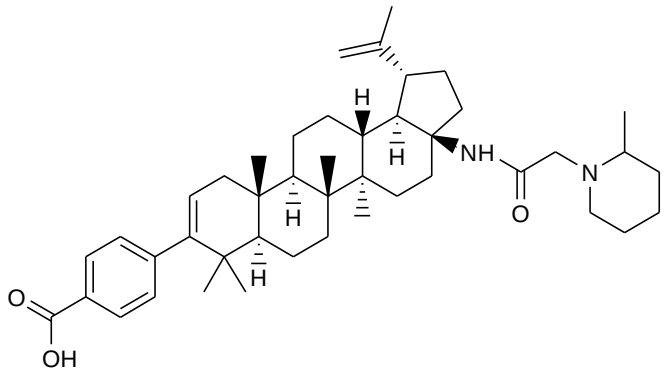


El compuesto del título se preparó de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo siguiendo el procedimiento general descrito para la síntesis paralela de C-17 amidas antes mencionado, usando ácido diisopropilamino-acético como el ácido carboxílico de reacción. LCMS: m/e 671.7 $(M+H)^+$, 4.99 min (método 3). ^{1}H NMR (599MHz,<*DMSO_CDCl$_3$*>) δ = 8.45-8.37 (m, 1 H), 7.89 (d, *J* = 8.2 Hz, 2 H), 7.69-7.65 (m, 1 H), 7.24-7.20 (m, 2 H), 5.31-5.24 (m, 1 H), 4.79-4.73 (m, 1 H), 4.67-4.62 (m, 1 H), 3.95 (br. s., 2 H), 3.66 (d, *J* = 5.9 Hz, 3 H), 2.94 (s, 1 H), 2.78 (s, 1 H), 2.74 (br. s., 1 H), 2.63 (d, *J* = 13.5 Hz, 1 H), 2.30 (t, *J* = 9.1 Hz, 1 H), 2.13 (dd, *J* = 6.2, 16.7 Hz, 1 H), 2.07-1.98 (m, 1 H), 1.75 (br. s., 1 H), 1.72 (s, 4 H), 1.69-1.61 (m, 1 H), 1.52-1.41 (m, 8 H), 1.36-1.33 (m, 3 H), 1.33-1.31 (m, 2 H), 1.30-1.28 (m, 3 H), 1.28-1.25 (m, 3 H),

1.09 (s, 6 H), 1.01 (s, 6 H), 0.93 (br. s., 6 H).

Ejemplo 124

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(2-metilpiperidin-1-il)acetamido)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

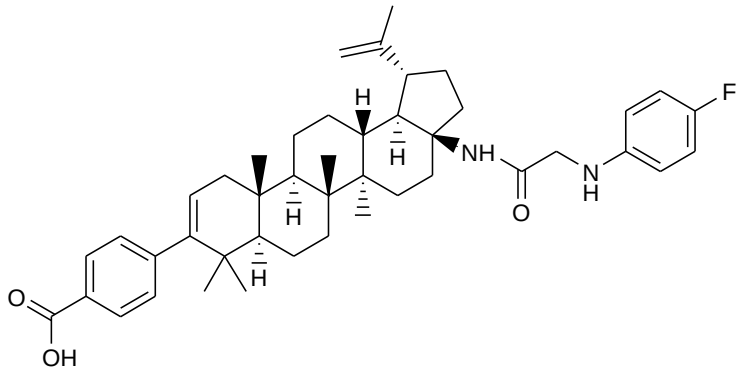


El compuesto del título se preparó de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo siguiendo el procedimiento general descrito para la síntesis de C-17 amidas antes mencionado, usando ácido (2-metilpiperidin-1-il)acético como el ácido carboxílico de reacción. LCMS: m/e 669.7 $(M+H)^+$, 4.73 min (método 3).

Ejemplo 125

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4-

fluorofenilamino)acetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

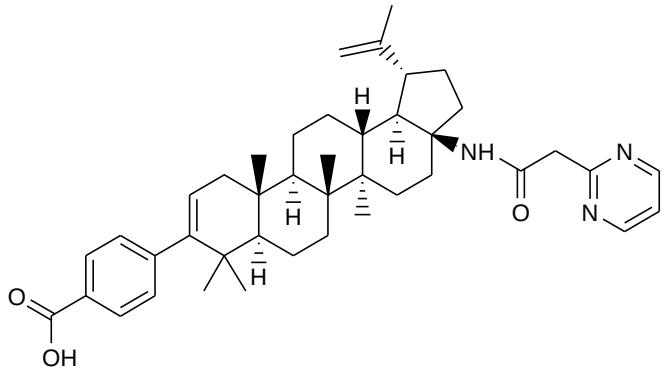


El compuesto del título se preparó de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo siguiendo el procedimiento general descrito para la síntesis de C-17 amidas antes mencionado, usando ácido (4-fluorofenilamino)acético como el ácido carboxílico de reacción. LCMS: m/e 681.7 $(M+H)^+$, 6.62 min (método 3).

Ejemplo 126

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(2-(pirimidin-2-il)acetamido)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

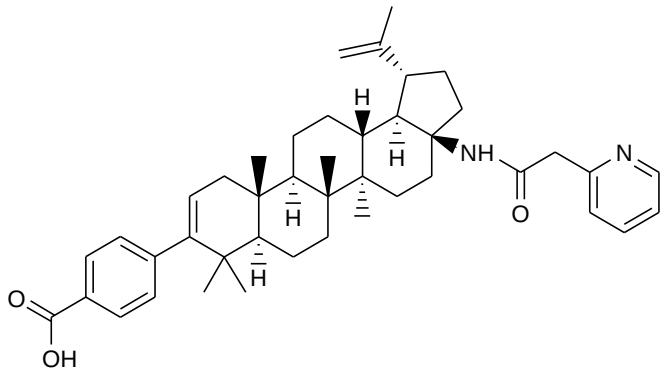
octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



El compuesto del título se preparó de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo siguiendo el procedimiento general descrito para la síntesis de C-17 amidas antes mencionado, usando ácido 2-pirimidinacético como el ácido carboxílico de reacción. LCMS: m/e 650.6 $(M+H)^+$, 5.57 min (método 3). ^1H NMR (599MHz,<*DMSO_CDCl3*>) δ = 8.78 (d, *J* = 4.7 Hz, 2 H), 7.88 (d, *J* = 8.2 Hz, 2 H), 7.29 (s, 1 H), 7.22 (d, *J* = 7.6 Hz, 2 H), 5.28 (d, *J* = 5.3 Hz, 1 H), 4.75 (s, 1 H), 4.62 (br. s., 1 H), 3.93 (s, 1 H), 3.82 (d, *J* = 14.6 Hz, 1 H), 2.77-2.72 (m, 1 H), 2.63 (d, *J* = 12.9 Hz, 1 H), 2.40-2.32 (m, 1 H), 2.16-2.04 (m, 1 H), 2.00-1.81 (m, 2 H), 1.73 (br. s., 2 H), 1.71 (s, 3 H), 1.67-1.52 (m, 4 H), 1.50-1.39 (m, 7 H), 1.36-1.20 (m, 7 H), 0.99 (br. s., 6 H), 0.98 (br. s., 3 H), 0.93 (br. s., 3 H), 0.93 (br. s., 3 H).

Ejemplo 127

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(2-(piridin-2-il)acetamido)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

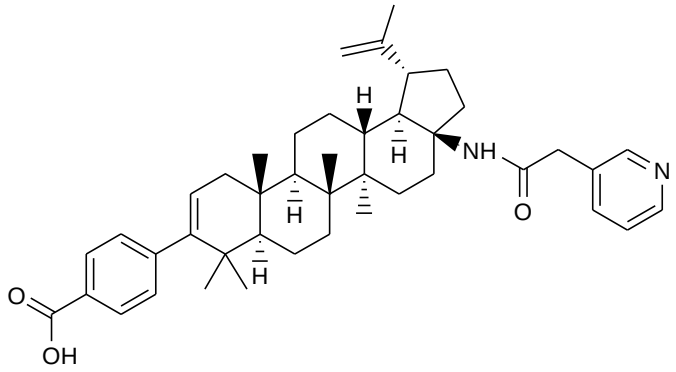


El compuesto del título se preparó de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo siguiendo el procedimiento general descrito para la síntesis de C-17 amidas antes mencionado, usando clorhidrato de ácido 2-piridilacético como el ácido carboxílico de reacción. LCMS: m/e 649.6 $(M+H)^+$, 4.23 min (método 3).

Ejemplo 128

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(2-(piridin-3-il)acetamido)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

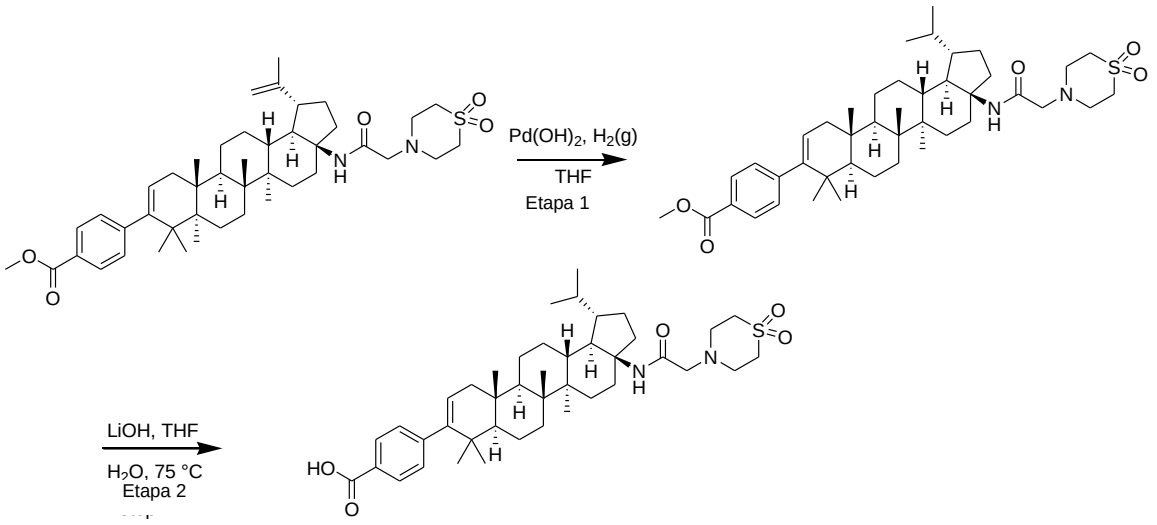


El compuesto del título se preparó de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo siguiendo el procedimiento general descrito para la síntesis de C-17 amidas antes mencionado, usando clorhidrato de ácido 3-piridilacético como el ácido carboxílico de reacción. LCMS: m/e 649.6 $(M+H)^+$, 4.07 min (método 3). ^{1}H NMR (599MHz,<*DMSO_CDCl$_3$*>) δ = 8.49 (d, *J* = 5.3 Hz, 2 H), 7.88 (s, 2 H), 7.33 (d, *J* = 5.3 Hz, 2 H), 7.22 (d, *J* = 8.2 Hz, 2 H), 7.17 (s, 1 H), 5.28 (d, *J* = 5.3 Hz, 1 H), 4.86-4.81 (m, 1 H), 4.76 (s, 1 H), 4.63 (br. s., 1 H), 3.66 (d, *J* = 12.9 Hz, 1 H), 3.49 (d, *J* = 12.9 Hz, 1 H), 2.85-2.79 (m, 1 H), 2.60-2.56 (m, 1 H), 2.35-2.28 (m, 1 H), 2.12 (dd, *J* = 6.4, 17.0 Hz, 1 H), 2.06 (t, *J* = 11.1 Hz, 1 H), 1.87-1.79 (m, 1 H), 1.73

(br. s., 2 H), 1.71 (s, 3 H), 1.61-1.50 (m, 2 H), 1.50-1.35 (m, 6 H), 1.37-1.27 (m, 3 H), 1.24 (d, *J* = 9.4 Hz, 3 H), 1.13-1.05 (m, *J* = 12.9 Hz, 1 H), 1.03-1.00 (m, 6 H), 0.97 (s, 3 H), 0.94 (s, 3 H), 0.93 (s, 3 H).

Ejemplo 129

Preparación de ácido 4-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((1,1-dioxido-4-tiomorfolinil)acetil)amino)-1-isopropil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



Etapa 1. Preparación de 4-[(1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxo-1,4-tiazinan-4-il)acetil]amino]-1-isopropil-5a,5b,8,8,11a-pentametil-1,2,3,4,5,6,7,7a,11,11b,12,13,13a,13b-

tetradecahidrociclopenta[a]crisen-9-il]benzoato de metilo.

Una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (152 mg, 0.211 mmol) en THF (10 mL) se purgó con N_2(g), y se agregó hidróxido de paladio (44.5 mg, 0.063 mmol). La mezcla de reacción se purgó con H_2 (g), luego se agitó en una atmósfera de H_2 (g). Después de 68 h, la reacción se purgó con N_2 (g), se retiró el catalizador mediante filtración a través de Celite y se lavó con DCM. El filtrado líquido resultante se concentró para obtener un aceite viscoso que se disolvió en THF (2.0 mL), se filtró y se inyectó en HPLC de fase inversa para la purificación usando el método 5 de HPLC para obtener el compuesto del título (28.8 mg, 0.040 mmol, 18.89 % de rendimiento; 62.8 % de rendimiento en función del material de inicio recuperado). LCMS: m/z 721.6 ($M+H^+$), tiempo de retención 2.655 min (método 6). ^{1}H NMR (500MHz, *CLOROFORMO-d*) δ = 8.47 (br. s., 2 H), 7.95 (d, *J* = 8.2 Hz, 2 H), 7.22 (d, *J* = 8.5 Hz, 2 H), 6.98 (s, 1 H), 5.32 (dd, *J* = 1.5, 6.1 Hz, 1 H), 3.94 (s, 3 H), 3.69-3.61 (m, 1 H), 3.58-3.52 (m, 4 H), 3.31-3.27 (m, 3

H), 2.65 (d, *J* = 11.6 Hz, 1 H), 2.37 (dd, *J* = 7.5, 12.7 Hz, 1 H), 2.20-2.11 (m, 1 H), 1.98-1.86 (m, 1 H), 1.72 (d, *J* = 15.9 Hz, 3 H), 1.62-1.52 (m, 3 H), 1.52-1.36 (m, 9 H), 1.34-1.23 (m, 3 H), 1.21-1.14 (m, 2 H), 1.03 (s, 3 H), 1.02 (br. s., 3 H), 1.01 (br. s., 3 H), 0.95 (s, 6 H), 0.91 (d, *J* = 7.0 Hz, 3 H), 0.81 (d, *J* = 6.7 Hz, 3 H).

Etapa 2. Preparación de ácido 4-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((1,1-dioxido-4-tiomorfolinil)acetil)amino)-1-isopropil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

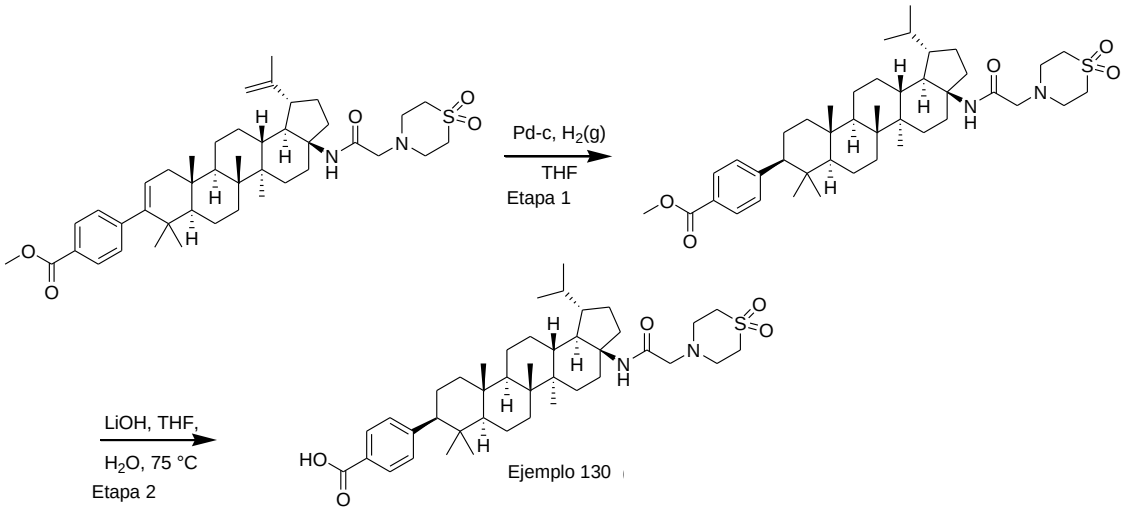
A una solución de 4-[(1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxo-1,4-tiazinan-4-il)acetil]amino]-1-isopropil-5a,5b,8,8,11a-pentametil-1,2,3,4,5,6,7,7a,11,11b,12,13,13a,13b-tetradecahidrociclopenta[a]crisen-9-il]benzoato de metilo, TFA (33 mg, 0.040 mmol) en THF (Volumen: 3 mL), se agregó una solución de hidróxido de litio monohidrato 0.753 molar (0.316 mL, 0.158 mmol) en H_2O. La mezcla de reacción se calentó a 75 °C. Después de 5.5 h, la reacción se concentró hasta secarse. El residuo crudo se disolvió en THF (1.2 mL), MeOH (0.3 mL) y HCl 1N (0.2

mL). La solución se filtró y se inyectó en HPLC de fase inversa para la purificación usando el método 3 de HPLC para obtener ácido 4-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((1,1-dioxido-4-tiomorfolinil)acetil)amino)-1-isopropil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, TFA (17,9 mg, 0.021 mmol, 54.1 % de rendimiento) como un sólido blanco. LCMS: m/z 707.6 ($M+H^+$), tiempo de retención 2.030 min (método 6). ^{1}H NMR (500MHz, *METANOL-d_4*) δ = 7.93 (d, *J* = 8.5 Hz, 2 H), 7.21 (d, *J* = 8.5 Hz, 2 H), 7.13 (s, 1 H), 5.31 (dd, *J* = 1.5, 6.1 Hz, 1 H), 3.26-3.22 (m, 5 H), 3.21-3.15 (m, 4 H), 2.66-2.59 (m, 1 H), 2.37 (dd, *J* = 6.7, 12.5 Hz, 1 H), 2.17 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.99-1.91 (m, 1 H), 1.80-1.70 (m, 4 H), 1.67-1.57 (m, 2 H), 1.57-1.45 (m, 9 H), 1.44-1.39 (m, 1 H), 1.39-1.26 (m, 3 H), 1.18-1.11 (m, 2 H), 1.09 (s, 3 H), 1.04 (s, 6 H), 0.96 (s, 3 H), 0.95 (s, 3 H), 0.91 (d, *J* = 7.0 Hz, 3 H), 0.82 (d, *J* = 6.7 Hz, 3 H).

Ejemplo 130

Preparación de ácido 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-(((1,1-dioxido-4-tiomorfolinil)acetil)amino)-1-isopropil-5a,5b,8,8,11a-pentametilicosahidro-1H-ciclopenta[a]crisen-9-

il)benzoico.



Etapa 1. Preparación de 4-[(1S,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxo-1,4-tiazinan-4-il)acetil]amino]-1-isopropil-5a,5b,8,8,11a-pentametil-1,2,3,4,5,6,7,7a,9,10,11,11b,12,13,13a,13b-hexadecahidrociclopenta[a]crisen-9-il]benzoato de metilo.

A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (51 mg, 0.071 mmol) en THF (3 mL) se agregó paladio en carbón activado (10 % de contenido de Pd) (18 mg, 0.017 mmol). La mezcla de reacción se purgó lentamente por burbujeo de H_2 (g) en la mezcla durante 30 min, y luego la mezcla se agitó a una atmósfera de H_2 (g). Después de 24 h, la mezcla de reacción se purgó con N_2 (g), y se agregó más

catalizador (36 mg, 0.034 mmol). La mezcla de reacción se agitó en H_2 (g) durante 24 h más. Luego, la mezcla se purgó con N_2 (g), y el catalizador se filtró y se lavó con THF. El filtrado líquido se concentró. El residuo crudo se purificó mediante HPLC preparativa usando el método 5 de HPLC para obtener 4-[(1S,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxo-1,4-tiazinan-4-il)acetil]amino]-1-isopropil-5a,5b,8,8,11a-pentametil-1,2,3,4,5,6,7,7a,9,10,11,11b,12,13,13a,13b-hexadecahidrociclopenta[a]crisen-9-il]benzoato de metilo, TFA (24.4 mg, 0.029 mmol, 41.1 % de rendimiento) como un sólido blanco. LCMS: m/z 723.6 ($M+H^+$), tiempo de retención 2.655 min (método 6). ^{1}H NMR (500MHz, *CLOROFORMO-d*) δ = 7.94 (d, *J* = 8.2 Hz, 2 H), 7.25 (d, *J* = 8.2 Hz, 2 H), 7.13 (br. s., 2 H), 7.05 (s, 1 H), 3.56-3.49 (m, 1 H), 3.48-3.39 (m, 5 H), 3.27-3.19 (m, 4 H), 2.66 (d, *J* = 12.5 Hz, 1 H), 2.42 (dd, *J* = 3.2, 13.3 Hz, 1 H), 2.40-2.34 (m, 1 H), 2.16-2.07 (m, 1 H), 1.96-1.90 (m, 1 H), 1.74-1.60 (m, 6 H), 1.59-1.51 (m, 2 H), 1.51-1.38 (m, 9 H), 1.37-1.31 (m, 2 H), 1.30-1.26 (m, 1 H), 1.21-1.10 (m, 2 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.98 (s, 3 H), 0.95 (s, 1 H), 0.91 (d, *J* = 7.0 Hz, 3 H), 0.81 (d, *J* = 6.7 Hz, 3 H), 0.78 (s, 3 H), 0.72 (s, 3 H). ^{13}C NMR (*CLOROFORMO-d*) δ ppm 167.7, 167.2, 149.5, 129.8, 129.4, 128.4, 128.3, 127.5, 65.9, 58.8, 57.3, 55.7, 51.8, 51.3, 49.9, 49.9, 48.2, 44.7, 41.9, 40.4, 40.3,

37.9, 37.4, 37.3, 34.5, 34.0, 29.4, 29.2, 28.1, 26.8, 26.2, 24.6, 22.6, 21.8, 20.4, 18.5, 17.4, 16.1, 15.6, 14.5, 14.1.

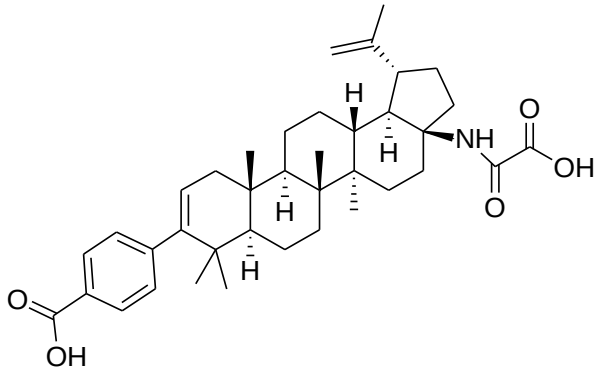
Etapa 2. Preparación de ácido 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-(((1,1-dioxido-4-tiomorfolinil)acetil)amino)-1-isopropil-5a,5b,8,8,11a-pentametilicosahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

A una solución de 4-[(1S,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxo-1,4-tiazinan-4-il)acetil]amino]-1-isopropil-5a,5b,8,8,11a-pentametil-1,2,3,4,5,6,7,7a,9,10,11,11b,12,13,13a,13b-hexadecahidrociclopenta[a]crisen-9-il]benzoato, TFA (24.3 mg, 0.029 mmol) en THF (3 mL), se agregó una solución acuosa 0.753 molar de hidróxido de litio monohidrato (0.232 mL, 0.116 mmol). La mezcla de reacción se calentó a 75 °C. Después de 5.5 h, la mezcla de reacción se concentró hasta secarse. El residuo crudo se disolvió en THF (1.2 mL), MeOH (0.3 mL) y HCl 1N (0.2 mL). La solución resultante se filtró y se purificó usando el método 3 de HPLC preparativa para obtener ácido 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-(((1,1-dioxido-4-tiomorfolinil)acetil)amino)-1-isopropil-5a,5b,8,8,11a-pentametilicosahidro-1H-ciclopenta[a]crisen-9-il)benzoico, TFA (16.5 mg, 0.020 mmol, 69.1 % de rendimiento) como un sólido blanco. LCMS: m/z 709.6 ($M+H^+$),

tiempo de retención 2.072 min (método 6). ^{1}H NMR (500MHz, *METANOL-d_4*) δ = 7.91 (d, *J* = 8.2 Hz, 2 H), 7.26 (d, *J* = 8.2 Hz, 2 H), 7.11 (s, 1 H), 3.25-3.20 (m, 6 H), 3.17 (d, *J* = 5.5 Hz, 4 H), 2.65-2.59 (m, 1 H), 2.44 (dd, *J* = 2.7, 13.1 Hz, 1 H), 2.37 (dd, *J* = 7.0, 12.5 Hz, 1 H), 2.19-2.04 (m, 1 H), 1.98-1.89 (m, 1 H), 1.85 (d, *J* = 13.1 Hz, 1 H), 1.74 (dd, *J* = 3.7, 7.9 Hz, 2 H), 1.71-1.60 (m, 3 H), 1.56-1.45 (m, 8 H), 1.44-1.37 (m, 4 H), 1.36-1.25 (m, 2 H), 1.16-1.09 (m, 2 H), 1.05 (s, 3 H), 1.04 (s, 3 H), 1.00 (s, 3 H), 0.95 (d, *J* = 2.1 Hz, 1 H), 0.91 (d, *J* = 6.7 Hz, 3 H), 0.81 (d, *J* = 6.7 Hz, 3 H), 0.78 (s, 3 H), 0.72 (s, 3 H).

Ejemplo 130-1

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(carboxiformamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



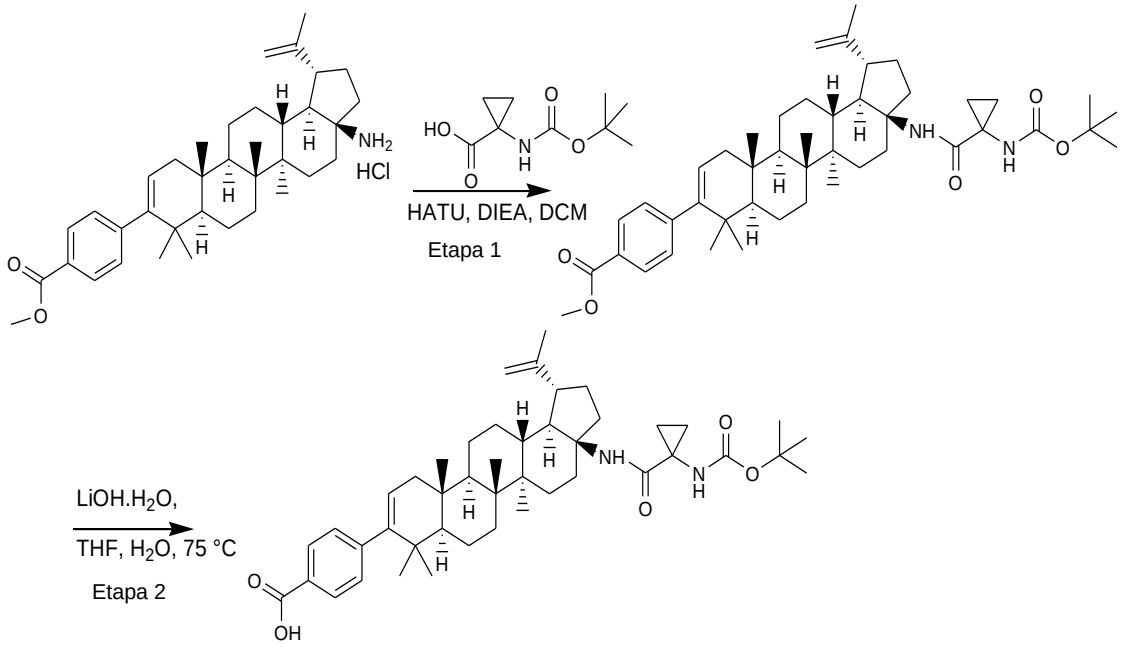
El compuesto del título se obtuvo en 25 % de

rendimiento como un subproducto durante la hidrólisis de éster en la Etapa 2 de la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimetilamino)-2-oxoacetamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico. LCMS: m/e 600.5 $(M-H)^-$, 1.33 min (método 5). ^{1}H NMR (500MHz, *CLOROFORMO-d*) δ = 8.02 (d, *J* = 8.2 Hz, 2 H), 7.26 (d, *J* = 8.2 Hz, 3 H), 5.33 (d, *J* = 4.9 Hz, 1 H), 4.80 (s, 1 H), 4.70 (s, 1 H), 3.84-3.80 (m, 1 H), 2.59 (d, *J* = 10.1 Hz, 1 H), 2.54 (d, *J* = 5.2 Hz, 1 H), 2.46 (dd, *J* = 8.4, 11.7 Hz, 1 H), 2.18-2.11 (m, 1 H), 1.91 (ddd, *J* = 3.1, 3.3, 6.8 Hz, 2 H), 1.83-1.75 (m, 2 H), 1.74 (s, 3 H), 1.62-1.34 (m, 12 H), 1.28 (s, 1 H), 1.27-1.12 (m, 3 H), 1.07 (s, 3 H), 1.05 (s, 3 H), 1.02 (s, 3 H), 0.97 (br. s., 3 H), 0.96 (br. s., 3 H).

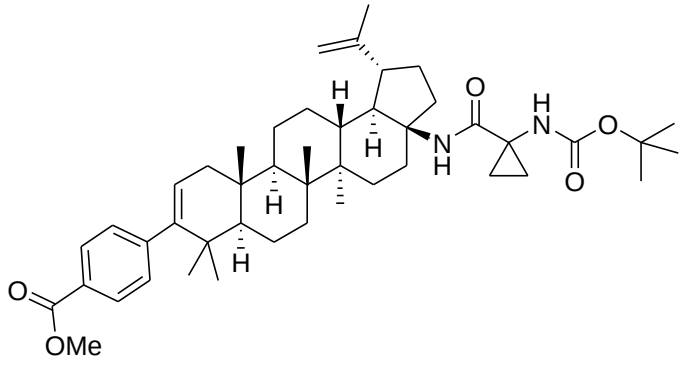
Ejemplo 130-2

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(1-(terc-butoxicarbonilamino)ciclopropancarboxamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-

il)benzoico.



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(1-(terc-butoxicarbonilamino)ciclopropancarboxamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

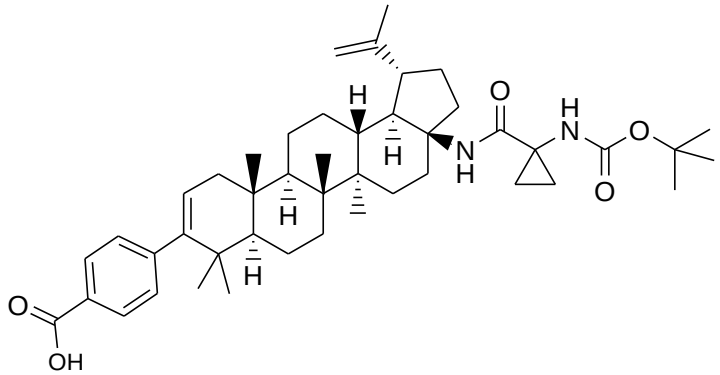


A una mezcla de la solución de 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (0.302 g, 0.555 mmol) y *N,N*-diisopropiletilamina (0.580 mL, 3.33 mmol) en DCM (5 mL), se agregaron hexafluorofosfato(V) de 2-(3H-[1,2,3]triazolo[4,5-b]piridin-3-il)-1,1,3,3-tetrametilisouronio (0.465 g, 1.222 mmol) y ácido 1-(terc-butoxicarbonilamino)ciclopropancarboxílico (0.223 g, 1.111 mmol). La mezcla de reacción se agitó a temperatura ambiente. Después de 18 h, la reacción se diluyó con DCM (20 mL), y se agregó gel de sílice (4 g). La mezcla se concentró hasta secarse y se secó al vacío para obtener un polvo de flujo libre. El material se cargó en una columna en gel de sílice (cartucho de 25 g) con un gradiente de 100 % en hexanos a 25 % de EtOAc en hexanos en 240 mL, se mantuvo en 25 % de EtOAc en hexanos para obtener 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(1-(terc-butoxicarbonilamino)ciclopropancarboxamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (234 mg, 0.309 mmol, 55.6 % de rendimiento) como un sólido blanco. LCMS: m/e 727.4 $(M+H)^+$, 5.17 min (método 2). ^{1}H NMR (500MHz, *CLOROFORMO-d*) δ 7.97-7.89 (m, 2H), 7.20 (d, *J*= 8.5

Hz, 2H), 6.47 (br. s., 1H), 5.30 (dd, *J*= 6.3, 1.7 Hz, 1H), 5.16-5.06 (m, 1H), 4.72 (d, *J*= 1.8 Hz, 1H), 4.62 (s, 1H), 4.19-4.09 (m, 1H), 3.92 (s, 3H), 2.66-2.60 (m, 1H), 2.49 (d, *J*= 4.6 Hz, 2H), 2.11 (dd, *J*= 17.1, 6.4 Hz, 1H), 2.07-1.96 (m, 1H), 1.53 (s, 9H), 1.46 (s, 3H), 1.43 (d, *J*= 2.7 Hz, 1H), 1.37 (d, *J*= 3.4 Hz, 1H), 1.34 (d, *J*= 3.7 Hz, 1H), 1.26 (dd, *J*= 7.0, 3.1 Hz, 1H), 1.19-1.16 (m, 1H), 1.12 (br. s., 3H), 1.10-1.07 (m, 1H), 1.01 (s, 3H), 1.01-0.99 (m, 3H), 0.94 (s, 3H), 0.94 (s, 3H).

Etapa 2. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(1-(terc-butoxicarbonilamino)ciclopropancarboxamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



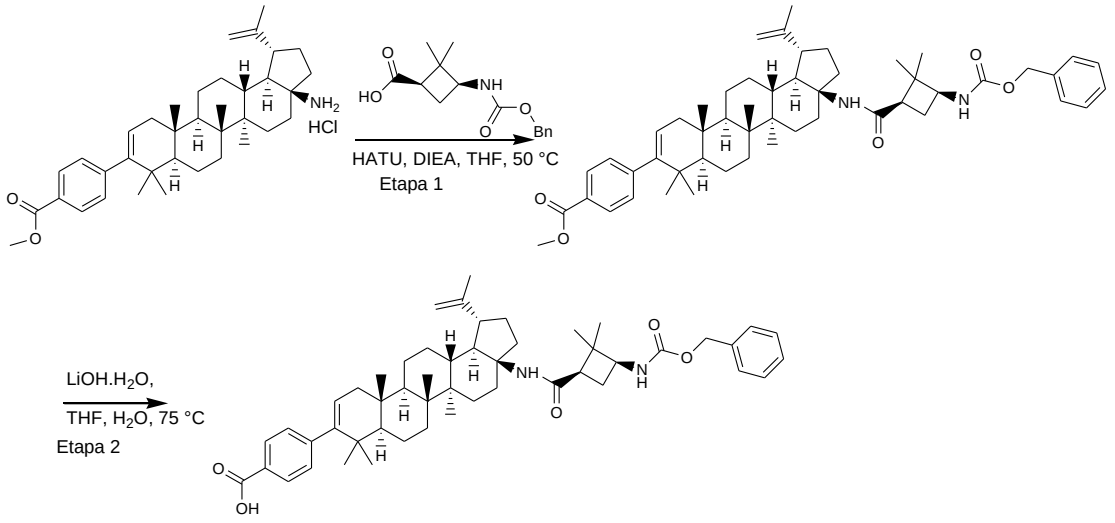
A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(1-(terc-butoxicarbonilamino)ciclopropancarboxamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (101 mg, 0.139 mmol) en THF (5 mL), se agregó una solución de hidróxido de litio monohidrato (17.49 mg, 0.417 mmol) en agua (1.000 mL). La mezcla resultante se agitó a 75 °C. Después de 18 h, la mezcla de reacción se concentró. El residuo se volvió a disolver en THF/MeOH, se agregó gel de sílice (2 g), y la mezcla se concentró hasta secarse. El material absorbido se cargó en una columna de gel de sílice (cartucho de 25 g) y se eluyó con 0 % de B (solvente B = (90:10 DCM:MeOH, A = 100 % DCM) a 50 % de B a 180 mL, luego se mantuvo a 50 % de B a 900 mL. Por ello, se obtuvo ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(1-(terc-butoxicarbonilamino)ciclopropancarboxamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico (39 mg, 0.054 mmol, 38.6 % de rendimiento) como un sólido blanco. LCMS: m/e 713.6 $(M+H)^+$, 2.32 min (método 1). ^{1}H NMR (500MHz, *1:1 $CDCl_3$:METANOL-d_4*) δ 7.92 (d, *J*= 8.2 Hz, 2H), 7.20 (d, *J*= 8.2 Hz, 3H), 6.62 (br. s., 1H), 5.33-5.24 (m, 1H), 4.72 (s, 1H), 4.63 (s, 1H), 2.61-2.36 (m, 3H), 2.13 (dd, *J*= 17.2, 6.3 Hz, 1H), 2.04-1.95 (m, 1H), 1.73 (br. s., 1H), 1.71 (s, 3H), 1.41 (d, *J*= 6.1 Hz, 2H), 1.26 (br. s., 9H), 1.15 (s, 3H), 1.10 (br. s., 1H), 1.03 (s, 3H), 1.02 (s, 3H), 0.95 (s, 3H),

0.94 (s, 3H), 0.88 (d, *J*= 6.7 Hz, 2H), 0.86-0.83 (m, 2H).

Ejemplo 130-3

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(1-(terc-butoxicarbonilamino)ciclopropancarboxamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1R,3S)-3-(((benciloxi)carbonil)amino)-2,2-dimetilciclobutancarboxamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

A una solución de 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo, HCl (265 mg, 0.457 mmol) en tetrahidrofurano (5 mL), se agregó *N,N*-di-iso-propiletilamina (0.278 mL, 1.598 mmol), ácido (1R,3S)-3-(((benciloxi)carbonil)amino)-2,2-dimetilciclobutancarboxílico (152 mg, 0.548 mmol) (para la preparación, véase: J. Aguilera et al. *Tetrahedron Asymmetry* **2008**, *19*, 302) y hexafluorofosfato de O-(7-azabenzotriazol-1-il)-*N,N,N',N'*-tetrametiluronio (226 mg, 0.594 mmol). La mezcla de reacción se calentó a 50 °C. Después de 6 h, la mezcla se diluyó con EtOAc (30 mL) y se lavó con HCl 1N (5 mL). La capa acuosa se extrajo con EtOAc (25 mL). La capa orgánica combinada se lavó con 5 % de $NaHCO_3$, salmuera, se secó en $MgSO_4$, se filtró y se concentró para obtener un aceite viscoso marrón claro. El material se disolvió en DCM, se cargó en una columna de gel de sílice y se eluyó con 97:3 DCM:MeOH para obtener 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1R,3S)-3-(((benciloxi)carbonil)amino)-2,2-dimetilciclobutancarboxamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo

(335 mg, 0.355 mmol, 78 % de rendimiento) como una espuma marrón. LC/MS: m/e 802.4 $(M+H)^+$, 4.23 min (método 8). ^{1}H NMR (400MHz, *Cloroformo-d*) δ 7.95 (d, *J*= 8.3 Hz, 2H), 7.40-7.37 (m, 5H), 7.21 (d, *J*= 8.3 Hz, 2H), 5.31 (d, *J*= 4.6 Hz, 1H), 5.18-5.12 (m, 2H), 5.10-5.06 (m, 1H), 4.97 (s, 1H), 4.76 (s, 1H), 4.66 (s, 1H), 3.93 (s, 3H), 2.85 (s, 6H), 2.69-2.55 (m, 2H), 2.44-2.29 (m, 3H), 2.17-2.09 (m, 2H), 1.94-1.81 (m, 3H), 1.72 (s, 3H), 1.70-1.66 (m, 1H), 1.62-1.52 (m, 4H), 1.46 (d, *J*= 7.3 Hz, 1H), 1.42 (d, *J*= 2.7 Hz, 1H), 1.37 (s, 3H), 1.32-1.22 (m, 3H), 1.15 (d, *J*= 11.7 Hz, 2H), 1.09 (s, 2H), 1.02 (s, 3H), 1.01 (s, 3H), 1.00 (s, 3H), 0.95 (s, 6H).

Etapa 2. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1R,3S)-3-(((benciloxi)carbonil)amino)-2,2-dimetilciclobutancarboxamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1R,3S)-3-(((benciloxi)carbonil)amino)-2,2-dimetilciclobutancarboxamido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo

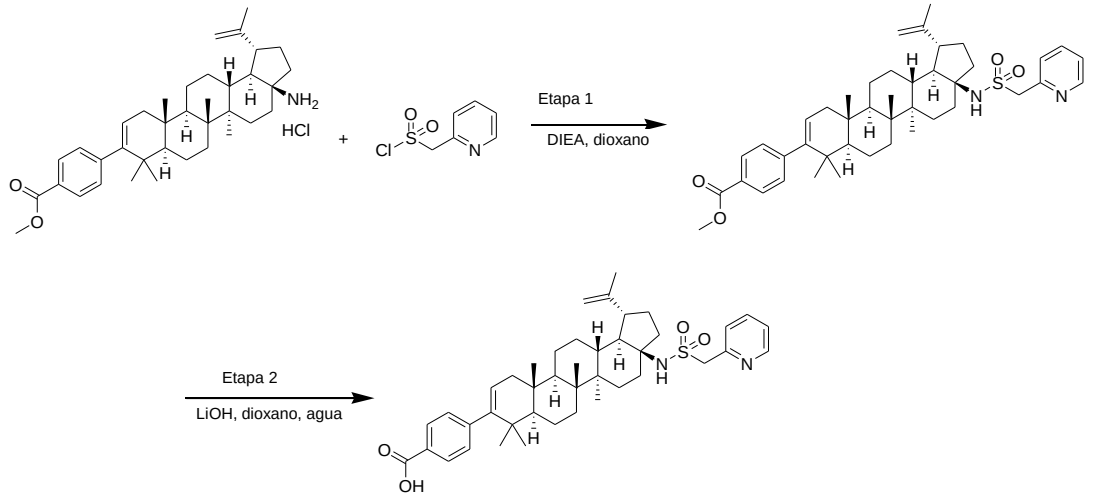
(135 mg, 0.168 mmol) en THF (5 mL), MeOH (2 mL), se agregó una solución de hidróxido de litio monohidrato (0.014 mL, 0.504 mmol) en agua (1 mL). La mezcla de reacción se agitó a 75 °C. Después de 4 h, la mezcla se concentró para obtener una pasta blanca. El material crudo se disolvió en THF (1.75 mL), MeOH (1 mL) y HCl 1N (0.25 mL), y se inyectó en una HPLC preparativa de fase inversa usando el método **11** de HPLC, y se secó en un horno de vacío para producir el compuesto del título (30.4 mg, 0.035 mmol, 21.09 % de rendimiento) como un sólido blanco. LCMS: m/e 789.4 $(M+H)^+$, 3.14 min (método 8). ^{1}H NMR (400MHz, *Cloroformo-d*) δ 8.02 (d, *J*= 8.3 Hz, 2H), 7.41-7.37 (m, 4H), 7.36 (d, *J*= 3.4 Hz, 1H), 7.25 (d, *J*= 8.3 Hz, 2H), 5.33 (d, *J*= 4.6 Hz, 1H), 5.19-5.07 (m, 3H), 4.99 (br. s., 1H), 4.77 (s, 1H), 4.66 (s, 1H), 3.98-3.88 (m, 1H), 2.70-2.55 (m, 3H), 2.47-2.28 (m, 3H), 2.19-2.09 (m, 2H), 1.99-1.87 (m, 1H), 1.76 (d, *J*= 7.8 Hz, 1H), 1.72 (s, 3H), 1.71-1.63 (m, 2H), 1.58 (d, *J*= 8.1 Hz, 3H), 1.50 (br. s., 3H), 1.43 (br. s., 1H), 1.37 (br. s., 3H), 1.33 (d, *J*= 12.2 Hz, 2H), 1.28 (s, 3H), 1.24 (d, *J*= 7.1 Hz, 1H), 1.16 (d, *J*= 12.2 Hz, 2H), 1.09 (s, 3H), 1.02 (s, 6H), 1.01 (br. s., 3H), 0.96 (s, 6H).

Sección 4. Sulfonilamidas

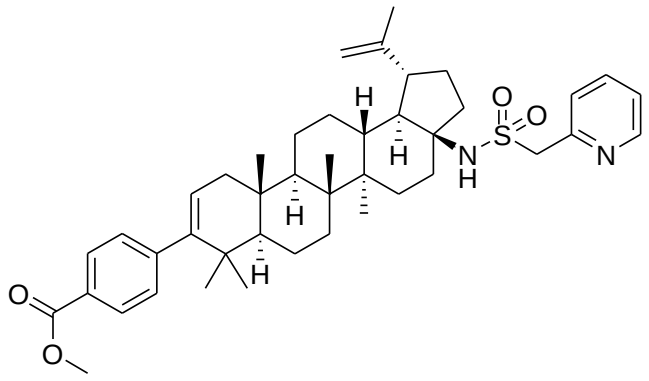
Ejemplo 131

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(piridin-2-

ilmetilsulfonamido)-
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-
octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



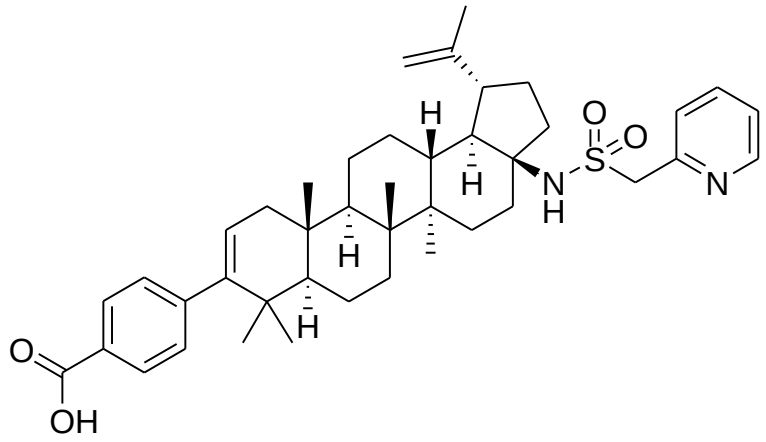
Etapa 1: Preparación de 4-
((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-
pentametil-1-(prop-1-en-2-il)-3a-(piridin-2-
ilmetilsulfonamido)-
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-
octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.



4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-

amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (0.100 g, 0.184 mmol) se combinó con cloruro de piridin-2-ilmetansulfonilo, sal de ácido tríflico (0.189 g, 0.552 mmol). A la mezcla, se agregó 1,4-dioxano seco (1.5 mL) y, luego, DIPEA (0.095 g, 0.736 mmol). La mezcla se agitó a temperatura ambiente durante 3 h. La mezcla de reacción cruda se concentró, se volvió a disolver en una mezcla de MeOH y THF, y se purificó mediante HPLC preparativa de fase inversa. El compuesto del título se aisló como un sólido blanco de la sal de mono-TFA (66 mg, 44 % de rendimiento). LCMS: m/z 699 ($M+H^+$), tiempo de retención 3.03 min (método 11). 1H NMR (400 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, *MeOD* estabilización) δ ppm 0.93 (s, 3 H) 0.94 (s, 3 H) 1.01 (d, *J*= 1.76 Hz, 6 H) 1.07-1.20 (m, 5 H) 1.21-1.28 (m, 1 H) 1.34-1.57 (m, 11 H) 1.63-1.78 (m, 6 H) 1.78-1.95 (m, 2 H) 1.95-2.05 (m, 1 H) 2.12 (dd, *J*= 17.19, 6.40 Hz, 1 H) 2.31-2.41 (m, 1 H) 2.41-2.51 (m, 1 H) 2.61 (td, *J*= 10.98, 4.64 Hz, 1 H) 3.90 (s, 3 H) 4.56-4.59 (m, 1 H) 4.64 (br. s., 1 H) 4.75 (d, *J*= 1.51 Hz, 1 H) 5.28 (dd, *J*= 6.02, 1.51 Hz, 1 H) 7.20 (m, *J*= 8.28 Hz, 2 H) 7.53 (br. s., 1 H) 7.70 (d, *J*= 6.27 Hz, 1 H) 7.90 (m, *J*= 8.28 Hz, 2 H) 7.98 (t, *J*= 7.78 Hz, 1 H) 8.67 (br. s., 1 H).

Etapa 2: Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(piridin-2-ilmetilsulfonamido)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



En un 1 vial dram con tapa a rosca con revestimiento PTFE, se combinaron 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(piridin-2-ilmetilsulfonamido)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (0.060 g, 0.086 mmol), hidróxido de litio monohidrato (0.022 g, 0.515 mmol), 1,4-dioxano (0.8 mL) y agua (0.4 mL). El vial se selló y se calentó con agitación a 75 °C durante 7 min. Se agregaron pequeñas

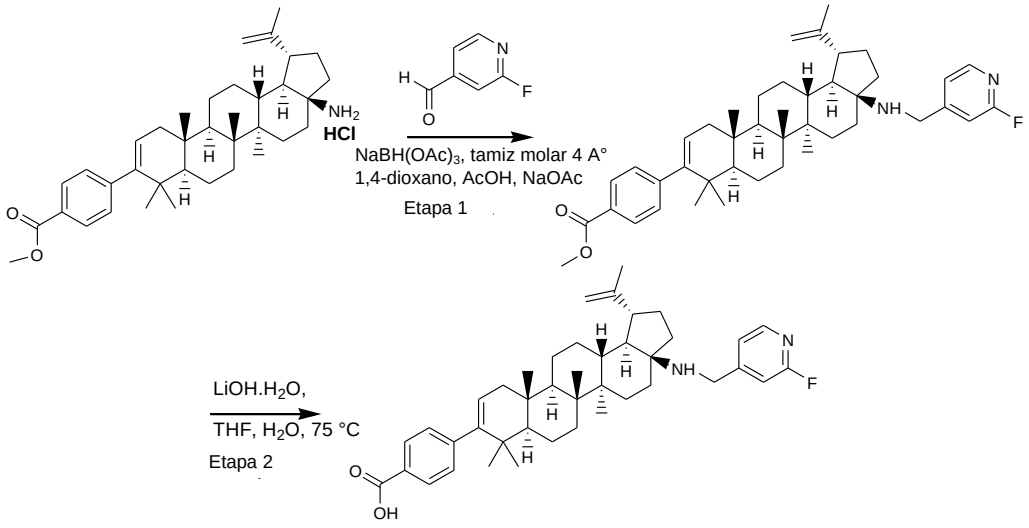
cantidades de MeOH y THF para disolver por completo todos los sólidos, y la mezcla se filtró y se purificó mediante HPLC preparativa de fase inversa. El producto salino de mono-TFA se aisló después de la purificación como un sólido blanco (56 mg, 96 % de rendimiento). LCMS: m/z 685 ($M+H^+$), tiempo de retención 2.62 min (método 11). 1H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, *MeOD* estabilización) δ ppm 0.94 (s, 3 H) 0.95 (s, 3 H) 1.02 (d, *J*= 2.14 Hz, 6 H) 1.09-1.20 (m, 5 H) 1.22-1.29 (m, 1 H) 1.29-1.40 (m, 1 H) 1.40-1.60 (m, 9 H) 1.65-1.80 (m, 6 H) 1.82-2.02 (m, 3 H) 2.13 (dd, *J*= 17.09, 6.41 Hz, 1 H) 2.33-2.41 (m, 1 H) 2.41-2.49 (m, 1 H) 2.64 (td, *J*= 11.06, 4.73 Hz, 1 H) 4.64 (s, 3 H) 4.77 (d, *J*= 1.53 Hz, 1 H) 5.29 (dd, *J*= 6.26, 1.68 Hz, 1 H) 7.20 (d, *J*= 8.54 Hz, 2 H) 7.61-7.67 (m, 1 H) 7.80 (d, *J*= 7.93 Hz, 1 H) 7.92 (d, *J*= 8.24 Hz, 2 H) 8.11 (td, *J*= 7.78, 1.53 Hz, 1 H) 8.69 (d, *J*= 3.97 Hz, 1 H).

Sección 5. Aminas

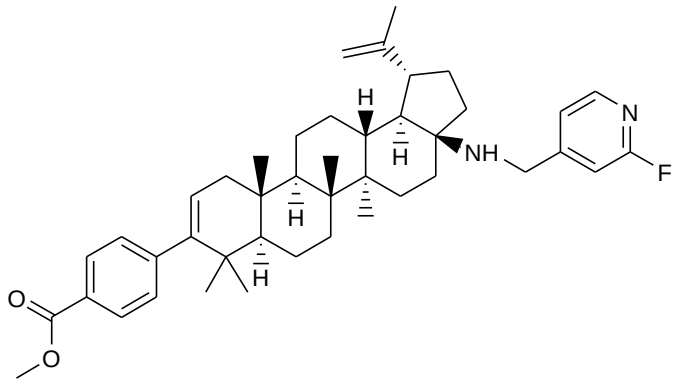
Ejemplo 132

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoropiridin-4-il)metilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-

il)benzoico.



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoropiridin-4-il)metilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

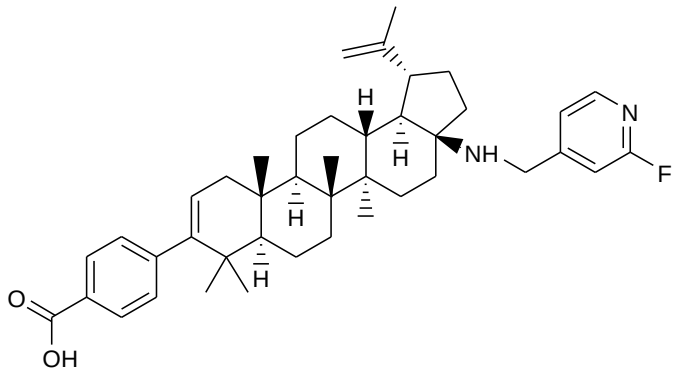


A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo, HCl (318 mg, 0.548 mmol) en DCE (10 mL), se agregó ácido acético glacial (0.314 mL, 5.48 mmol), acetato de sodio (67.4 mg, 0.822 mmol), 2-fluoropiridin-4-carboxaldehído (206 mg, 1.644 mmol) y tamices moleculares 4A. La mezcla de reacción se calentó a 65 °C durante 18 h. A la mezcla de reacción, se agregó triacetoxihidroborato de sodio (581 mg, 2.74 mmol), y la mezcla resultante se calentó a 65 °C durante 7.5 h, luego la mezcla se dejó reposar a temperatura ambiente durante 48 h. La reacción se diluyó con DCM (50 mL) y se lavó con $NaHCO_3$ (20 mL) saturado. La capa acuosa se extrajo con DCM (2 x 25 mL). La capa orgánica combinada se secó en $MgSO_4$, se filtró y se concentró. El residuo marrón oscuro resultante se disolvió en THF (3 mL) y MeOH (0.6 mL), se filtró y se purificó mediante HPLC preparativa de fase inversa usando el método 3 de HPLC para obtener 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoropiridin-4-il)metilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo, TFA (218.4 mg, 0.285 mmol, 52.0 % de rendimiento) como un sólido blanco. LCMS: m/e 653.4 $(M+H)^+$, 2.69 min (método 6).

Etapa 2. Preparación de ácido 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoropiridin-4-il)metilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



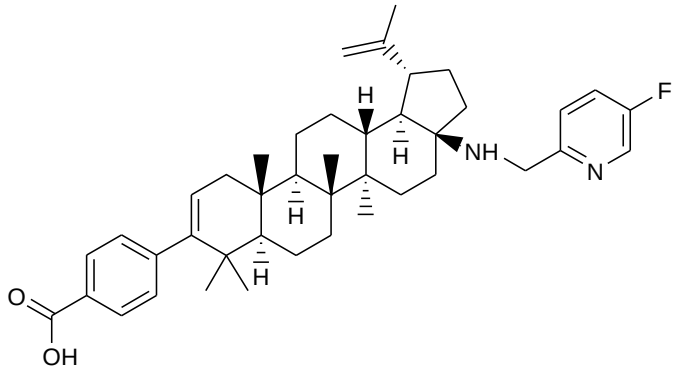
A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoropiridin-4-il)metilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo, TFA (77.7 mg, 0.101 mmol) en THF (3 mL), se agregó una solución acuosa de LiOH 0.753 molar. H_2O (0.539 mL, 0.405 mmol). La mezcla de reacción se calentó a 75 °C. Después de 4 h, la mezcla de reacción se concentró. El residuo crudo se disolvió en THF (1.5 mL) y MeOH (200 µL), se filtró y se purificó mediante HPLC preparativa de fase inversa usando el método 2 de HPLC para obtener ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-

fluoropiridin-4-il)metilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, TFA (30.6 mg, 0.037 mmol, 36.1 % de rendimiento) como un sólido blanco. LCMS: m/e 637.7 $(M-H)^-$, 3.12 min (método 6). ^{1}H NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ = 8.24 (d, *J* = 5.2 Hz, 1 H), 7.92 (d, *J* = 8.2 Hz, 2 H), 7.43 (d, *J* = 5.2 Hz, 1 H), 7.24 (s, 1 H), 7.20 (d, *J* = 8.5 Hz, 2 H), 5.29 (dd, *J* = 1.7, 6.3 Hz, 1 H), 4.78 (s, 1 H), 4.17 (br. s., 2 H), 2.78-2.69 (m, 1 H), 2.18-2.10 (m, 2 H), 2.09-2.01 (m, 2 H), 1.98 (dd, *J* = 3.1, 11.9 Hz, 1 H), 1.96-1.88 (m, 1 H), 1.83-1.76 (m, 1 H), 1.72 (s, 3 H), 1.70-1.64 (m, 1 H), 1.63-1.40 (m, 10 H), 1.39-1.31 (m, 1 H), 1.31-1.23 (m, 2 H), 1.13 (s, 3 H), 1.07 (s, 3 H), 1.02 (s, 3 H), 0.95 (s, 3 H), 0.94 (s, 3 H). ^{13}C NMR (1:1 *$CDCl_3$:MeOD*) d ppm 15.3, 16.6, 17.4, 19.5, 20.6, 21.8, 22.2, 26.1, 27.6, 29.0, 29.5, 30.2, 33.9, 34.6, 37.2, 38.2, 38.4, 41.8, 42.8, 43.1, 45.7, 47.2, 49.7, 49.9, 50.3, 50.5, 53.9, 78.8, 123.1, 123.2, 124.9, 129.3, 129.7, 131.0, 147.4, 149.7, 164.0, 166.0, 170.1.

Ejemplo 133

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((5-fluoropiridin-2-il)metilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

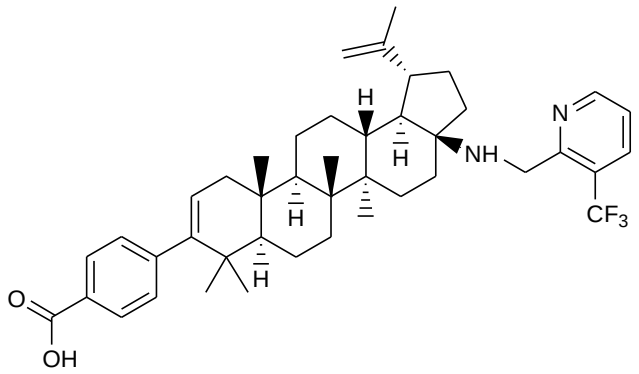


El compuesto del título se preparó en 47 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoropiridin-4-il)metilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó 5-fluoro-2-formilpiridina en lugar de 2-fluoropiridin-4-carboxaldehído en la Etapa 1. LCMS: m/e 639.5 $(M+H)^+$, 3.33 min (método 6). ^{1}H NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ = 8.46 (d, *J* = 2.7 Hz, 1 H), 7.93 (d, *J* = 8.2 Hz, 2 H), 7.68 (dt, *J* = 2.7, 8.2 Hz, 1 H), 7.53 (dd, *J* = 4.1, 8.7 Hz,

1 H), 7.21 (d, *J* = 8.5 Hz, 2 H), 5.31 (dd, *J* = 1.7, 6.3 Hz, 1 H), 4.83 (s, 1 H), 4.74 (s, 1 H), 4.49 (d, *J* = 15.3 Hz, 1 H), 4.32 (d, *J* = 15.0 Hz, 1 H), 2.78 (dt, *J* = 5.3, 10.9 Hz, 1 H), 2.22-2.06 (m, 5 H), 1.96 (dt, *J* = 3.4, 12.2 Hz, 1 H), 1.89-1.82 (m, 1 H), 1.80 (d, *J* = 10.7 Hz, 2 H), 1.76 (s, 3 H), 1.74-1.66 (m, 2 H), 1.64-1.54 (m, 4 H), 1.53-1.47 (m, 2 H), 1.46-1.42 (m, 1 H), 1.41-1.37 (m, 1 H), 1.33 (s, 3 H), 1.29 (dd, *J* = 3.8, 9.9 Hz, 1 H), 1.24 (dd, *J* = 4.1, 13.0 Hz, 1 H), 1.13 (s, 3 H), 1.07 (s, 3 H), 0.97 (s, 3 H), 0.95 (s, 3 H).

Ejemplo 134

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-((3-(trifluorometil)piridin-2-il)metilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



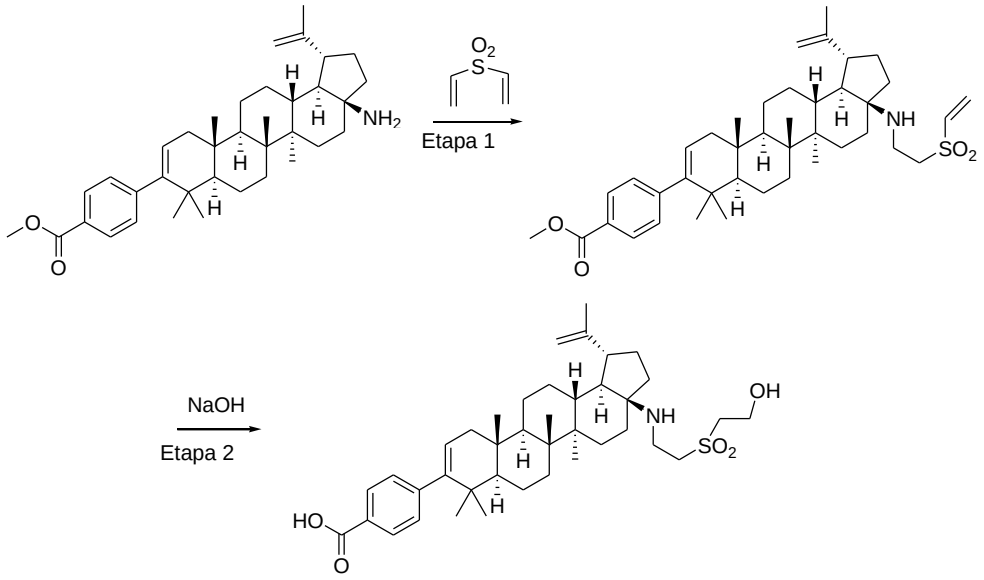
El compuesto del título se preparó en 42 % de rendimiento de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-

3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el mismo procedimiento que el descrito para la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoropiridin-4-il)metilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó 3-trifluorometilpiridin-2-carbaldehído en lugar de 2-fluoropiridin-4-carboxaldehído en la Etapa 1. LCMS: m/e 689.6 $(M+H)^+$, 4.12 min (método 6). ^{1}H NMR (500MHz, 1:1 *$CDCl_3$:MeOD*) δ = 8.83 (d, *J* = 4.3 Hz, 1 H), 8.28 (d, *J* = 7.9 Hz, 1 H), 7.93 (d, *J* = 8.5 Hz, 2 H), 7.72 (dd, *J* = 5.0, 7.8 Hz, 1 H), 7.21 (d, *J* = 8.5 Hz, 2 H), 5.31 (dd, *J* = 1.5, 6.1 Hz, 1 H), 4.85 (s, 1 H), 4.76 (s, 1 H), 4.44 (d, *J* = 16.2 Hz, 1 H), 2.80 (dt, *J* = 5.5, 11.0 Hz, 1 H), 2.25-2.10 (m, 5 H), 2.02 (dt, *J* = 3.5, 12.1 Hz, 1 H), 1.92-1.79 (m, 2 H), 1.78 (s, 3 H), 1.76-1.68 (m, 3 H), 1.64-1.54 (m, 4 H), 1.52-1.43 (m, 3 H), 1.40 (br. s., 1 H), 1.36 (s, 3 H), 1.32-1.22 (m, 2 H), 1.16-1.13 (m, 3 H), 1.08 (s, 3 H), 0.97 (s, 3 H), 0.95 (s, 3 H).

Ejemplo 135

Preparación de ácido 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-hidroxietilsulfonil)etilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(2-(vinilsulfonil)etilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

Una mezcla de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (30 mg, 0.055 mmol), TEA (0.023 mL, 0.165 mmol) y vinilsulfonileteno (19.5 mg, 0.165 mmol) en EtOH (1 mL) se calentó durante 3 h a 100 °C. La mezcla de reacción se inactivó con agua y se extrajo con DCM (3 x 2 mL). Las fases orgánicas se combinaron, se secaron en sulfato de sodio, se filtraron y se concentraron a presión reducida para obtener el compuesto del título como un aceite marrón (25 mg, 68 %). LCMS: m/e 662.42 $(M+H)^+$, 3.45 min (método 10).

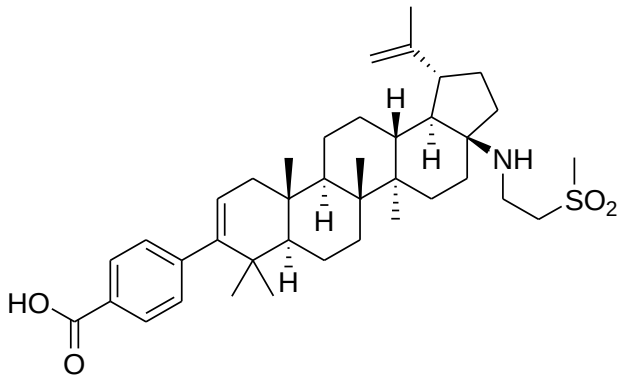
Etapa 2. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-hidroxietilsulfonil)etilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

Una mezcla de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(2-(vinilsulfonil)etilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (25 mg, 0.038 mmol) e hidróxido de sodio (0.189 mL, 0.189 mmol) en dioxano (1 mL) se calentó a 78 °C

durante 3 h. La mezcla de reacción se filtró, y la solución transparente se purificó mediante HPLC preparativa para obtener el compuesto del título como un sólido blanco (14 mg, 53 %). LCMS: m/e 666.39 $(M+H)^+$, 2.48 min (método 10). ^{1}H NMR (500 MHz, *Ácido acético d4*) δ ppm 8.03 (d, *J*= 8.24 Hz, 2 H), 7.30 (d, *J*= 8.24 Hz, 2 H), 5.37 (d, *J*= 4.27 Hz, 1 H), 4.87 (s, 1 H), 4.75 (s, 1 H), 4.31-4.01 (m, 3 H), 3.93-3.74 (m, 3 H), 3.68-3.41 (m, 2 H), 3.06 – 2.73 (m, 1 H), 2.48 – 1.26 (m, 22 H), 1.76 (s, 3 H), 1.23 (s, 3 H), 1.14 (s, 3 H), 1.09 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H).

Ejemplo 136

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(metilsulfonil)etilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

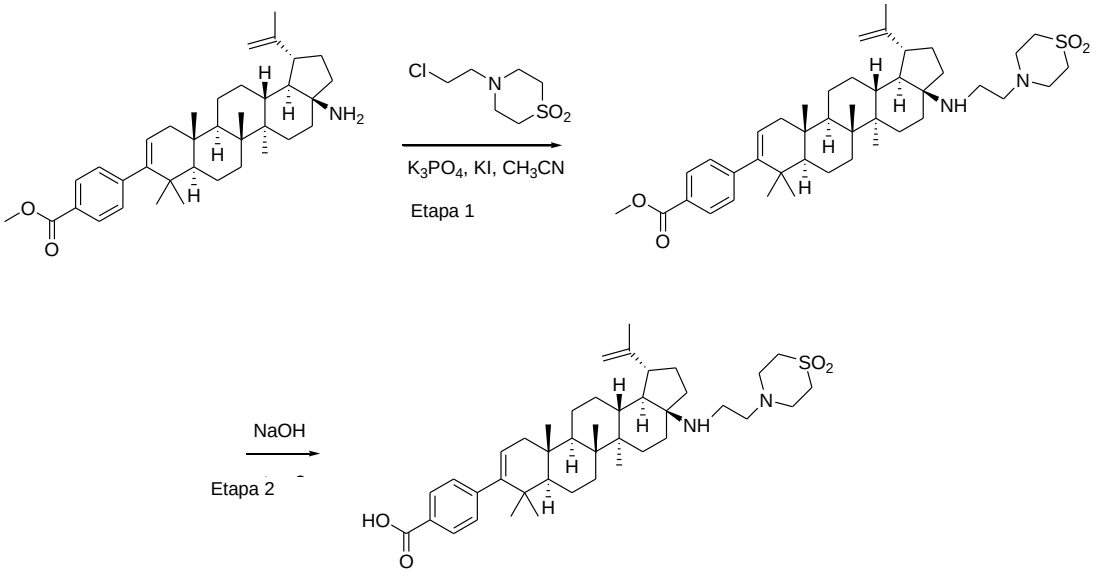


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis

de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-hidroxietilsulfonil)etilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando metilsulfonileteno en lugar de vinilsulfonileteno en la Etapa 1. El producto se aisló como un sólido blanco (6 mg, 39 %). LCMS: m/e 636.37 $(M+H)^+$, 2.53 min (método 10). ^{1}H NMR (500 MHz, *Ácido acético d4*) δ ppm 8.04 (d, *J*= 8.24 Hz, 2 H), 7.30 (d, *J*= 8.24 Hz, 2 H), 5.44-5.33 (m, 1 H), 4.88 (s, 1 H), 4.76 (s, 1 H), 4.17-4.00 (m, 1 H), 3.93-3.69 (m, 3 H), 3.22 (s, 3 H), 3.00 – 2.85 (m, 1 H), 2.40 – 1.26 (m, 22 H), 1.77 (s, 3 H), 1.23 (s, 3 H), 1.14 (s, 3 H), 1.10 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H).

Ejemplo 137

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-tiomorfolinil)etil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-tiomorfolinil)etil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

Una mezcla de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-1-

isopropenil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (600 mg, 1.10 mmol), 4-(2-cloroetil)tiomorfolina 1,1-dióxido (600 mg, 2.56 mmol) (preparado según se describe en WO2002045652), fosfato de potasio anhidro (3.00 g, 14.1 mmol) y yoduro de potasio (10 mg, 0.060 mmol) en acetonitrilo (50 mL) se colocó en un recipiente de presión resellable AceGlass de 150 mL. La suspensión blanca se cubrió con nitrógeno. El recipiente se selló y se calentó a 115-125 °C durante 48 h. La reacción cruda se filtró a través de una almohadilla pequeña de gel de sílice y se lavó con acetato de etilo. El filtrado se concentró al vacío y se purificó mediante cromatografía en gel de sílice, se eluyó con acetato de etilo y hexanos (0-50 %) para obtener el compuesto del título como una espuma incolora (566 mg, 73 %). ^{1}H NMR (500MHz, Cloroformo-d) δ 7.95 (d, J= 8.2 Hz, 2H), 7.22 (d, J= 8.2 Hz, 2H), 5.31 (d, J= 4.6 Hz, 1H), 4.74 (d, J= 1.8 Hz, 1H), 4.62 (s, 1H), 3.93 (s, 3H), 3.22-2.99 (m, 9H), 2.79-2.55 (m, 4H), 2.52-2.42 (m, 1H), 2.18-2.09 (m, 1H), 1.99-1.02 (m, 20H), 1.72 (s, 3H), 1.11 (s, 3H), 1.01 (s., 3H), 1.10 (s, 3H), 0.95 (s, 3H), 0.95 (s., 3H).LCMS: m/e 705.51 $(M+H)^{+}$, 3.01 min (método 10).

Etapa 2. Preparación de ácido 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-

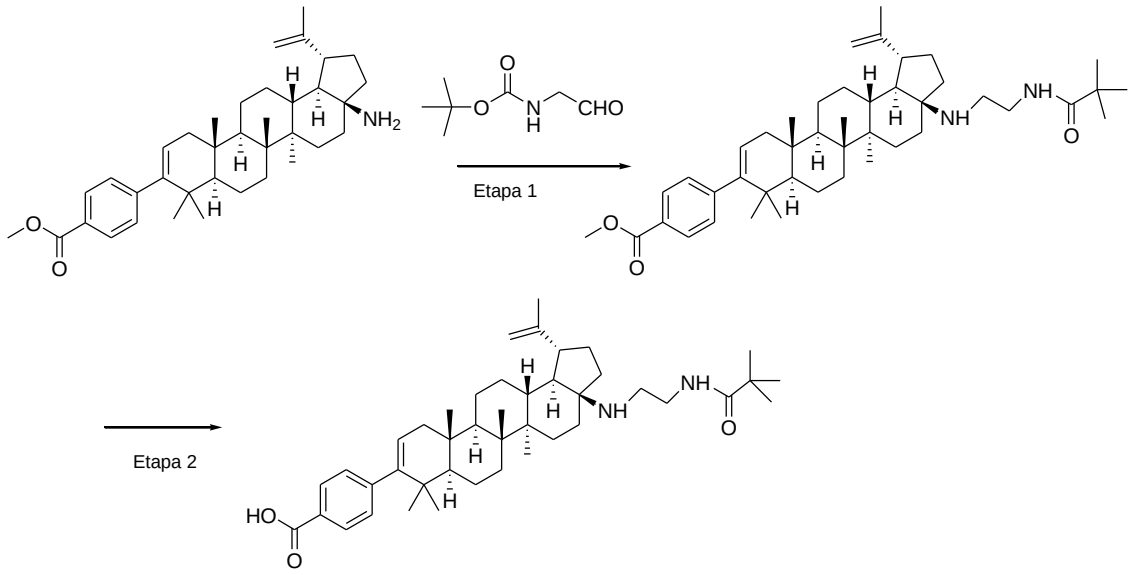
dioxido-4-tiomorfolinil)etil]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-1H-ciclopenta[a]crisen-9-il]- benzoico

Una mezcla de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-tiomorfolinil)etil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (500 mg, 0.709 mmol) e hidróxido de sodio acuoso 10 N (1.42 mL, 14.2 mmol) en dioxano (10 mL) se calentó a 78 °C durante 3 h. La reacción se filtró, y la solución transparente resultante se purificó mediante HPLC preparativa para obtener el compuesto del título como un sólido blanco (200 mg, 39 %). LCMS: m/e 691.59 $(M+H)^+$, 2.53 min (método 10). ^{1}H NMR (500 MHz, *Ácido acético d4*) δ ppm 8.04 (d, *J*= 8.24 Hz, 2 H), 7.30 (d, *J*= 8.24 Hz, 2 H), 5.45-5.34 (m, 1 H), 4.85 (s, 1 H), 4.74 (s, 1 H), 3.55-3.40 (m, 1 H), 3.39-3.22 (m, 6 H), 3.22-3.11 (m, 4 H), 3.11-3.03 (m, 1 H), 3.04 – 2.94 (m, 1 H), 2.36 – 1.18 (m, 22 H), 1.76 (s, 3 H), 1.30 (s, 3 H), 1.15 (s, 3 H), 1.12 (s, 3 H), 1.03 (s, 3 H), 1.00 (s, 3 H).

Ejemplo 138

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(terc-

butoxicarbonilamino)etilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(terc-butoxicarbonilamino)etilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

A 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de

metilo (1.00 g, 1.84 mmol) en DCE (5 mL), se agregaron 2-oxoetilcarbamato de *terc-butilo* (1.17 g, 7.36 mmol) y tetraisopropoxititanio (0.700 mL, 2.39 mmol). La mezcla de reacción se agitó durante 1 h; luego, se agregó triacetoxiborohidruro de sodio (1.17 g, 5.52 mmol). La mezcla de reacción se agitó durante 18 h. La mezcla de reacción se inactivó con bicarbonato de sodio y se extrajo con DCM (3 x 40 mL). Las capas orgánicas combinadas se secaron en sulfato de sodio, se filtraron y se concentraron a presión reducida. El residuo se purificó mediante cromatografía usando acetato de etilo y hexanos (20-100 %) como el eluyente para obtener el compuesto del título como un aceite amarillo pálido. (900 mg, 71 %). LCMS: m/e 688.24 $(M+H)^+$, 2.51 min (método 11).

Etapa 2. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(terc-butoxicarbonilamino)etilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

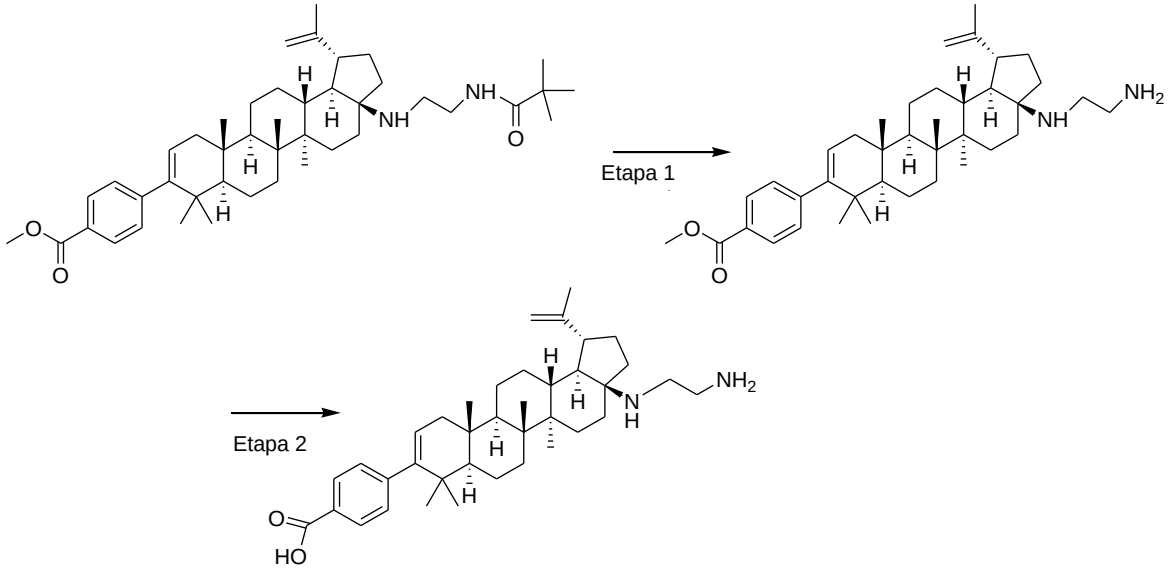
El compuesto del título se preparó de acuerdo con el método de hidrólisis descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-

hidroxietilsulfonil)etilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(terc-butoxicarbonilamino)etilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (10 mg, 0.015 mmol) como el material de inicio. El compuesto del título se aisló como un sólido blanco (4 mg, 39 %). LCMS: m/e 673.45 $(M+H)^+$, 2.65 min (método 10). ^{1}H NMR (500 MHz, *Ácido acético d4*) δ ppm 8.04 (d, *J*= 8.24 Hz, 2 H), 7.30 (d, *J*= 8.55 Hz, 2 H), 5.51-5.32 (m, 1 H), 4.87 (s, 1 H), 4.75 (s, 1 H), 3.82-3.53 (m, 1 H), 3.53-3.24 (m, 3 H), 3.04 – 2.83 (m, 1 H), 2.37 – 1.15 (m, 22 H), 1.77 (s, 3 H), 1.53-1.49 (m, 9 H), 1.27 (s, 3 H), 1.14 (s, 3 H), 1.11 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H).

Ejemplo 139

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-aminoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-aminoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(terc-butoxicarbonilamino)etilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (900 mg, 1.310 mmol) en dioxano (1 mL), se agregó HCl (4 M en dioxano) (4.26 mL, 17.03 mmol), y la mezcla de reacción se agitó durante 4 h a temperatura ambiente. La mezcla de reacción se concentró a presión reducida para obtener el compuesto del

título como un sólido marrón (769 mg, 100 %). LCMS: m/e 588.08 $(M+H)^+$, 2.44 min (método 11).

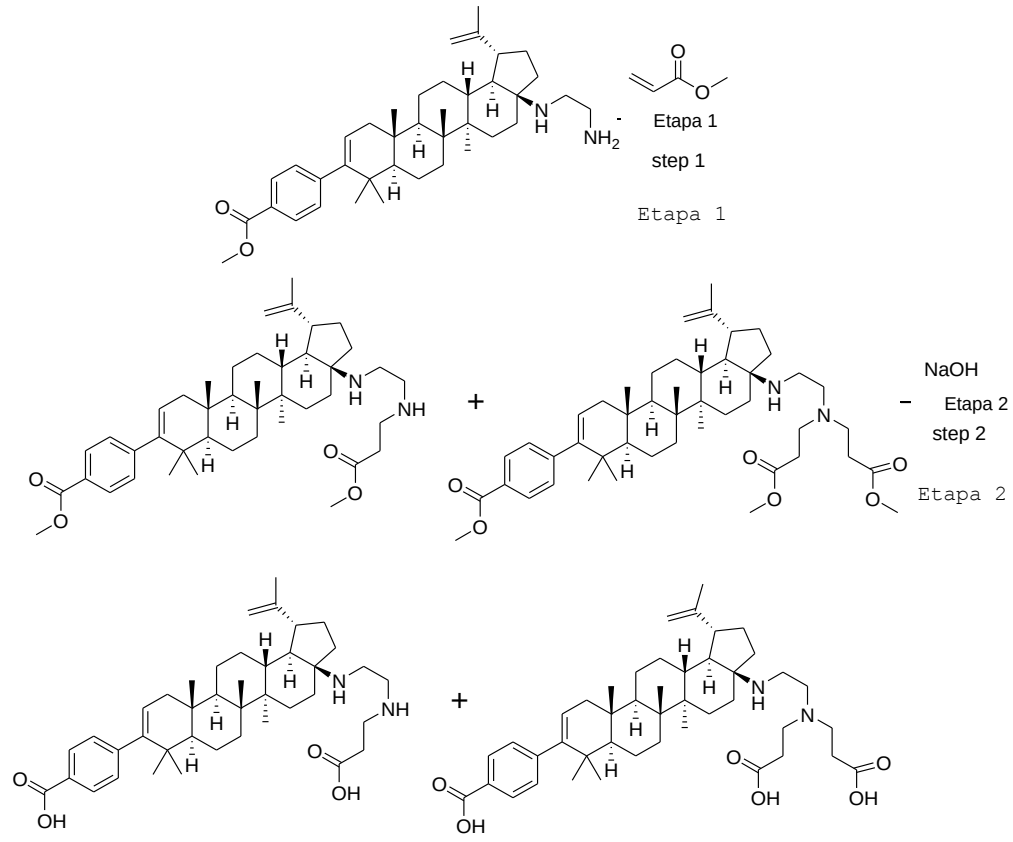
Etapa 2. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-aminoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

El compuesto del título se preparó de acuerdo con el método de hidrólisis descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-hidroxietilsulfonil)etilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-aminoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (4 mg, 0.006 mmol) como material de inicio. El compuesto del título se aisló como un sólido blanco (2.4 mg, 67 %). LCMS: m/e 573.2 $(M+H)^+$, 2.39 min (método 10). ^{1}H NMR (500 MHz, *Ácido acético d4*) δ ppm 8.03 (d, *J*= 8.24 Hz, 2 H), 7.30 (d, *J*= 8.24 Hz, 2 H), 5.37 (d, *J*= 4.27 Hz, 1 H), 4.87 (s, 1 H), 4.76 (s, 1 H), 3.80-3.68 (m, 3 H), 3.68-3.59 (m, 1 H), 2.97-2.80 (m, 1 H), 2.38 – 1.21 (m, 22 H), 1.78 (s, 3 H), 1.20 (s, 3 H), 1.14 (s, 3

H), 1.09 (s, 3 H), 1.01 (s, 3 H), 1.00 (s, 3 H).

Ejemplos 140 y 141

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-carboxietilamino)etilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico y ácido 3,3'-(2-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-carboxifenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-ilamino)etilazanediil)dipropanoico.



Etapa 1. Preparación de 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3-metoxi-3-oxopropilamino)etilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo y 3,3'-(2-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(metoxicarbonil)fenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-ilamino)etilazanediil)dipropanoato de dimetilo.

Se agregó acrilato de metilo (9.97 mg, 0.116 mmol) a una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-aminoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (34 mg, 0.058 mmol) en MeOH (2 mL), y la mezcla se agitó durante 16 h a temperatura ambiente. La mezcla de reacción se concentró a presión reducida para obtener una mezcla de los dos compuestos del título como un aceite marrón (20 mg, 51 %). LCMS: m/e 673.47 $(M+H)^+$, 2.96 min y 759.51 $(M+H)^+$, 3.43 min (método 10). La mezcla se usó en la siguiente etapa sin purificación adicional.

Etapa 2. Hidrólisis de éster.

La mezcla de ésteres antes mencionada (20 mg) en dioxano (1 mL) se trató con hidróxido de sodio (0.297 mL,

0.297 mmol) a 78 °C durante 3 horas. La mezcla de reacción se filtró y se purificó mediante HPLC preparativa para obtener los dos siguientes compuestos:

Ejemplo 140

Ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-carboxietilamino)etilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

Sólido blanco (16 mg, 43 % en las 2 etapas). LCMS: m/e 645.44 $(M+H)^+$, 2.37 min (método 10). ^{1}H NMR (500 MHz, *Ácido acético d4*) δ ppm 8.04 (d, *J*= 8.2 Hz, 2 H), 7.30 (d, *J*= 8.5 Hz, 2 H), 5.37 (d, *J*= 4.6 Hz, 1 H), 4.87 (s, 1 H), 4.75 (s, 1 H), 3.78 (s., 2 H), 3.77-3.59 (m, 2 H), 3.45 (t, *J*= 6.4 Hz, 2 H), 2.90 (t, *J*= 6.4 Hz, 2 H), 2.87-2.72 (m, 1 H), 2.42 – 1.22 (m, 22 H), 1.78 (s, 3 H), 1.20 (s, 3 H), 1.13 (s, 3 H), 1.09 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H).

Ejemplo 141

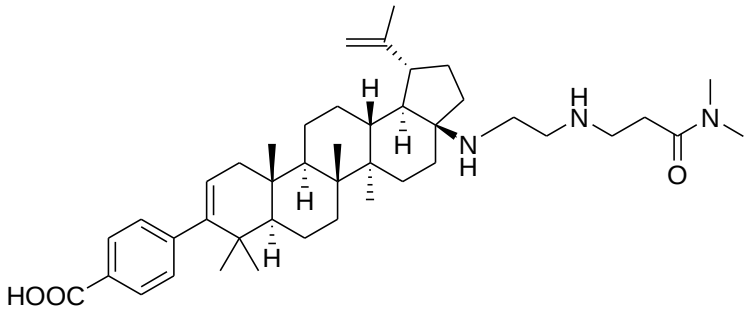
Ácido 3,3'-(2-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-carboxifenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-ilamino)etilazanediil)dipropanoico

Sólido blanco (5.7 mg, 57 % en 2 etapas). LCMS: m/e

717.51 $(M+H)^+$, 2.25 min (método 10). ^{1}H NMR (500 MHz, *Ácido acético d4*) δ ppm 8.03 (d, *J*= 8.2 Hz, 2 H), 7.29 (d, *J*= 8.2 Hz, 2 H), 5.36 (d, *J*= 4.9 Hz, 1 H), 4.88 (s, 1 H), 4.76 (s, 1 H), 3.83-3.66 (m, 4 H), 3.51 (t, *J*= 6.3 Hz, 4 H), 2.93 (t, *J*= 6.9 Hz, 4 H), 2.88-2.74 (m, 1 H), 2.42 – 1.22 (m, 22 H), 1.78 (s, 3 H), 1.19 (s, 3 H), 1.14 (s, 3 H), 1.08 (s, 3 H), 1.01 (s, 3 H), 0.99 (s, 3 H).

Ejemplo 142

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(3-(dimetilamino)-3-oxopropilamino)etilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

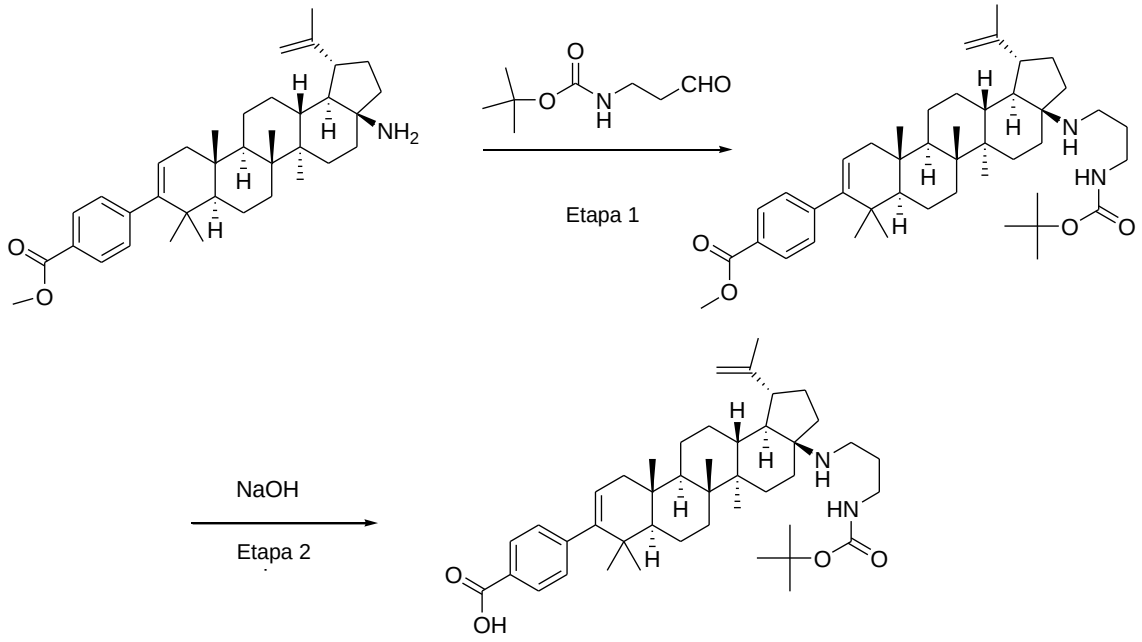


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-carboxietilamino)etilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando *N,N*-dimetilacrilamida como el reactivo aceptor de Michael en la primera etapa. El producto se aisló como un sólido blanco (9 mg, 50 %). LCMS: m/e 672.47 $(M+H)^+$, 2.33 min (método 2). ^{1}H NMR (500 MHz, *Ácido acético d4*) δ ppm 8.04 (d, J= 8.2 Hz, 2 H), 7.30 (d, J= 8.2 Hz, 2 H), 5.37 (d, J= 4.6 Hz, 1 H), 4.88 (s, 1 H), 4.76 (s, 1 H), 3.86-3.59 (m, 4 H), 3.51-3.37 (m, 2 H), 3.07 (s, 3 H), 2.99 (s, 3 H), 2.95 (t, J= 5.6 Hz, 2 H), 2.90-2.76 (m, 1 H), 2.37 – 1.22 (m, 22 H), 1.78 (s, 3 H), 1.20 (s, 3 H), 1.14 (s, 3 H), 1.09 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H).

Ejemplo 142

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(terc-butoxicarbonilamino)propilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(terc-butoxicarbonilamino)propilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

Se agregaron ácido acético (0.013 mL, 0.221 mmol) y 3-oxopropilcarbamato de *terc-butilo* (38.2 mg, 0.221

mmol) a una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (40 mg, 0.074 mmol) en EtOH (1 mL) y dioxano (1.0 mL), y la mezcla se agitó durante 2 h a temperatura ambiente. Se agregó triacetoxiborohidruro de sodio (78 mg, 0.368 mmol), y la mezcla de reacción se agitó a 20 °C durante dos horas. La reacción se inactivó con una solución acuosa saturada de bicarbonato de sodio (3 mL), se lavó con HCl 0.1 N (5 mL) y salmuera (5 mL) y se extrajo con DCM (3 x 5 mL). Se combinaron todos los extractos, se secaron en sulfato de sodio, se filtraron y se concentraron a presión reducida para producir el compuesto del título como un aceite amarillo pálido (28 mg, 54 %). LCMS: m/e 701.51 $(M+H)^+$, 4.0 min (método 10).

Etapa 2. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(terc-butoxicarbonilamino)propilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

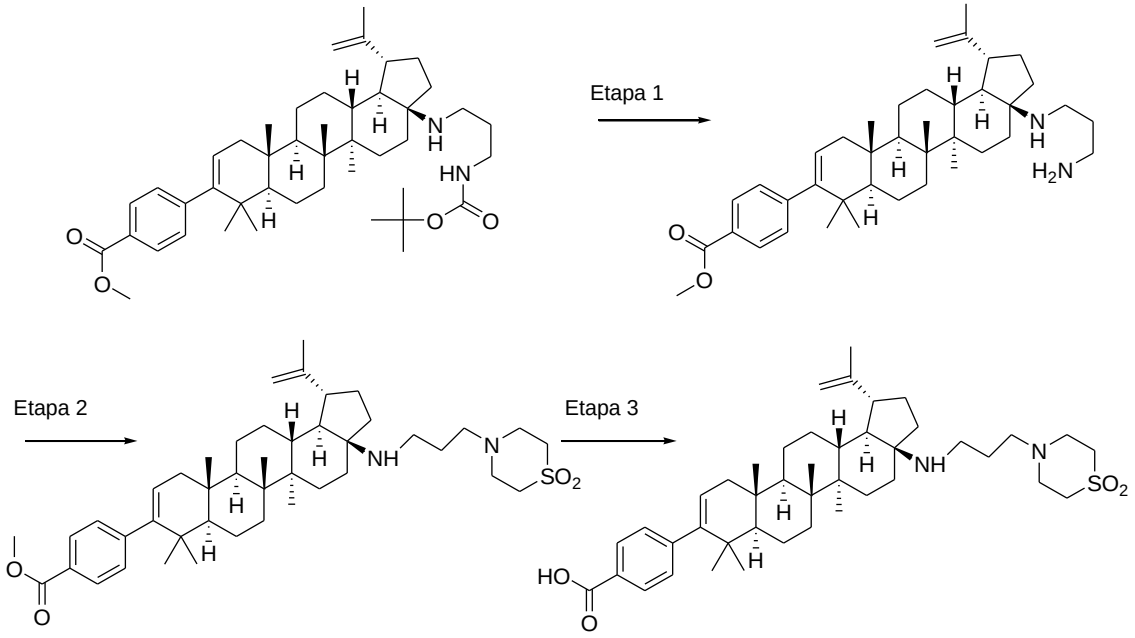
El compuesto del título se preparó de acuerdo con el método de hidrólisis descrito anteriormente para la

síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(2-hidroxietilsulfonil)etilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(terc-butoxicarbonilamino)propilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (5 mg, 0.007 mmol) como el material de inicio. El compuesto del título se aisló como un sólido blanco (3 mg, 58 %). LCMS: m/e 687.54 $(M+H)^+$, 2.69 min (método 10). ^{1}H NMR (500 MHz, *Ácido acético d4*) δ ppm 8.04 (d, *J*= 8.24 Hz, 2 H), 7.30 (d, *J*= 8.24 Hz, 2 H), 5.37 (d, *J*= 4.58 Hz, 1 H), 4.87 (s, 1 H), 4.74 (s, 1 H), 3.38-3.17 (m, 4 H), 3.04 – 2.86 (m, 1 H), 2.36 – 1.17 (m, 24 H), 1.77 (s, 3 H), 1.50 (s, 9 H), 1.25 (s, 3 H), 1.14 (s, 3 H), 1.09 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H).

Ejemplo 144

Preparación de ácido 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-tiomorfolinil)propil]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-1H-ciclopenta[a]crisen-9-il]-benzoico



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-aminopropilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

Se agregó HCl 4.0 M en dioxano (32.8 µl, 0.131 mmol) a una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(terc-butoxicarbonilamino)propilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo

(23 mg, 0.033 mmol) en dioxano (1 mL), y la mezcla se agitó durante 6 h a temperatura ambiente. La mezcla de reacción se concentró a presión reducida para proporcionar el compuesto del título como un aceite marrón (15 mg, 76 %). LCMS: m/e 601.48 $(M+H)^+$, 2.88 min (método 10).

Etapa 2. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((3-(1,1-dioxido-4-tiomorfolinil)propil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico de metilo.

Se agregaron vinilsulfonileteno (5.90 mg, 0.050 mmol) y trietilamina (6.96 µl, 0.050 mmol) a una mezcla de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-aminopropilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (15 mg, 0.025 mmol) en EtOH (1 mL). La mezcla de reacción se calentó a 100 °C durante 3 horas. La mezcla de reacción se concentró a presión reducida para obtener el producto deseado como un sólido marrón (15 mg, 76 %). LCMS: m/e 719.46 $(M+H)^+$, 3.68 min (método 10).

Etapa 3. Preparación de ácido 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-tiomorfolinil)propil]amino]-

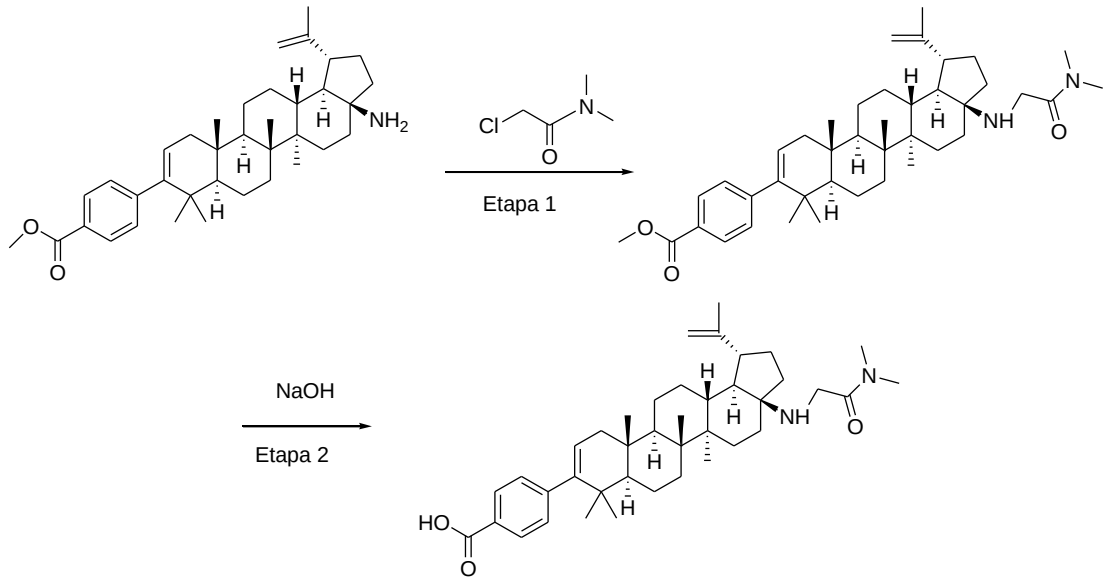
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-1H-ciclopenta[a]crisen-9-il] benzoico

Una mezcla de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((3-(1,1-dioxido-4-tiomorfolinil)propil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico de metilo (15 mg, 0.021 mmol) e hidróxido de sodio 1 N (0.104 mL, 0.104 mmol) en dioxano (1 mL) se calentó a 78 °C durante 3 horas. La mezcla de reacción se purificó mediante HPLC preparativa para obtener el compuesto del título como un sólido blanco (9 mg, 58 %). LCMS: m/e 705.49 $(M+H)^+$, 2.60 min (método 10). ^1H NMR (400 MHz, *Ácido acético d4*) δ ppm 7.99 (d, *J*= 8.28 Hz, 2 H), 7.25 (d, *J*= 8.28 Hz, 2 H), 5.33 (d, *J*= 4.77 Hz, 1 H), 4.82 (s, 1 H), 4.71 (s, 1 H), 3.87 (br. s., 4 H), 3.56 (d, *J*= 4.27 Hz, 4 H), 3.51-3.40 (m, 2 H), 3.39-3.22 (m, 2 H), 2.86-2.69 (m, 1 H), 2.57-2.34 (m, 2 H), 2.27 – 1.18 (m, 22 H), 1.72 (s, 3 H), 1.16 (s, 3 H), 1.10 (s, 3 H), 1.04 (s, 3 H), 0.98 (s, 3 H), 0.96 (s, 3 H).

Ejemplo 145

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimetilamino)-2-oxoetilamino)-5a,5b,8,8,11a-pentametil-1-

(prop-1-en-2-il)-
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimetilamino)-2-oxoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

Una mezcla de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (50 mg, 0.092 mmol), 2-cloro-*N*,*N*-dimetilacetamida (33.5 mg,

0.276 mmol), fosfato de potasio (78 mg, 0.368 mmol) y yoduro de potasio (36,6 mg, 0.221 mmol) en acetonitrilo (1 mL) se calentó a 120 °C durante 33 h en un tubo sellado. La mezcla de reacción se inactivó con agua destilada (5 mL) y se extrajo con DCM (3 x 5 mL). Las capas orgánicas combinadas se secaron en sulfato de sodio, se filtraron y se concentraron a presión reducida para producir el compuesto del título como un sólido amarillo (30 mg, 52 %). LCMS: m/e 629.51 $(M+H)^+$, 3.03 min (método 10). El producto se usó en la siguiente etapa sin purificación adicional.

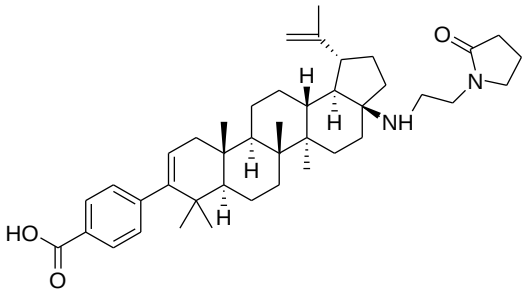
Etapa 2. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimetilamino)-2-oxoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

Una mezcla de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimetilamino)-2-oxoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (30 mg, 0.048 mmol) e hidróxido de sodio acuoso 1 N (0.048 mL, 0.048 mmol) en dioxano (1 mL) se calentó a 78 °C durante 3 h. La mezcla de reacción se filtró, y la solución

transparente se purificó mediante HPLC preparativa para obtener el compuesto del título como un sólido blanco (9.5 mg, 31 %). LCMS: m/e 615.56 $(M+H)^+$, 2.52 min (método 10). ^{1}H NMR (500 MHz, *Ácido acético d4*) δ ppm 8.04 (d, *J*= 8.24 Hz, 2 H), 7.30 (d, *J*= 8.24 Hz, 2 H), 5.38 (d, *J*= 4.58 Hz, 1 H), 4.89 (s, 1 H), 4.76 (s, 1 H), 4.52 (d, *J*= 16.17 Hz, 1 H), 4.04 (d, *J*= 16.17 Hz, 1 H), 3.08 (d, *J*= 10.99 Hz, 6 H), 3.01 – 2.86 (m, 1 H), 2.37 – 1.22 (m, 22 H), 1.79 (s, 3 H), 1.30 (s, 3 H), 1.14 (s, 3 H), 1.10 (s, 3 H), 1.03 (s, 3 H), 1.00 (s, 3 H).

Ejemplo 146

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(2-oxopirrolidin-1-il)etilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

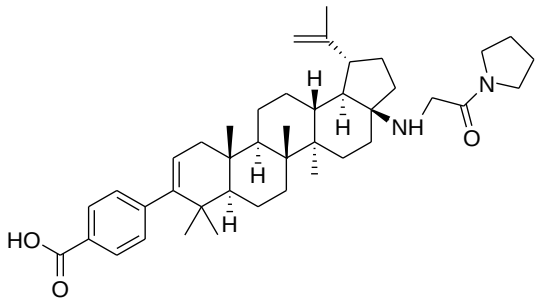


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimetilamino)-2-oxoetilamino)-5a,5b,8,8,11a-pentametil-1-

(prop-1-en-2-il)-
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando 1-(2-cloroetil)pirrolidin-2-ona como el reactivo alquilante en la Etapa 1. El producto se aisló como un sólido blanco (19 mg, 62 %). LCMS: m/e 641.57 $(M+H)^+$, 2.58 min (método 10). ^{1}H NMR (500 MHz, *Ácido acético d4*) δ ppm 8.04 (d, *J*= 8.24 Hz, 2 H), 7.30 (d, *J*= 8.55 Hz, 2 H), 5.37 (d, *J*= 4.88 Hz, 1 H), 4.91 (s, 1 H), 4.76 (s, 1 H), 3.89-3.73 (m, 2 H), 3.72-3.56 (m, 3 H), 3.55-3.45 (m, 1 H), 2.93-2.80 (m, 1 H), 2.57 (td, *J*= 8.24, 3.97 Hz, 2 H), 2.34 – 1.19 (m, 24 H), 1.78 (s, 3 H), 1.23 (s, 3 H), 1.13 (s, 3 H), 1.10 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H).

Ejemplo 147

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-oxo-2-(pirrolidin-1-il)etilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

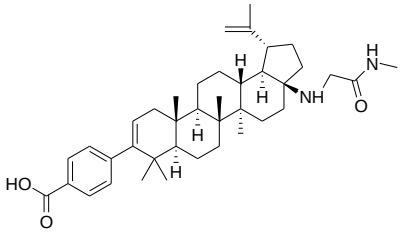


El compuesto del título se preparó de acuerdo con el

método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimetilamino)-2-oxoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando 2-cloro-1-(pirrolidin-1-il)etanona como el reactivo alquilante en la Etapa 1. El producto se aisló como un sólido blanco (19 mg, 46 %). LCMS: m/e 641.46 $(M+H)^+$, 2.55 min (método 10). ^{1}H NMR (500 MHz, *Ácido acético d4*) δ ppm 8.04 (d, *J*= 8.24 Hz, 2 H), 7.30 (d, *J*= 8.24 Hz, 2 H), 5.38 (d, *J*= 4.58 Hz, 1 H), 4.89 (s, 1 H), 4.76 (s, 1 H), 4.43 (d, *J*= 16.48 Hz, 1 H), 3.99 (d, *J*= 16.17 Hz, 1 H), 3.73-3.42 (m, 4 H), 3.15 – 2.86 (m, 1 H), 2.41 – 1.19 (m, 26 H), 1.79 (s, 3 H), 1.28 (s, 3 H), 1.14 (s, 3 H), 1.10 (s, 3 H), 1.03 (s, 3 H), 1.00 (s, 3 H).

Ejemplo 148

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(metilamino)-2-oxoetilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

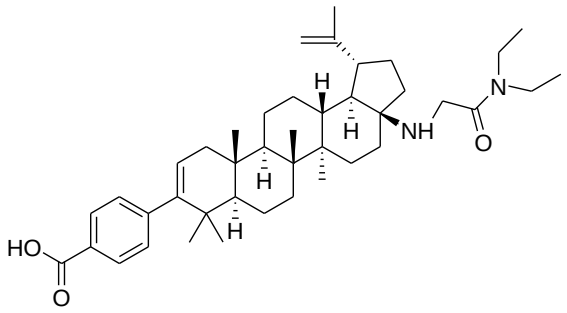


El compuesto del título se preparó de acuerdo

con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimetilamino)-2-oxoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando 2-cloro-*N*-metilacetamida como el reactivo alquilante en la Etapa 1. El producto se aisló como un sólido blanco (41 mg, 80 %). LCMS: m/e 601.45 $(M+H)^+$, 2.31 min (método 11). ^{1}H NMR (500 MHz, *Ácido acético d4*) δ ppm 8.04 (d, *J*= 8.24 Hz, 2 H), 7.30 (d, *J*= 8.24 Hz, 2 H), 5.38 (d, *J*= 4.58 Hz, 1 H), 4.88 (s, 1 H), 4.76 (s, 1 H), 4.24 (d, *J*= 15.56 Hz, 1 H), 3.92 (d, *J*= 15.26 Hz, 1 H), 2.88 (s, 3 H), 3.08 – 2.74 (m, 1 H), 2.31 – 1.30 (m, 22 H), 1.78 (s, 3 H), 1.29 (s, 3 H), 1.14 (s, 3 H), 1.10 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 3 H).

Ejemplo 149

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dietilamino)-2-oxoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

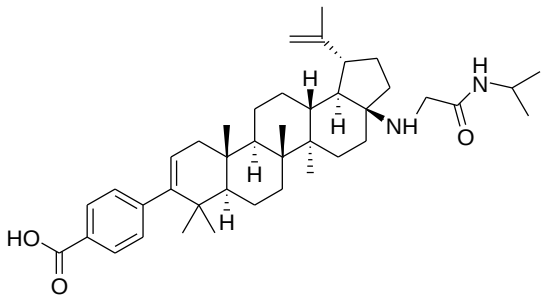


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimetilamino)-2-oxoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando 2-cloro-*N,N*-dietilacetamida como el reactivo alquilante en la Etapa 1. El producto se aisló como un sólido blanco (20 mg, 39 %). LCMS: m/e 643.50 $(M+H)^+$, 2.35 min (método 11). ^{1}H NMR (400 MHz, *Cloroformo-d*) δ ppm 7.99 (d, *J*= 8.28 Hz, 2 H), 7.24 (d, *J*= 8.28 Hz, 2 H), 5.31 (d, *J*= 4.52 Hz, 1 H), 4.74 (d, *J*= 1.76 Hz, 1 H), 4.60 (s, 1 H), 3.58-3.21 (m, 6 H), 2.82-2.69 (m, 1 H), 2.22 – 1.02 (m, 28 H), 1.72 (s, 3 H), 1.18 (s, 3 H), 1.01 (s, 3 H), 1.00 (s, 3 H), 0.95 (s, 6 H).

Ejemplo 150

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(isopropilamino)-2-oxoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-

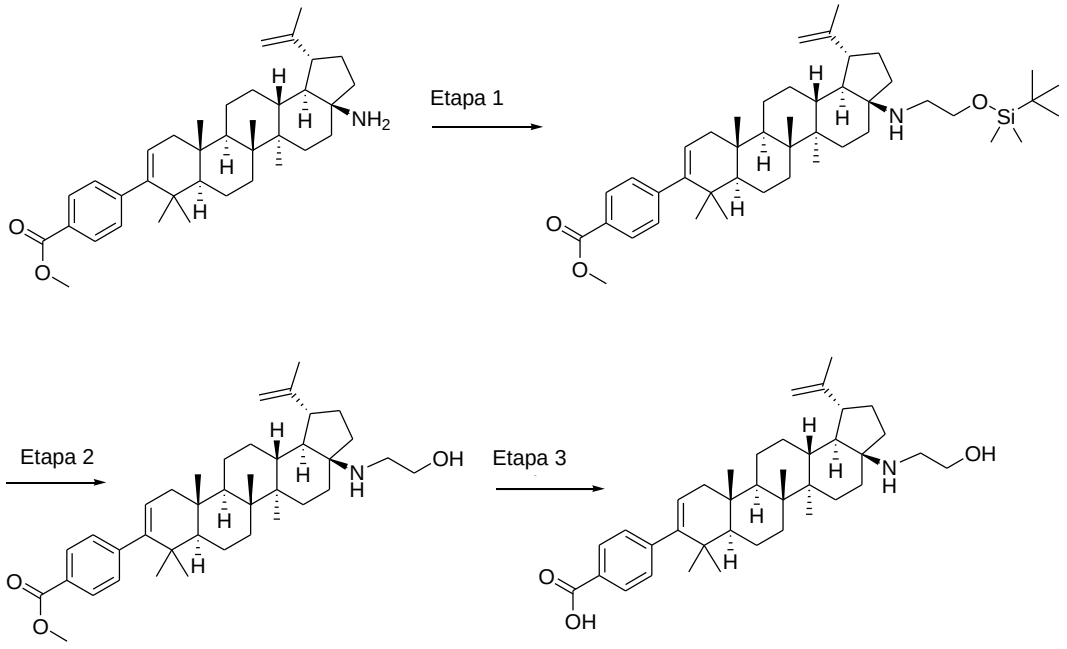
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimetilamino)-2-oxoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando 2-cloro-*N*-isopropilacetamida como el reactivo alquilante en la Etapa 1. El producto se aisló como un sólido blanco (50 mg, 81 %). LCMS: m/e 629.46 $(M+H)^+$, 2.60 min (método 10). ^{1}H NMR (400 MHz, *Ácido acético d4*) δ ppm 7.99 (d, *J*= 8.53 Hz, 2 H), 7.26 (d, *J*= 8.53 Hz, 2 H), 5.34 (d, *J*= 4.77 Hz, 1 H), 4.84 (s, 1 H), 4.72 (s, 1 H), 4.15 (d, *J*= 15.31 Hz, 1 H), 4.06 (dt, *J*= 13.11, 6.62 Hz, 1 H), 3.85 (d, *J*= 15.31 Hz, 1 H), 3.07 – 2.77 (m, 1 H), 2.41 – 1.26 (m, 22 H), 1.74 (s, 3 H), 1.24 (s, 3 H), 1.16 (d, *J*= 6.53 Hz, 6 H), 1.10 (s, 3 H), 1.06 (s, 3 H), 0.99 (s, 3 H), 0.97 (s, 3 H).

Ejemplo 151

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-hidroxietilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(*terc*-*butil*dimetilsililoxi)etilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (300 mg, 0.552 mmol) en DCE (4 mL), se agregaron (*terc-butil*dimetilsililoxi)acetaldehído (131 mL, 0.690 mmol) e isopropóxido de titanio(IV) (0.202 mL, 0.690 mmol). La mezcla se agitó a temperatura ambiente durante 45 minutos, y se agregó triacetoxiborohidruro de sodio (234 mg, 1.103 mmol). La mezcla se agitó a temperatura ambiente durante 23 h y se agregaron 0.1 mL de (*terc-butil*dimetilsililoxi)acetaldehído y 150 mg de triacetoxiborohidruro de sodio de manera adicional. La mezcla se agitó a temperatura ambiente durante 22 h más; luego, se diluyó con 15 mL de $NaHCO_3$ saturado y se extrajo con diclorometano (3 x 15 mL). Las capas orgánicas combinadas se secaron con Na_2SO_4, el agente de secado se retiró mediante filtración, y el filtrado se concentró a presión reducida. El residuo se adsorbió en gel de sílice y se purificó mediante cromatografía instantánea usando un gradiente de 0-10 % de EtOAc en hexanos. Las fracciones que contenían el producto previsto se combinaron y concentraron a presión reducida para producir el compuesto del título (0.211 g, 0.301 mmol, 54.5 % de rendimiento) como una película amarilla transparente. El producto se usó en la siguiente etapa sin purificación adicional. LCMS: m/e 702.7 $(M+H)^+$, 2.35 min (método 2).

Etapa 2. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-

hidroxietilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(*terc*-*butil*dimetilsililoxi)etilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (0.211 g, 0.301 mmol) en THF (2 mL), se agregó TBAF (1 M en THF) (0.601 mL, 0.601 mmol). La mezcla se agitó a temperatura ambiente durante 2.75 h, luego se diluyó con agua (10 mL) y se extrajo con diclorometano (3 x 10 mL). Las capas orgánicas combinadas se secaron con Na_2SO_4, el agente de secado se retiró mediante filtración, y el filtrado se concentró a presión reducida. El residuo se adsorbió en gel de sílice y se purificó mediante cromatografía instantánea usando un gradiente de 0-25 % de EtOAc en hexanos. El compuesto del título (93.4 mg, 0.159 mmol, 52.9 % de rendimiento), se aisló como una película incolora. LCMS: m/e 588.6 $(M+H)^+$, 1.98 min (método 2). ^{1}H NMR (500 MHz, *Cloroformo-d*) d ppm 7.91 (d, *J*= 8.24 Hz, 2 H), 7.18 (d, *J*= 8.24 Hz, 2 H), 5.27 (d, *J*= 4.58 Hz, 1 H), 4.70 (d, *J*= 1.83 Hz, 1 H), 4.59 (s, 1 H), 3.89 (s, 3 H), 3.54-3.64 (m, 2 H), 2.52-2.69 (m, 3 H), 2.09 (dd, *J*= 17.09, 6.41 Hz, 1 H), 1.68 (s, 3 H), 1.07 (s, 3 H), 0.98 (s,

3 H), 0.97 (s, 3 H), 0.93-2.05 (m, 21 H), 0.91 (s, 3 H), 0.91 (s, 3 H).

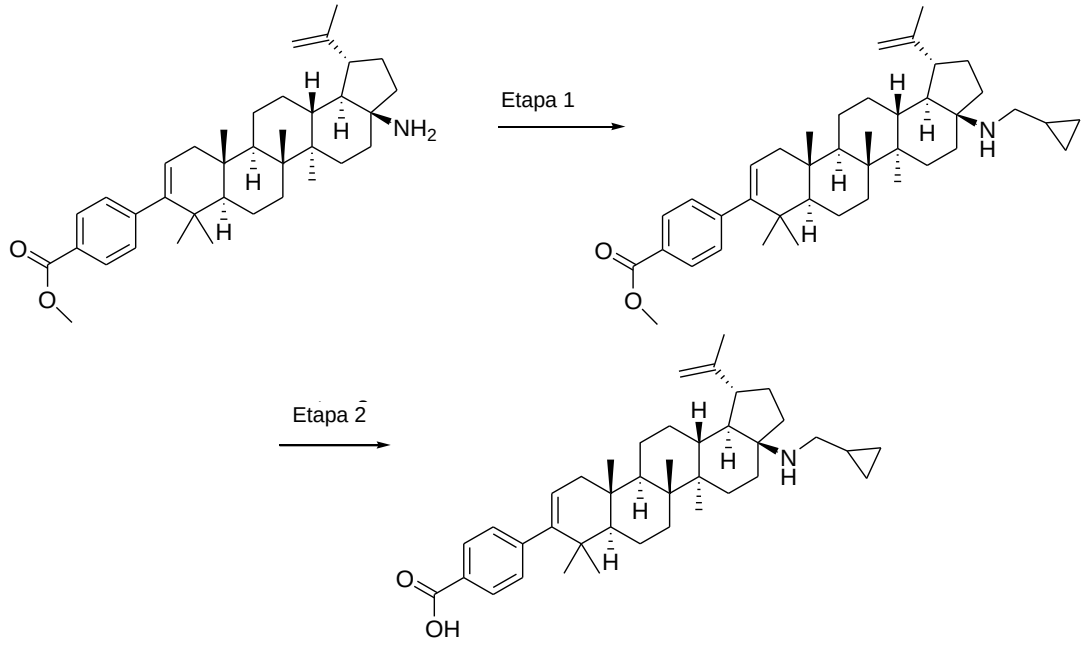
Etapa 3. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-hidroxietilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-hidroxietilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (35 mg, 0.060 mmol) en dioxano (1 mL), se agregó NaOH (1N) (0.298 mL, 0.298 mmol). La mezcla se calentó a 85 °C durante 15 h, luego se enfrió a temperatura ambiente. La mezcla se diluyó con MeOH y se purificó mediante HPLC preparativa. Las fracciones que contenían el producto previsto se combinaron y concentraron a presión reducida para producir el compuesto del título (25 mg, 0.041 mmol, 69.5 % de rendimiento) como un sólido blanco. LCMS: m/e 574.5 $(M+H)^+$, 1.69 min (método 2). ^{1}H NMR (500 MHz, *Ácido acético d4*) δ ppm 8.04 (2 H, d, *J*= 8.2 Hz), 7.30 (2 H, d, *J*= 8.2 Hz), 5.37 (1 H, d, *J*= 4.6 Hz), 4.86 (1 H, s), 4.75 (1 H, s), 3.95-4.11 (2 H, m), 3.25-3.43 (2 H, m), 2.90-2.98 (1 H, m), 1.77 (3 H, s), 1.21 (3 H, s), 1.14 (3 H, s), 1.09 (3 H, s), 1.02 (3 H, s), 1.00 (3 H, s), 0.97-2.32

(22 H, m).

Ejemplo 152

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(ciclopropilmetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(ciclopropilmetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

A una solución de 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (0.022 g, 0.040 mmol) en DCE (0.25 mL), se agregaron clopropancarbaldehído (2.84 mg, 0.040 mmol) e isopropóxido de titanio (IV) (0.015 mL, 0.051 mmol). La mezcla se agitó a temperatura ambiente durante 1 h, y se agregó triacetoxiborohidruro de sodio (0.017 g, 0.081 mmol). Después de agitar la mezcla durante 16.75 h, la mezcla se diluyó con 3 mL de agua y se filtró a través de una almohadilla de Celite; luego, se extrajo con diclorometano (3 x 4 mL). Las capas orgánicas combinadas se secaron con Na_2SO_4. El agente de secado se retiró mediante filtración, y el filtrado se concentró a presión reducida para obtener el compuesto del título (0.024 g, 0.040 mmol) como una película amarilla. El producto crudo se usó en la siguiente etapa sin purificación adicional. LCMS: m/e 598.6 $(M+H)^+$, 2.13 min (método 2).

Etapa 2. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(ciclopropilmetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

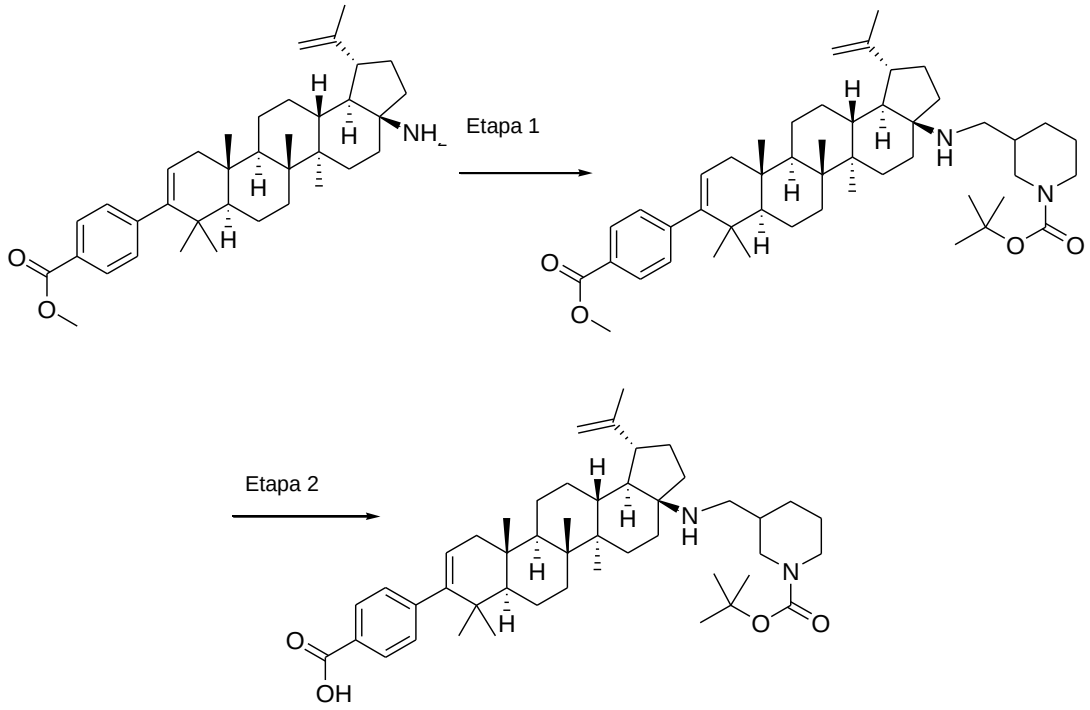
A una mezcla turbia de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-

(ciclopropilmetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (0.024 g, 0.040 mmol) en 1,4-dioxano (1.5 mL), se agregó NaOH (1 N) (0.5 mL, 0.5 mmol). La mezcla se calentó a 65 °C. Después de dos horas, la mezcla se enfrió a temperatura ambiente y se agitó a temperatura ambiente durante la noche. La mezcla se filtró a través de un tapón de lana de vidrio y se purificó mediante HPLC preparativa para obtener el compuesto del título (0.007 g, 10.79 µmol, 26.9 % de rendimiento) como una película blanca. LCMS: m/e 584.6 $(M+H)^+$, 1.83 min (método 2). ^{1}H NMR (400 MHz, *CLOROFORMO-d*) δ ppm 8.00 (2 H, d, *J*= 8.0 Hz), 7.21 (2 H, d, *J*= 8.0 Hz), 5.31 (1 H, d, *J*= 5.0 Hz), 4.75 (1 H, d, *J*= 1.5 Hz), 4.61 (1 H, s), 2.76 (1 H, td, *J*= 10.9, 5.6 Hz), 2.62 (1 H, dd, *J*= 11.2, 6.1 Hz), 2.23 (1 H, dd, *J*= 11.5, 7.8 Hz), 1.97-2.16 (3 H, m), 1.82-1.95 (2 H, m), 1.70 (3 H, s), 1.16 (3 H, s), 1.01 (3 H, s), 1.00 (3 H, s), 0.96 (3 H, s), 0.95 (3 H, s), 0.80-1.77 (19 H, m), 0.48-0.58 (2 H, m), 0.09-0.24 (2 H, m).

Ejemplo 153

Preparación de 3-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(metoxicarbonil)fenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-

ilamino)metil)piperidin-1-carboxilato de *terc-butilo*.



Etapa 1. Preparación de 3-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(metoxicarbonil)fenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-ilamino)metil)piperidin-1-carboxilato de terc-butilo.

A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (30 mg, 0.055 mmol) en DCE (0.5 mL), se agregaron *terc-*

*butil*éster del ácido 3-formil-piperidin-1-carboxílico (14.71 mg, 0.069 mmol) e isopropóxido de titanio(IV) (0.020 mL, 0.069 mmol). La mezcla se agitó a temperatura ambiente durante 1 h, y se agregó triacetoxiborohidruro de sodio (23.38 mg, 0.110 mmol). Después de agitar la mezcla durante 16.5 h, la mezcla se diluyó con 3 mL de $NaHCO_3$ saturado y se extrajo con diclorometano (3 x 5 mL). Las capas orgánicas combinadas se secaron con Na_2SO_4. El agente de secado se retiró mediante filtración, y el filtrado se concentró a presión reducida. El residuo se adsorbió en gel de sílice y se purificó mediante cromatografía instantánea en gel de sílice usando un gradiente de 0-10 % de EtOAc en hexanos y una columna Thomson de gel de sílice de 12 g. Las fracciones que contenían el producto previsto se combinaron y concentraron a presión reducida para obtener el compuesto del título (29 mg, 0.039 mmol, 70.9 % de rendimiento) como una película blancuzca. El producto se usó en la siguiente etapa sin purificación adicional. LCMS: m/e 741.7 $(M+H)^+$, 3.76 min (método 2).

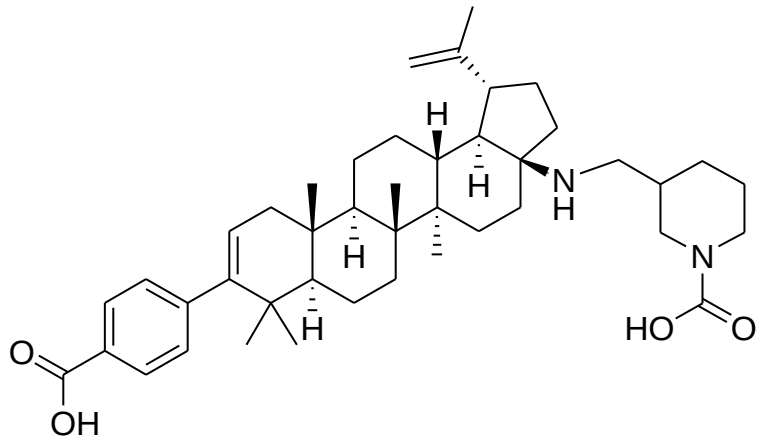
Etapa 2. Preparación de 3-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(metoxicarbonil)fenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-ilamino)metil)piperidin-1-carboxilato de *terc-butilo*.

A una solución de 3-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(metoxicarbonil)fenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-ilamino)metil)piperidin-1-carboxilato de *terc-butilo* (0.029 g, 0.039 mmol) en dioxano (2 mL), se agregó NaOH (1 N) (0.196 mL, 0.196 mmol). La mezcla se calentó a 85 °C durante la noche. Después de calentar la mezcla durante 22 h, se enfrió a temperatura ambiente, se diluyó con MeOH y se purificó mediante HPLC preparativa para obtener el compuesto del título (24 mg, 0.031 mmol, 80 % de rendimiento) como una película transparente incolora. LCMS: m/e 727.7 $(M+H)^+$, 2.00 min (método 2). ^{1}H NMR (500 MHz, *CLOROFORMO-d*) δ ppm 7.98 (2 H, d, *J*= 7.9 Hz), 7.21 (2 H, d, *J*= 7.9 Hz), 5.29 (1 H, d, *J*= 5.5 Hz), 4.70 (1 H, br. s.), 4.58 (1 H, br. s.), 3.83-4.22 (4 H, m), 2.46-2.85 (4 H, m), 2.29 (2 H, br. s.), 1.68 (3 H, s), 1.47 (9 H, d, *J*= 4.6 Hz), 1.10 (3 H, d, *J*= 7.9 Hz), 0.98 (6 H, br. s.), 0.93 (3 H, s), 0.92 (3 H, s), 0.77-2.15 (25 H, m).

Ejemplo 154

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(piperidin-3-ilmetilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

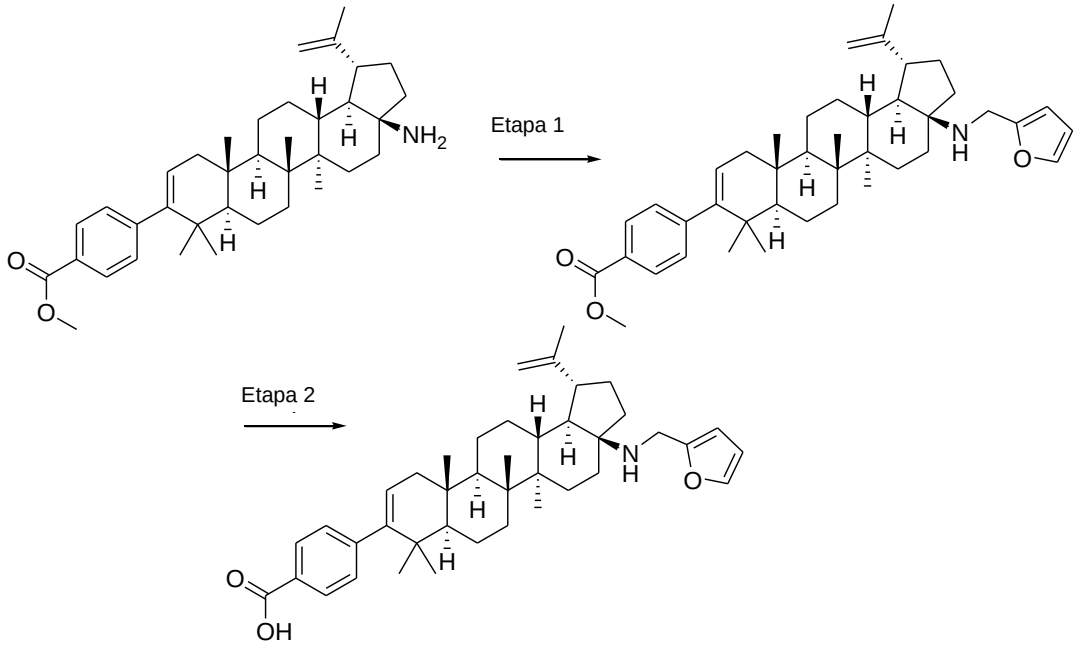
octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



A una solución de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1-(terc-butoxicarbonil)piperidin-3-il)metilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico (0.019 g, 0.026 mmol) en DCM, (1 mL) se agregó TFA (0.25 mL, 3.24 mmol). La mezcla se agitó a temperatura ambiente durante 1.75 h. Luego, la mezcla se concentró a presión reducida y se purificó mediante HPLC preparativa para obtener el compuesto del título (14.2 mg, 0.021 mmol, 81 % de rendimiento) como un sólido blanco. LCMS: m/e 627.6 $(M+H)^+$, 1.50 min (método 2). ^{1}H NMR (500 MHz, *Ácido acético d4*) δ ppm 8.04 (2 H, d, *J*= 8.2 Hz), 7.30 (2 H, d, *J*= 7.9 Hz), 5.37 (1 H, s), 4.85 (1 H, d, *J*= 5.5 Hz), 4.75 (1 H, s), 2.98-3.83 (6 H, m), 2.82-2.91 (1 H, m), 2.57-2.72 (1 H, m), 0.85-2.33 (44 H, m).

Ejemplo 155

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(furan-2-ilmetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(furan-2-ilmetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (30 mg, 0.055 mmol) en DCE (0.5 mL), se agregaron furfural (5.71 µL, 0.069 mmol) e isopropóxido de titanio(IV) (0.020 mL, 0.069 mmol). La mezcla se agitó a temperatura ambiente durante 1 h, y se agregó triacetoxiborohidruro de sodio (23.38 mg, 0.110 mmol). Después de agitar la mezcla durante 16 h a temperatura ambiente, se agregaron 5 µL de furfural junto con 0.025 g de triacetoxiborohidruro de sodio adicional. Después de agitar la mezcla durante la noche a temperatura ambiente, se purificó colocándola a través de un tapón de gel de sílice y lavándola con 0-25 % de EtOAc en hexanos. Las fracciones que contenían el producto se combinaron y concentraron a presión reducida para producir el compuesto del título (31 mg, 0.050 mmol, 90 % de rendimiento) como un sólido blanco. El producto se usó en la siguiente etapa sin purificación adicional. LCMS: m/e 625.6 $(M+H)^+$, 3.08 min (método 2).

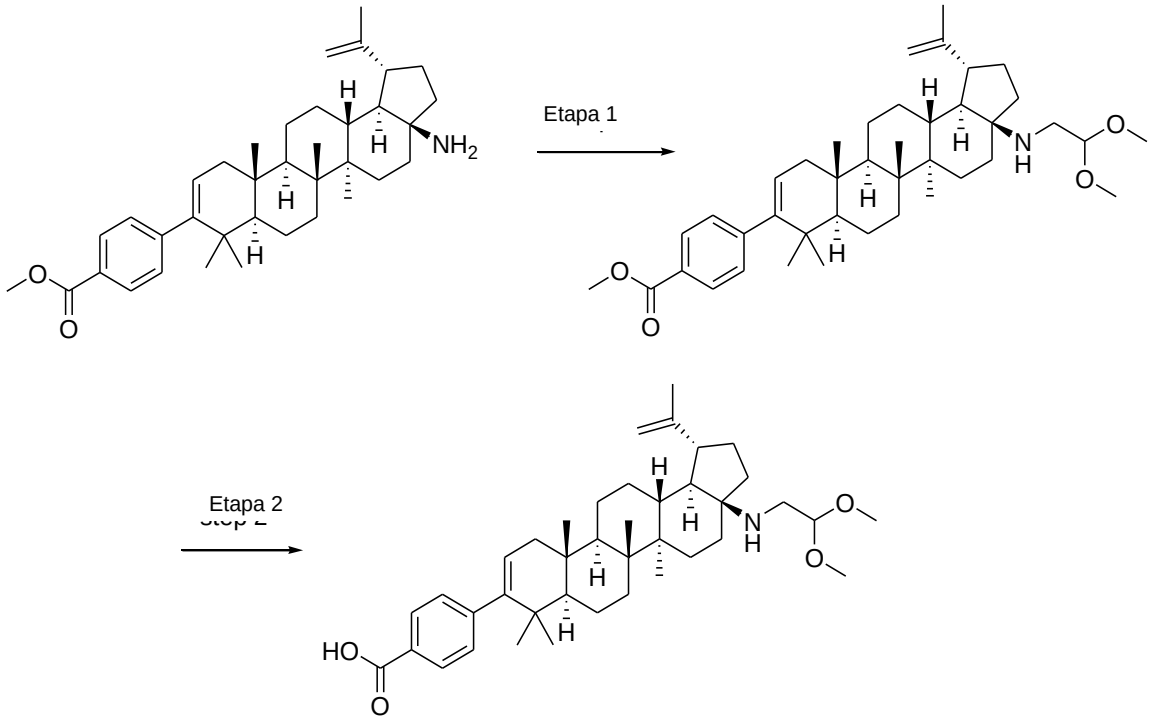
Etapa 2. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(furan-2-ilmetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(furan-2-

ilmetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (31 mg, 0.050 mmol) en 1,4-dioxano (2 mL), se agregó NaOH 1 N (0.248 mL, 0.248 mmol). La mezcla se calentó a 85 °C durante 22 horas, luego se enfrió a temperatura ambiente. El producto crudo se purificó mediante HPLC preparativa. Las fracciones que contenían el producto previsto se combinaron y concentraron a presión reducida para producir el compuesto del título (19.3 mg, 0.030 mmol, 60.5 % de rendimiento) como una película transparente. LCMS: m/e 610.69 $(M+H)^+$, 2.35 min (método 2). ^{1}H NMR (400 MHz, *CLOROFORMO-d*) d ppm 8.00 (d, *J*= 7.78 Hz, 2 H), 7.37 (d, *J*= 1.00 Hz, 1 H), 7.23 (d, *J*= 7.78 Hz, 2 H), 6.33 (dd, *J*= 3.14, 1.88 Hz, 1 H), 6.21 (d, *J*= 2.76 Hz, 1 H), 5.53 (br. s., 1 H), 5.29-5.34 (m, 1 H), 4.72 (d, *J*= 1.76 Hz, 1 H), 4.60 (s, 1 H), 3.67 (s, 2 H), 2.64 (td, *J*= 10.85, 5.40 Hz, 1 H), 1.71 (s, 3 H), 1.10-1.15 (m, 3 H), 1.01 (s, 3 H), 1.00 (s, 3 H), 0.97-2.18 (m, 22 H), 0.96 (s, 6 H).

Ejemplo 156

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2,2-dimetoxietilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2,2-dimetoxietilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo, HCl (0.9 g, 1.551 mmol) en DCM (Volumen: 15 mL), se agregaron una solución de 1,1-dimetilacetal de glioxal (45 % en MTBE) (0.498 mL, 1.939 mmol), ácido acético (0.178 mL, 3.10 mmol) y

triacetoxiborohidruro de sodio (0.493 g, 2.326 mmol). La mezcla se agitó a temperatura ambiente. Después de 4 h de agitación, se agregaron una solución de 0.5 mL de 1,1-dimetilacetal glioxal (45 % en MTBE) junto con 0.5 g de triacetoxiborohidruro de sodio adicionales. Después de un total de 7 h de agitación, la mezcla se diluyó con 25 mL de $NaHCO_3$ saturado y se extrajo con diclorometano (3 x 25 mL). Las capas orgánicas combinadas se secaron con Na_2SO_4. El agente de secado se retiró mediante filtración, y el filtrado se concentró a presión reducida. El residuo se adsorbió en gel de sílice y se purificó mediante cromatografía instantánea usando un gradiente de 0-10 % de EtOAc en hexanos para obtener el compuesto del título (0.67 g, 1.060 mmol, 68.4 % de rendimiento) como una espuma blanca. LCMS: m/e 632.75 $(M+H)^+$, 2.45 min (método 11).

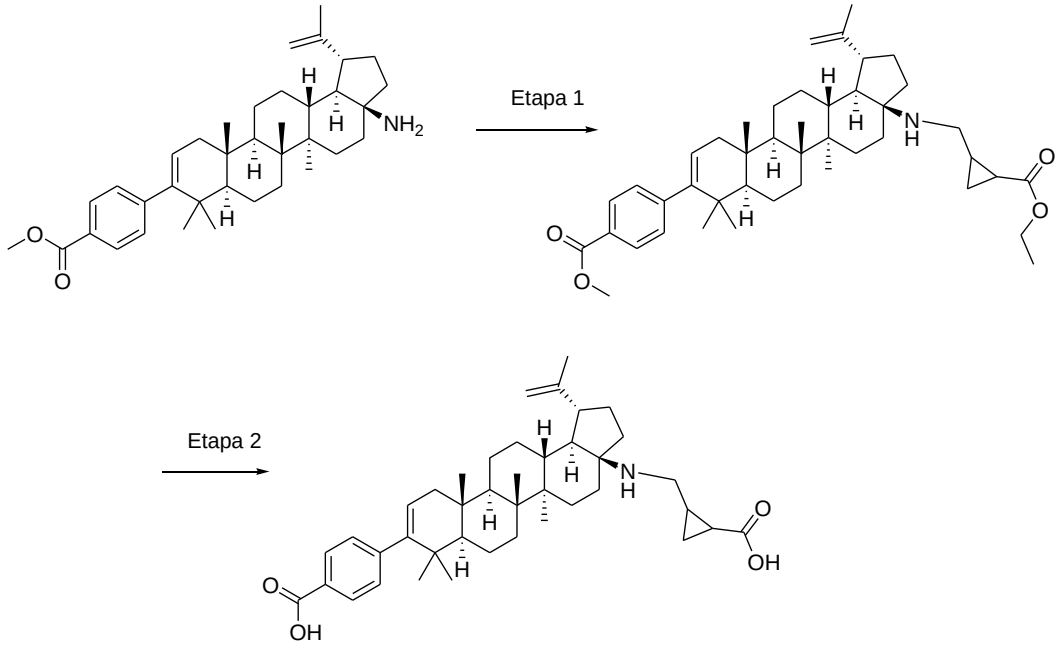
Etapa 2. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2,2-dimetoxietilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2,2-dimetoxietilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de

metilo (0.025 g, 0.040 mmol) en 1,4-dioxano (1 mL), se agregó NaOH (1 N) (0.198 mL, 0.198 mmol). La mezcla se calentó a 85 °C. Después de 6 h de calentamiento, la mezcla se enfrió a temperatura ambiente, la mezcla de reacción se diluyó con MeOH y se purificó mediante HPLC preparativa. Las fracciones que contenían el producto previsto se combinaron y concentraron a presión reducida para producir el compuesto del título (17 mg, 0.026 mmol, 66.1 % de rendimiento) como una película transparente. LCMS: m/e 618.8 $(M+H)^+$, 2.28 min (método 11). ^{1}H NMR (500 MHz, *Cloroformo-d*) d ppm 7.99 (d, *J*= 7.93 Hz, 2 H), 7.20 (d, *J*= 7.93 Hz, 2 H), 5.28 (d, *J*= 4.88 Hz, 1 H), 5.12 (br. s., 1 H), 4.72 (s, 1 H), 4.58 (s, 1 H), 4.53 (t, *J*= 5.49 Hz, 1 H), 3.44 (s, 3 H), 3.41 (s, 3 H), 2.64-2.74 (m, 2 H), 2.60 (dd, *J*= 11.44, 6.56 Hz, 1 H), 1.97-2.13 (m, 2 H), 1.86-1.95 (m, 2 H), 1.81 (dd, *J*= 12.51, 8.24 Hz, 1 H), 1.68 (s, 3 H), 1.11 (s, 3 H), 0.98 (s, 3 H), 0.97 (br. s., 3 H), 0.95-1.72 (m, 17 H), 0.93 (br. s., 6 H).

Ejemplo 157

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-carboxiciclopropil)metilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(etoxicarbonil)ciclopropil)metilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (30 mg, 0.055 mmol) en DCE (0.5 mL), se agregaron 2-formil-1-ciclopropancarboxilato de etilo (9.13 mL, 0.069 mmol) e isopropóxido de titanio(IV) (0.020 mL, 0.069 mmol). La mezcla

se agitó a temperatura ambiente durante 1 h, y se agregó triacetoxiborohidruro de sodio (23.38 mg, 0.110 mmol). Después de agitar la mezcla durante 16.25 h, se agregaron 2-formil-1-ciclopropancarboxilato de etilo (9.13 mL, 0.069 mmol) y triacetoxiborohidruro de sodio (23.38 mg, 0.110 mmol) de manera adicional, y la mezcla se volvió a agitar a temperatura ambiente durante 24 h. La mezcla de reacción se cargó directamente en una columna de gel de sílice y se purificó mediante cromatografía instantánea usando un gradiente de 0-25 % de EtOAc en hexanos. Las fracciones que contenían el producto previsto se combinaron y concentraron a presión reducida para producir 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(etoxicarbonil)ciclopropil)metilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (33 mg, 0.049 mmol, 89 % de rendimiento). LCMS: m/e 670.8 $(M+H)^+$, 2.47 min (método 11).

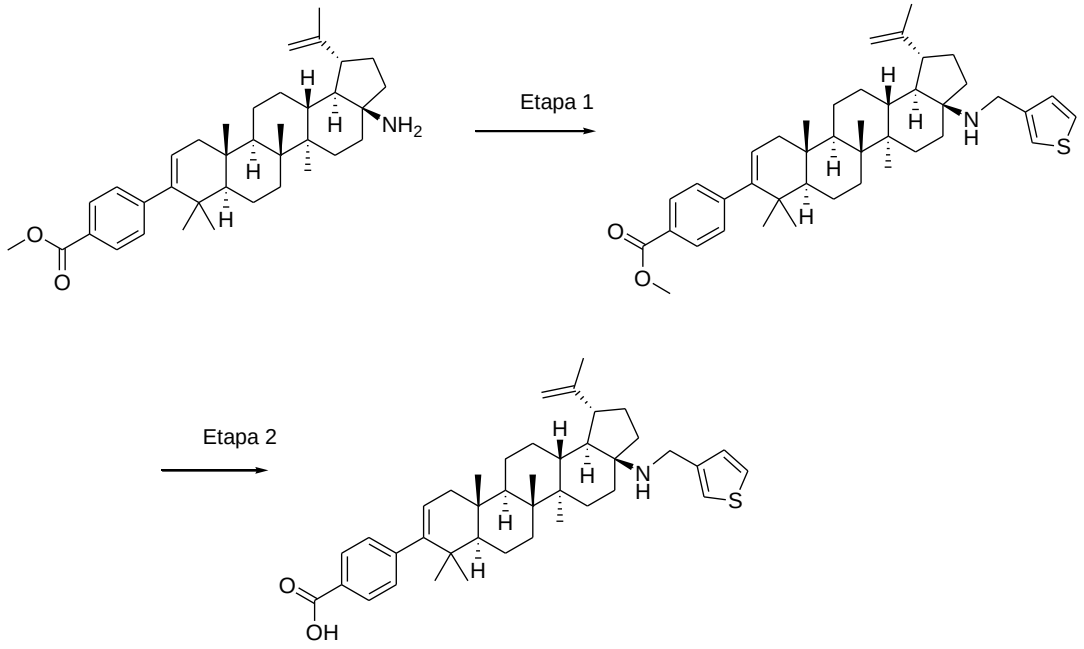
Etapa 2. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-carboxiciclopropil)metilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(etoxicarbonil)ciclopropil)metilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (33 mg, 0.049 mmol) en 1,4-dioxano (2 mL), se agregó NaOH (1 N) (0.246 mL, 0.246 mmol). La mezcla se calentó a 85 °C durante 22 horas, luego se enfrió a temperatura ambiente. Se agregaron 0.25 mL de NaOH 1 N a la mezcla, y se volvió a calentar a 85 °C. Después de agitar la mezcla durante el fin de semana, la mezcla de reacción se purificó mediante HPLC preparativa. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida. La 1H RMN mostró que aún había impurezas; por lo tanto, la mezcla se purificó por segunda vez mediante HPLC preparativa. Las fracciones que contenían el producto se combinaron y concentraron a presión reducida para producir el compuesto del título (8.3 mg, 0.012 mmol, 24.15 % de rendimiento) como un sólido blanco. LCMS: m/e 628.6 $(M+H)^+$, 1.66 min (método 2).

Ejemplo 158

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(tiofen-3-ilmetilamino)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(tiofen-3-ilmetilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (30 mg, 0.055 mmol) en DCE (0.5 mL), se agregaron 3-

tiofencarboxaldehído (7.73 mg, 0.069 mmol) e isopropóxido de titanio (IV) (0.020 mL, 0.069 mmol). La mezcla se agitó a temperatura ambiente durante 1 h, y se agregó triacetoxiborohidruro de sodio (23.38 mg, 0.110 mmol). La mezcla se agitó durante 18 h a temperatura ambiente. La mezcla de reacción se cargó directamente en una columna de gel de sílice y se purificó mediante cromatografía instantánea usando un gradiente de 0-25 % de EtOAc en hexanos. Las fracciones que contenían el producto previsto se combinaron y concentraron a presión reducida para producir el compuesto del título (32 mg, 0.05 mmol, 91 % de rendimiento). LCMS: m/e 640.6 $(M+H)^+$, 2.13 min (método 2).

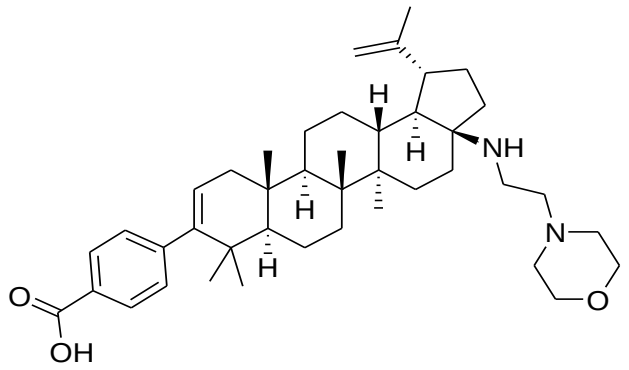
Etapa 2. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(tiofen-3-ilmetilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(tiofen-3-ilmetilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (32 mg, 0.050 mmol) en dioxano (1 mL), se agregó NaOH (1N) (0.250 mL, 0.250 mmol). La mezcla se calentó a 85 °C durante 15 h. La mezcla se enfrió a temperatura ambiente

y se purificó mediante HPLC preparativa para obtener el compuesto del título (18 mg, 0.027 mmol, 53.5 % de rendimiento) como un sólido blanco. LCMS: m/e 626.5 $(M+H)^+$, 1.82 min (método 2). ^{1}H NMR (400 MHz, *Cloroformo-d*) δ ppm 8.00 (2 H, d, *J*= 8.3 Hz), 7.30 (1 H, dd, *J*= 4.8, 3.0 Hz), 7.24 (2 H, d, *J*= 8.3 Hz), 7.20 (1 H, d, *J*= 2.0 Hz), 7.12 (1 H, dd, *J*= 5.0, 1.0 Hz), 5.30-5.34 (1 H, m), 4.72 (1 H, d, *J*= 1.8 Hz), 4.61 (1 H, s), 2.61 (1 H, td, *J*= 10.7, 5.4 Hz), 1.89-2.17 (5 H, m), 1.77-1.88 (1 H, m), 1.72 (3 H, s), 1.14 (3 H, s), 1.02 (3 H, s), 1.00 (3 H, s), 0.94-1.74 (18 H, m), 0.96 (6 H, s).

Ejemplo 159

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-morfolinoetilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

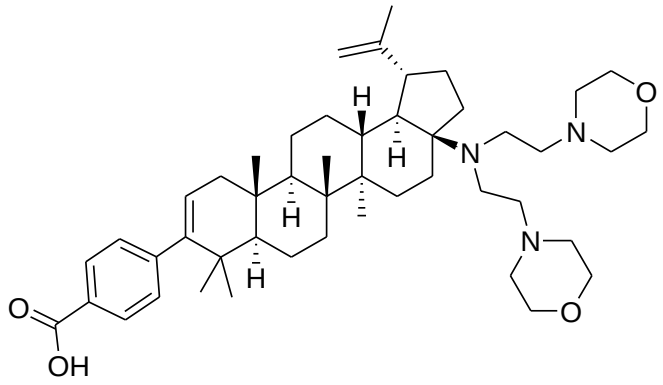


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de

ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimetilamino)-2-oxoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando clorhidrato de 4-(2-cloroetil)morfolina como el agente alquilante en la Etapa 1. El producto se aisló como un sólido blanco (65 mg, 49.4 %). LCMS: m/e 643.6 (MH^+), 2.35 min (método 13). ^{1}H NMR (400 MHz, *MeOD*) δ ppm 7.95 (m, *J*= 8.3 Hz, 2 H), 7.24 (m, *J*= 8.3 Hz, 2 H), 5.31 (d, *J*= 4.8 Hz, 1 H), 4.86 (s, 1 H), 4.74 (s, 1 H), 3.82-3.99 (m, 4 H), 3.37-3.58 (m, 4 H), 3.21 (d, *J*= 4.5 Hz, 2 H), 3.19 (br. s., 2 H), 2.67-2.86 (m, 1 H), 2.02-2.26 (m, 5 H), 1.83-1.90 (m, 1 H), 1.64-1.81 (m, 8 H), 1.45-1.64 (m, 7 H), 1.34-1.45 (m, 2 H), 1.27-1.34 (m, 1 H), 1.15-1.27 (m, 4 H), 1.12 (s, 3 H), 1.04 (s, 3 H), 0.99 (s, 3 H), 0.93 (s, 3 H).

Ejemplo 160

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(bis(2-morfolinoetil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

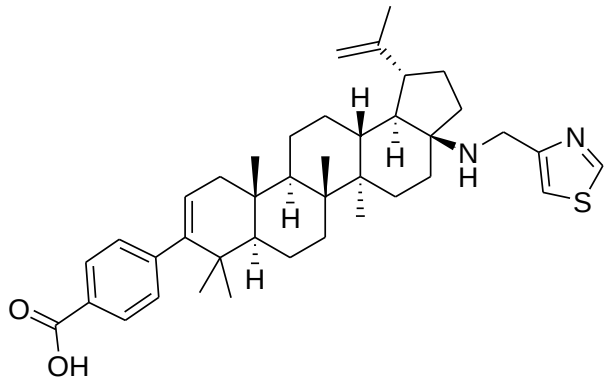


El compuesto del título se obtuvo como un subproducto en la preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-morfolinoetilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico. El producto se aisló como un sólido blanco (20 mg, 12.2 %). LCMS: m/e 756.7 (MH^+), 2.41 min (método 13). ^{1}H NMR (400 MHz, *MeOD*) δ ppm 7.95 (m, *J*= 8.3 Hz, 2 H), 7.24 (m, *J*= 8.3 Hz, 2 H), 5.32 (d, *J*= 4.8 Hz, 1 H), 4.86 (s, 1 H), 4.73 (s, 1 H), 4.19 (t, *J*= 7.5 Hz, 2 H), 4.02-4.14 (m, 6 H), 3.88 (t, *J*= 4.4 Hz, 4 H), 3.70-3.84 (m, 4 H), 3.57 (br. s., 2 H), 3.42-3.51 (m, 2 H), 2.96-3.19 (m, 4 H), 2.79 (br. s., 1 H), 2.01-2.26 (m, 5 H), 1.87-1.96 (m, 1 H), 1.68-1.82 (m, 6 H), 1.46-1.68 (m, 8 H), 1.26-1.45 (m, 4 H), 1.17-1.26 (m, 4 H), 1.13 (s, 3 H), 1.05 (s, 3 H), 0.99 (s, 3 H), 0.97 (s, 3 H).

Ejemplo 161

Preparación ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-

pentametil-1-(prop-1-en-2-il)-3a-(tiazol-4-ilmetilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

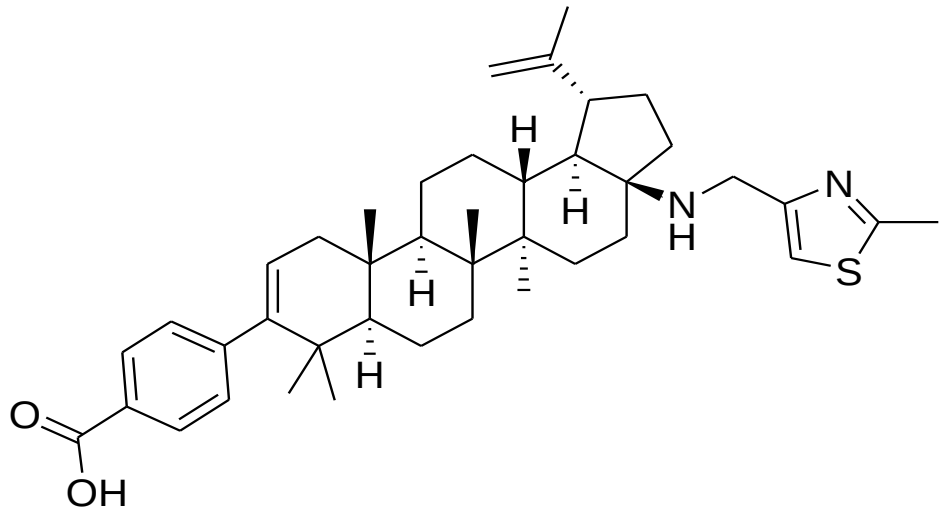


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimetilamino)-2-oxoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando 4-(clorometil)tiazol como el agente alquilante en la Etapa 1. MS: m/e 627.5 $(M+H)^+$, 1.56 min (método 12). ^{1}H NMR (400 MHz, *CLOROFORMO-d*) δ ppm 0.95 (s., 3 H) 0.96 (s, 3 H) 1.01 (s, 3 H) 1.10 (s, 3 H) 1.21 (s, 3 H) 1.72 (s, 3 H) 0.89-1. 83 (m, 16 H) 1.84-2.05 (m, 3 H) 2.07-2.22 (m, 1 H) 2.13 (dd, *J*= 17.07, 6.53 Hz, 1 H) 2.22-2.32 (m, 1 H) 2.33-2.49 (m, 1 H) 4.24 (d, *J*= 14.05 Hz, 1 H) 4.70 (s, 1 H) 4.72 (d, *J*= 13.55 Hz, 1 H) 4.81 (s, 1 H) 5.31 (dd, *J*= 6.02, 1.51 Hz, 1 H) 7.24 (d, *J*= 8.28 Hz, 2 H) 7.59 (s, 1 H) 8.00 (d, *J*= 8.28 Hz, 2 H)

8.83 (s, 1 H).

Ejemplo 162

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-metiltiazol-4-il)metilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

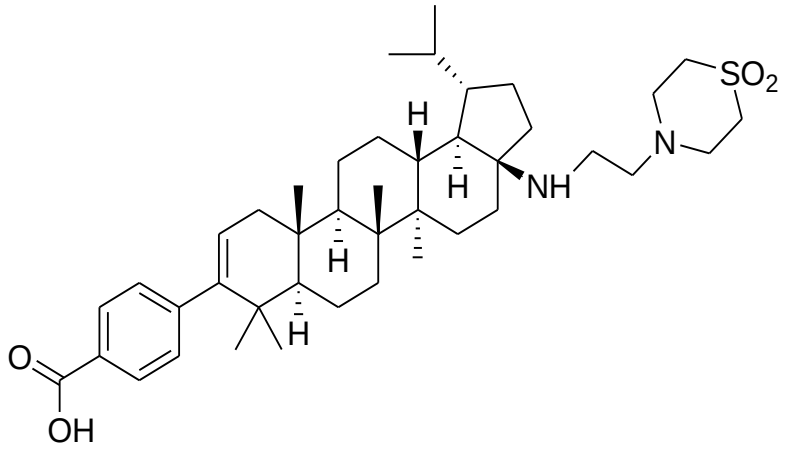


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimetilamino)-2-oxoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando clorhidrato de 4-(clorometil)-2-metiltiazol como el agente alquilante en la Etapa 1. MS: m/e 641.5 $(M+H)^+$, 1.56 min (método 12). ^{1}H NMR (400 MHz, *Cloroformo-d*) δ ppm 0.96 (s, 3

H) 0.97 (s, 3 H) 1.02 (s, 3 H) 1.10 (s, 3 H) 1.26 (s, 3 H) 1.71 (s, 3 H) 0.88-1.83 (m, 16 H) 1.89-2.04 (m, 3 H) 2.08-2.21 (m, 1 H) 2.14 (dd, *J*= 17.19, 6.15 Hz, 1 H) 2.22-2.30 (m, 1 H) 2.33-2.45 (m, 1 H) 2.68 (s, 3 H) 4.09 (d, *J*= 13.05 Hz, 1 H) 4.64 (d, *J*= 12.80 Hz, 1 H) 4.69 (s, 1 H) 4.80 (s, 1 H) 5.32 (d, *J*= 4.52 Hz, 1 H) 7.24 (d, *J*= 8.28 Hz, 2 H) 7.28 (s, 1 H) 8.00 (d, *J*= 8.28 Hz, 2 H).

Ejemplo 163

Preparación de ácido 4-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-tiomorfolinil)etil)amino)-1-isopropil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

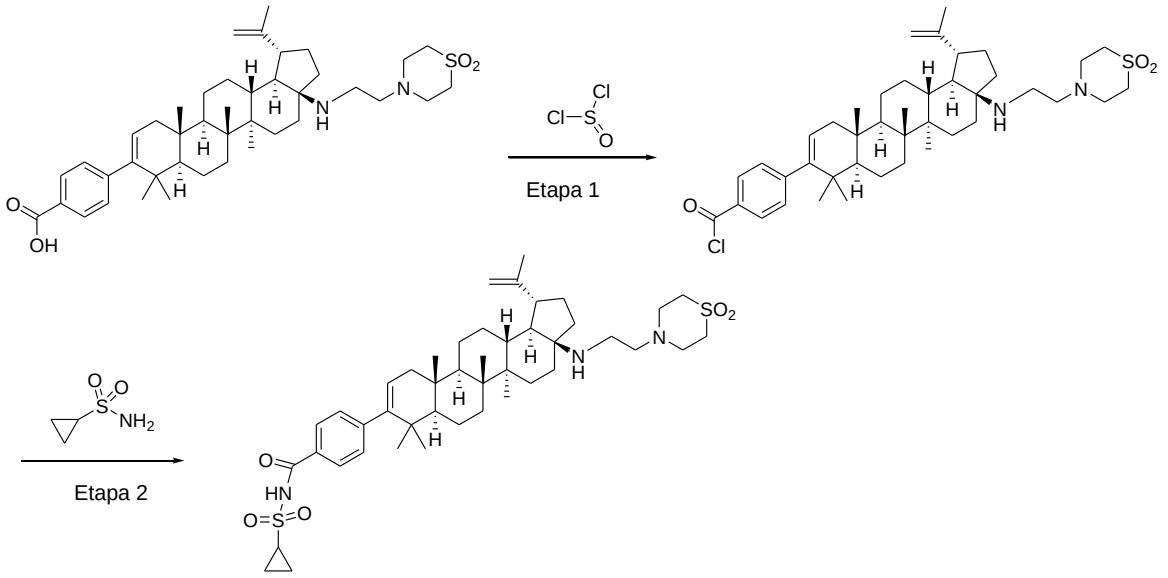


Una mezcla de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-tiomorfolinil)etil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico (100 mg, 0.145 mmol) y 10 % Pd/C (90 mg, 0.087 mmol) en metanol (5 mL) y acetato de etilo (5 mL) se cargó en un reactor agitador PARR y se trató con hidrógeno durante 25 horas a 40 psi a temperatura ambiente. La mezcla de reacción se filtró a través de una almohadilla de Celite para retirar el catalizador. El filtrado se purificó mediante HPLC para obtener el compuesto del título como un sólido blanco (5.6 mg, 28 %). LCMS: m/e 693.46 $(M+H)^+$, 2.46 min (método 10). ^{1}H NMR (500 MHz, *Ácido acético d4*) δ ppm 8.04 (d, *J*= 8.2 Hz, 2 H), 7.31 (d, *J*= 8.2 Hz, 2 H), 5.39 (d, *J*= 4.6 Hz, 1 H), 3.50-3.36 (m, 1 H), 3.36-3.21 (m, 6 H), 3.21 – 2.98 (m, 5 H), 2.31 – 1.29 (m, 24 H), 1.29 (s, 3 H), 1.13 (s, 6 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.94 (d, *J*= 6.7 Hz, 3 H), 0.86 (d, *J*= 6.7 Hz, 3 H).

Ejemplo 164

Preparación de *N*-(ciclopropilsulfonil)-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-tiomorfolinil)etil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzamida.



Etapa 1. Preparación de cloruro de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-tiomorfolinil)etil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoilo.

Una mezcla de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-tiomorfolinil)etil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico (200 mg, 0.289 mmol) y cloruro de tionilo (0.211 mL, 2.89 mmol) en dicloroetano (5 mL) se sometió a reflujo durante 30 h. La mezcla de reacción se concentró a presión reducida para

obtener el compuesto del título como un sólido blanco (150 mg, 73 %). LCMS: m/e 705.46 $(M-Cl+OMe+H)^+$, 3.0 min (método 10).

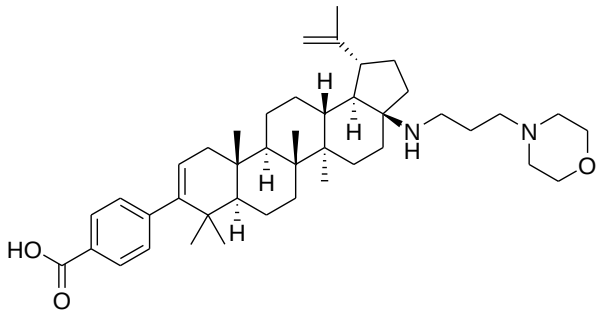
Etapa 2. Preparación de *N*-(ciclopropilsulfonil)-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-tiomorfolinil)etil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzamida

Una mezcla de cloruro de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxido-4-tiomorfolinil)etil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoilo (30 mg, 0.042 mmol), ciclopropansulfonamida (6.15 mg, 0.051 mmol), base de Hunig (0.022 mL, 0.127 mmol) y DMAP (2.58 mg, 0.021 mmol) en diclorometano (1 mL) se agitó durante 16 h a temperatura ambiente. La mezcla de reacción cruda se purificó mediante HPLC preparativa para obtener el compuesto del título como un sólido blanco (4 mg, 11 %). LCMS: m/e 794.53 $(M+H)^+$, 2.44 min (método 10). ^{1}H NMR (500 MHz, *Ácido acético d4*) δ ppm 7.94 (d, *J*= 8.5 Hz, 2 H), 7.32 (d, *J*= 8.2 Hz, 2 H), 5.38 (d, *J*= 4.6 Hz, 1 H), 4.84 (s, 1 H), 4.74 (s, 1 H), 3.56-3.39 (m, 1 H), 3.38-3.21 (m, 7 H), 3.21-3.11 (m, 3 H), 3.11-

3.03 (m, 2 H), 3.01 – 2.89 (m, 1 H), 2.41 – 1.16 (m, 26 H), 1.76 (s, 3 H), 1.29 (s, 3 H), 1.15 (s, 3 H), 1.11 (s, 3 H), 1.03 (s, 3 H), 1.00 (s, 3 H).

Ejemplo 165

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(3-morfolinopropilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

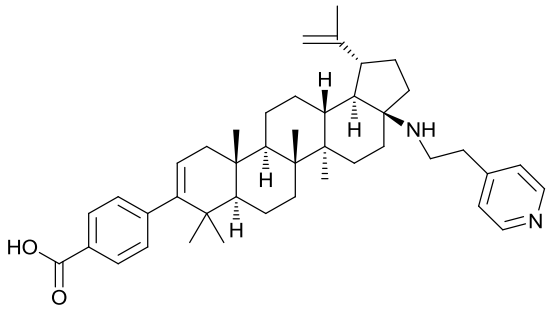


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimetilamino)-2-oxoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando clorhidrato de 4-(3-cloropropil)morfolina como el reactivo alquilante en la Etapa 1. El producto se aisló como un sólido blanco (60 mg, 48.1 %). LCMS: m/e 657.55 $(M+H)^+$, 2.24 min (método 13). ^{1}H NMR (400MHz, METANOL-d_4) δ 7.95 (d, *J*= 8.3 Hz,

2H), 7.26 (d, *J*= 8.3 Hz, 2H), 5.33 (d, *J*= 4.5 Hz, 1H), 4.88 (s, 1H), 4.75 (s, 1H), 3.97 (m, 4H), 3.30-3.04 (m, 8H), 2.85-2.66 (m, 1H), 2.46-2.24 (m, 2H), 2.24-1.85 (m, 7H), 1.82-1.65 (m, 7H), 1.65-1.45 (m, 7H), 1.45-1.26 (m, 4H), 1.22 (s, 3H), 1.14 (s, 3H), 1.08 (s, 3H), 1.00 (s, 3H), 0.98 (s, 3H)

Ejemplo 166

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-((2-(piridin-4-il)etil)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

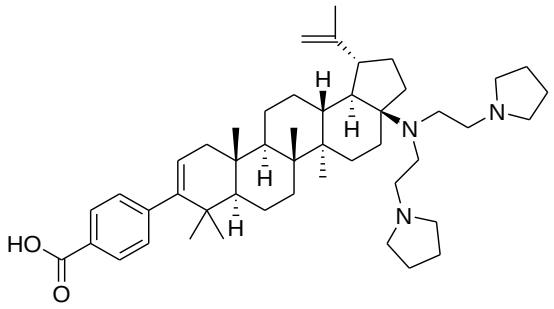


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimetilamino)-2-oxoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando 4-(2-cloroetil)piridina como el reactivo alquilante en la Etapa

1. El producto se aisló como un sólido blancuzco (10 mg, 2.9 %). LCMS: m/e 635.40 $(M+H)^+$, 2.31 min (método 13). ^1H NMR (400MHz, METANOL-d_4) δ 8.83 (d, *J*= 5.8 Hz, 2H), 8.06 (d, *J*= 6.0 Hz, 2H), 7.95 (d, *J*= 8.5 Hz, 2H), 7.25 (d, *J*= 8.3 Hz, 2H), 5.33 (d, *J*= 4.5 Hz, 1H), 4.90 (s, 1H), 4.76 (s, 1H), 3.57-3.46 (m, 4H), 2.86-2.75 (m, 1H), 2.27-2.08 (m, 5H), 2.05-1.89 (m, 2H), 1.79 (s, 3H), 1.85-1.67 (m, 4H), 1.66-1.49 (m, 7H), 1.45-1.23 (m, 4H), 1.21 (s, 3H), 1.14 (s, 3H), 1.09 (s, 3H), 1.00 (s, 3H), 0.98 (s, 3H).

Ejemplo 167

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(bis(2-(pirrolidin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

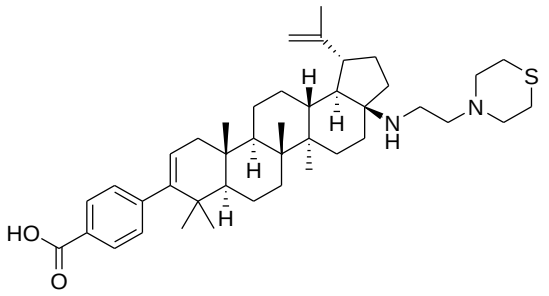


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimetilamino)-2-oxoetilamino)-5a,5b,8,8,11a-pentametil-1-

(prop-1-en-2-il)-
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando clorhidrato de 1-(2-cloroetil)pirrolidina como el reactivo alquilante en la Etapa 1. El producto se aisló como un sólido blanco (10 mg, 2.57 %). LCMS: m/e 724.52 $(M+H)^+$, 1.43 min (método 15). ^{1}H NMR (400MHz, METANOL-d) δ 7.88 (d, *J*= 8.0 Hz, 2H), 7.19 (d, *J*= 8.0 Hz, 2H), 5.26 (d, *J*= 4.8 Hz, 1H), 4.79 (s, 1H), 4.66 (s, 1H), 4.03-3.86 (m, 4H), 3.86-3.62 (m, 6H), 3.59-3.29 (m, 6H), 2.81-2.58 (m, 1H), 2.26 (br. s., 4H), 2.21-1.88 (m, 9H), 1.82 (d, *J*= 13.1 Hz, 1H), 1.73-1.62 (m, 5H), 1.62-1.40 (m, 9H), 1.40-1.19 (m, 4H), 1.13 (s, 4H), 1.06 (s, 3H), 1.01 (s, 3H), 0.93 (s, 3H), 0.91 (s, 3H),

Ejemplo 168

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(2-tiomorfolinoetilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

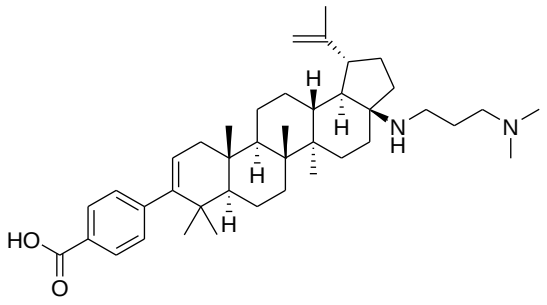


El compuesto del título se preparó de acuerdo

con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimetilamino)-2-oxoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando clorhidrato de 4-(2-cloroetil)tiomorfolina (preparado como se describe en WO 2009058859) como el reactivo alquilante en la Etapa 1. El producto se aisló como un sólido blanco (3 mg, 0.85 %). LCMS: m/e 659.37 $(M+H)^+$, 2.38 min (método 13). ^1H NMR (400MHz, Cloroformo-d) δ 8.00 (d, *J*= 8.3 Hz, 2H), 7.21 (d, *J*= 8.5 Hz, 2H), 5.32-5.19 (m, 1H), 4.77 (s, 1H), 4.65 (s, 1H), 3.11-2.98 (m, 1H), 2.89 (m, 5H), 2.75 (m, 5H), 2.67-2.57 (m, 1H), 2.31-2.16 (m, 1H), 2.14-1.85 (m, 6H), 1.71 (s, 7H), 1.59-1.40 (m, 6H), 1.38-1.15 (m, 8H), 1.08-0.96 (m, 10H), 0.94 (s, 3H)

Ejemplo 169

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(dimetilamino)propilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

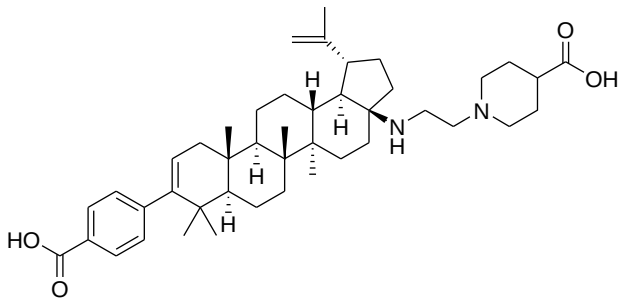


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimetilamino)-2-oxoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando clorhidrato de 3-cloro-N,N-dimetilpropan-1-amina como el reactivo alquilante en la Etapa 1. El producto se aisló como un sólido blanco (3 mg, 0.85 %). LCMS: m/e 615.75 $(M+H)^+$, 2.24 min (método 13). ^{1}H NMR (400MHz, METANOL-d_4) δ 7.95 (d, *J*= 8.0 Hz, 2H), 7.25 (d, *J*= 8.0 Hz, 2H), 5.34 (s, 1H), 4.89 (s, 1H), 4.75 (s, 1H), 3.58-3.36 (m, 2H), 3.26 (br. s., 8H), 2.78 (d, *J*= 7.5 Hz, 1H), 2.51-2.26 (m, 3H), 2.26-1.97 (m, 7H), 1.92 (m, 1H), 1.78 (m, 6H), 1.63-1.47 (m, 6H), 1.45-1.36 (m, 2H), 1.32-1.18 (m, 5H), 1.14 (s, 3H), 1.08 (s, 3H), 1.00 (s, 3H), 0.98 (s, 3H)

Ejemplo 170

Preparación de ácido 1-(2-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-carboxifenil)-

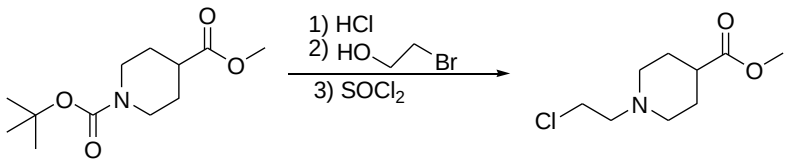
5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-il)amino)etil)piperidin-4-carboxílico



El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimetilamino)-2-oxoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando clorhidrato de 1-(2-cloroetil)piperidin-4-carboxilato de metilo (preparado como se describe más adelante) como el reactivo alquilante en la Etapa 1. El producto se aisló como un sólido blanco (8 mg, 83 %). LCMS: m/e 685.6 $(M+H)^+$, 2.33 min (método 10). ^{1}H NMR (400MHz, METANOL-d_4) δ 7.94 (d, *J*= 8.3 Hz, 2H), 7.23 (d, *J*= 8.3 Hz, 2H), 5.31 (d, *J*= 4.5 Hz, 1H), 4.86 (s, 1H), 4.74 (s, 1H), 3.48-3.36 (m, 5H), 3.12-2.88 (m, 2H), 2.79-2.69 (m 1H), 2.68-2.60 (m, 1H), 2.24-2.11 (m, 4H), 2.11-2.00 (m, 4H), 1.97-1.81 (m, 3H), 1.77 (s, 3H), 1.81-1.71 (m, 2H), 1.70-1.46 (m, 10H), 1.45-1.27 (m, 4H), 1.21 (s, 3H),

1.12 (s, 3H), 1.06 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H).

Preparación de 1-(2-cloroetil)piperidin-4-carboxilato de metilo

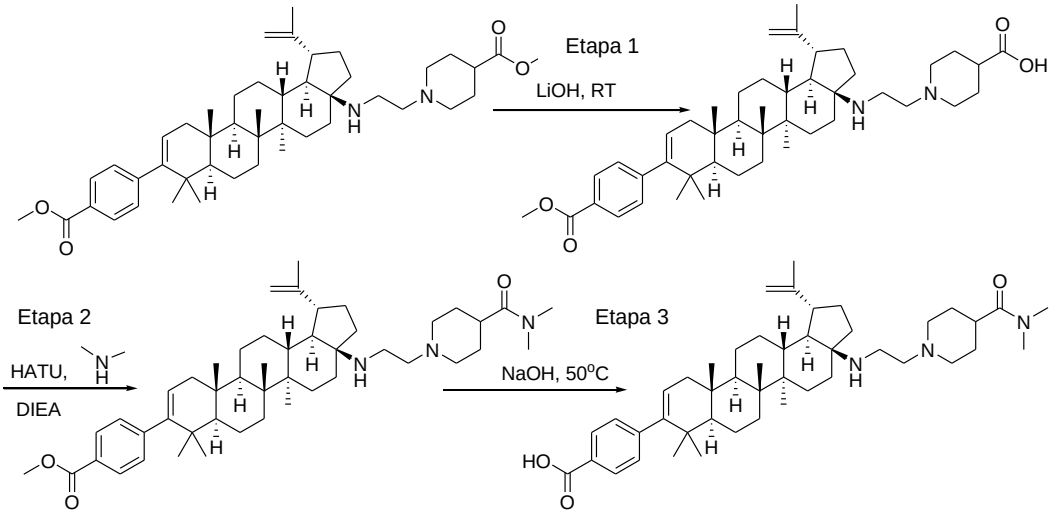


A una solución de 4-metilpiperidin-1,4-dicarboxilato de 1-terc-butilo (5.4 g, 22.19 mmol) en éter, se agregó cloruro de hidrógeno (27.7 mL, 111 mmol) en dioxano. La solución transparente resultante se agitó durante 4 horas. Se observaron burbujas y precipitados blancos. Luego, el solvente se retiró y se secó al vacío. El residuo se suspendió en acetonitrilo (50 mL), se agregó 2-bromoetanol (1.567 mL, 22.19 mmol) y, luego, K_2CO_3 en polvo (14.72 g, 107 mmol). Después de que la mezcla de reacción se sometió a reflujo durante 18 horas, se filtró y se concentró. El residuo se volvió a disolver en agua (50.0 mL) y se extrajo con acetato de etilo (50.0 mL). La capa orgánica se secó en sulfato de sodio. Después de la filtración, el solvente se retiró al vacío. El residuo se disolvió en DCE (50.0 mL) antes de que se agregara dicloruro sulfuroso (2.428 mL, 33,3 mmol). La mezcla de reacción se sometió a reflujo durante 3 horas; luego, todos los volátiles se retiraron al vacío, el sólido resultante se suspendió en éter, luego se filtró y se lavó con éter (50.0 mL), se volvió a suspender en acetato de

etilo y se neutralizó con bicarbonato de sodio. Las capas orgánicas se recolectaron y se secaron con sulfato de sodio para obtener 1-(2-cloroetil)piperidin-4-carboxilato de metilo (1 g, 4.86 mmol, 21.91 % de rendimiento) como un aceite marrón. ^{1}H NMR (400MHz, Cloroformo-d) δ 3.70 (s, 3H), 3.61 (t, *J*= 7.0 Hz, 2H), 2.97-2.86 (m, 2H), 2.75 (t, *J*= 7.2 Hz, 2H), 2.40-2.27 (m, 1H), 2.19 (m, 2H), 2.01-1.88 (m, 2H), 1.87-1.72 (m, 2H).

Ejemplo 171

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4-(dimetilcarbamoil)piperidin-1-il)etilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



Etapa 1. A una solución de 1-(2-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-

(metoxicarbonil)fenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-ilamino)etil)piperidin-4-carboxilato de metilo (40 mg) en dioxano (1 mL), se agregó hidróxido de litio (2.7 mg, 0.112 mmol) en agua (1 mL). Se observó un precipitado blanco. La mezcla se agitó a 25 °C durante 3 horas. El producto deseado se observó a m/e 699.7 $(M+H)^+$, 2.703 min, método 10. La mezcla de reacción se neutralizó con HCl 1 N a pH~4 y se diluyó con cloruro de metileno (10 mL). Luego, las capas orgánicas se recolectaron, se secaron en sulfato de sodio y se filtraron. Después de retirar el solvente, el producto crudo se obtuvo como un aceite (40 mg, ~ 100 %) que se usó sin purificación adicional.

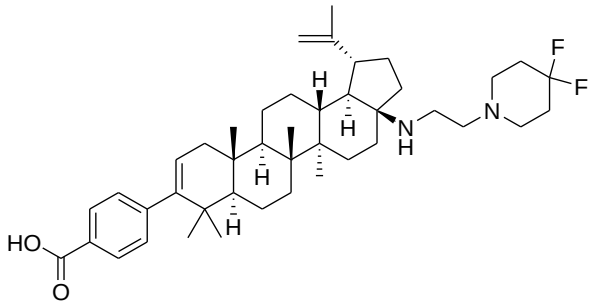
Etapa 2. A una solución de ácido 1-(2-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(metoxicarbonil)fenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-il)amino)etil)piperidin-4-carboxílico (40 mg, 0.057 mmol) en CH_2Cl_2 (5 ml) a temperatura ambiente, se agregaron dimetilamina (7.6 mg, 0.17 mmol) y HATU (65 mg, 0.18 mmol) y, luego, DIEA (29 mg, 0.23 mmol). La mezcla se agitó durante 3 horas a temperatura ambiente. La mezcla resultante se diluyó con acetato de etilo y se lavó con agua. Las capas orgánicas

se secaron en sulfato de sodio. EL producto crudo se obtuvo después de retirar el solvente como un sólido blanco (40 mg, ~ 100 %) que se usó sin purificación adicional

Etapa 3. Se preparó ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4-(dimetilcarbamoil)piperidin-1-il)etilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico de acuerdo con la etapa 2 del método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(dimetilamino)-2-oxoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico. El producto se aisló como un sólido blanco (9 mg, 23.0 %). LCMS: m/e 712.64 $(M+H)^+$, 2.265 min (método 11). ^{1}H NMR (400MHz, METANOL-d_4) δ 7.95 (d, *J*= 8.3 Hz, 2H), 7.25 (d, *J*= 8.3 Hz, 2H), 5.33 (d, *J*= 4.5 Hz, 1H), 4.87 (s, 1H), 4.74 (s, 1H), 3.65-3.38 (m, 6H), 3.16 (s, 3H), 3.05 (m, 2H), 2.96 (s, 3H), 2.75 (m, 1H), 2.23-1.85 (m, 11H), 1.82-1.74 (m, 6H), 1.70-1.48 (m, 9H), 1.44-1.28 (m, 3H), 1.22 (m, 4H), 1.13 (s, 3H), 1.08 (s, 3H), 1.00 (s, 3H), 0.98 (s, 3H),

Ejemplo 172

Preparación de ácido 4-(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-(4,4-difluoropiperidin-1-il)etilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

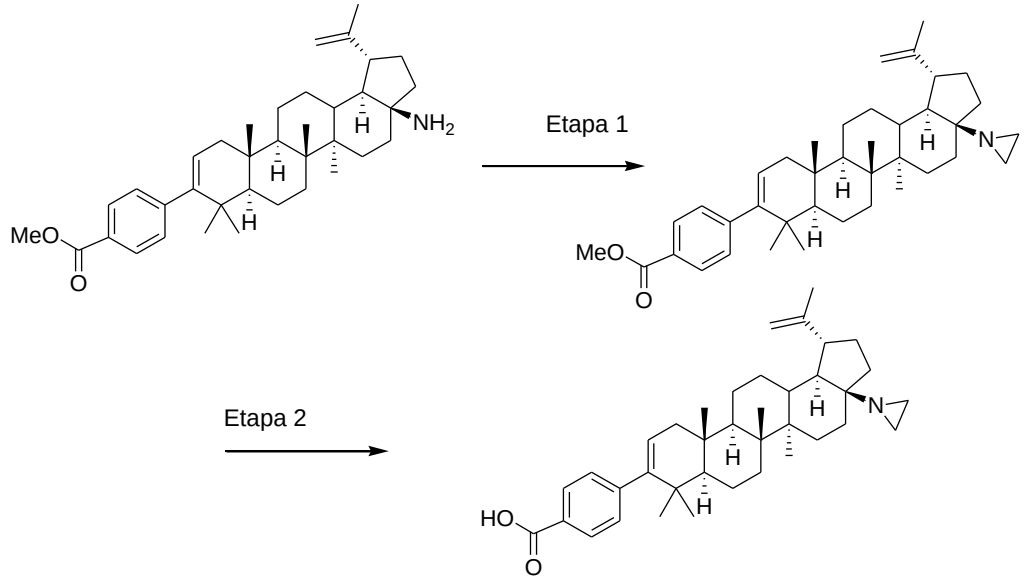


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(terc-butoxicarbonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando clorhidrato de 4,4-difluoropiperidina como reactivo de alquilación en la Etapa 3. El producto se aisló como un sólido blanco (20 mg, 58.3 %). LCMS: m/e 677.57 $(M+H)^+$, 2.30 min (método 11). ^{1}H NMR (400MHz, Cloroformo-d) δ 7.97 (d, *J*= 8.3 Hz, 2H), 7.22 (d, *J*= 8.3 Hz, 2H), 5.27 (d, *J*= 4.8 Hz, 1H), 4.82 (s, 1H), 4.70 (s, 1H), 3.32 (m, 1H), 3.19-3.05 (m, 1H), 2.94 (m, 2H), 2.83-2.68 (m, 5H), 2.36-2.21 (m, 2H),

2.15-1.90 (m, 7H), 1.74 (br. s., 7H), 1.60-1.45 (m, 6H), 1.44-1.30 (m, 4H), 1.26 (s, 2H), 1.18 (s, 3H), 1.06 (s, 4H) 0.98 (s, 3H), 0.97 (s, 3H), 0.95 (s, 3H). ^{19}F NMR (376MHz, CLOROFORMO-d) δ -98.39 (br. s., 2F)

Ejemplo 173

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13bR)-3a-(aziridin-1-il)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13bR)-3a-(aziridin-1-il)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (0.160 g, 0.276 mmol) en una mezcla de acetonitrilo (25 mL) y dicloroetano (5 mL), se agregó fosfato de potasio anhidro (0.25 gm, 1.18 mmol). La suspensión resultante se calentó a 120 °C con nitrógeno en un tubo de paredes gruesas durante 24 horas. La suspensión de reacción enfriada se filtró a través de una almohadilla pequeña de gel de sílice (Tipe-H) y se lavó con acetato de etilo (60 mL). El filtrado transparente se concentró al vacío para obtener un sólido blanco (0.150 g, 96 %). LCMS: m/e 570.5 $(M+H)^+$, 3.32 min (método 12, pero modificado a un gradiente superior a 3 minutos). ^{1}H NMR (400MHz, Cloroformo-d) δ 7.95 (d, *J*= 8.3 Hz, 2H), 7.22 (d, *J*= 8.5 Hz, 2H), 5.31 (dd, *J*= 6.1, 1.6 Hz, 1H), 4.81-4.73 (m, 1H), 4.67-4.59 (m, 1H), 3.93 (s, 3H), 2.82-2.45 (m, 1H), 2.19-2.04 (m, 1H), 1.88-1.74 (m, 1H), 1.71 (s, 3H), 1.68 (br. s., 1H), 1.63-1.21 (m, 7H), 1.11 (s, 3H), 1.01 (s,3H), 1.00 (s, 3H), 0.95 (s, 6H).

Etapa 2. A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13bR)-3a-(aziridin-1-il)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (0.150 g, 0.264 mmol) en una mezcla de metanol (2 mL) y THF (6 mL) a temperatura ambiente, se agregó una solución de reserva de hidróxido de litio (1.0 Molar, 2 mL, 2.0 mmol), lo que produce la formación de una suspensión espesa. La mezcla se mantuvo a 50 °C en nitrógeno durante 60 horas. La mezcla de reacción se neutralizó con HCl (0.5 Molar, 10 mL), el material orgánico se extrajo en acetato de etilo (30 mL). Cuando la mezcla bifásica se agitó a temperatura ambiente, se separó lentamente un precipitado blanco. Se filtró para obtener ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13bR)-3a-(aziridin-1-il)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico como un sólido blanco (99 mg, 68 %). LCMS: m/e 592.5 $(M+MeOH+Na)^+$, 3.03 min (método 12, pero modificado a un gradiente superior a 3 minutos). ^{1}H NMR seleccionado (400MHz, Cloroformo-d) δ 8.01 (d, *J*= 8.3 Hz, 2H), 7.24 (d, *J*= 8.3 Hz, 2H), 5.28 (m, 1H), 4.94 (br. s, 1H), 4.73 (br. s, 1H), 1.74 (s, 3H), 1.20 (s, 3H), 1.09 (s, 3H), 1.01 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H).

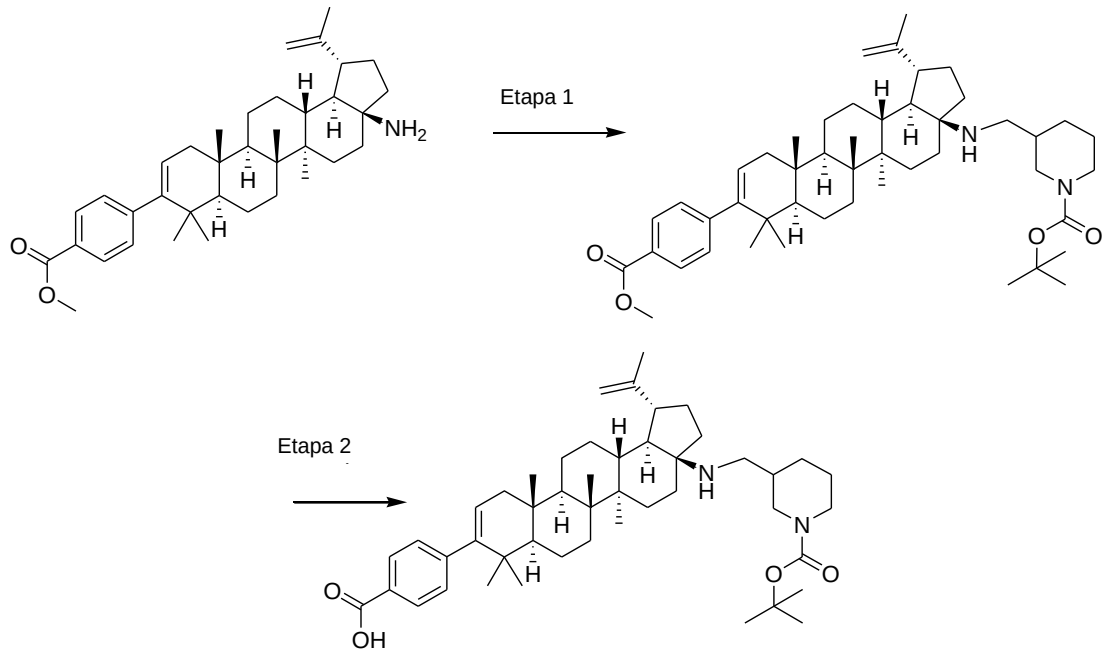
Ejemplo 174

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1-(terc-butoxicarbonil)piperidin-3-il)metilamino)-5a,5b,8,8,11a-

pentametil-1-(prop-1-en-2-il)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



Etapa 1. Preparación de 3-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(metoxicarbonil)fenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-ilamino)metil)piperidin-1-carboxilato de terc-butilo.

A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

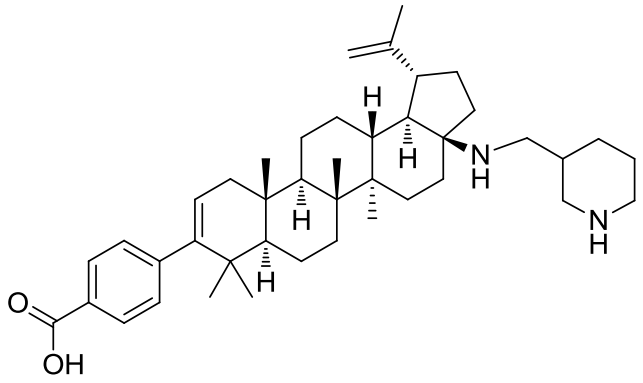
octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (30 mg, 0.055 mmol) en dicloroetano (0.5 mL), se agregaron terc-butiléster del ácido 3-formil-piperidin-1-carboxílico (14.71 mg, 0.069 mmol) e isopropóxido de titanio (IV) (0.020 mL, 0.069 mmol). La mezcla se agitó a temperatura ambiente durante 1 h y se agregó triacetoxiborohidruro de sodio (23.38 mg, 0.110 mmol). La mezcla se agitó a temperatura ambiente durante 16.5 h, luego se diluyó con 3 mL de $NaHCO_3$ saturado y se extrajo con diclorometano (3 x 5 mL). Las capas orgánicas combinadas se secaron con Na_2SO_4, se filtraron y concentraron a presión reducida. El residuo se adsorbió en gel de sílice y se purificó mediante cromatografía instantánea usando un gradiente de 0-10 % de acetato de etilo en hexanos y una columna de gel de sílice Thomson de 12 g. Las fracciones que contenían el producto previsto se combinaron y concentraron a presión reducida para obtener el compuesto del título como una espuma blancuzca. LCMS: m/e 741.7 $(M+H)^+$, 3.76 min (método 2).

Etapa 2. A una solución de 3-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(metoxicarbonil)fenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-ilamino)metil)piperidin-1-carboxilato terc-butilo (0.029 g,

0.039 mmol) en 1,4-dioxano (2 mL) se agregó NaOH (1 N) (0.196 mL, 0.196 mmol). La mezcla se calentó a 85 °C durante 22 h, luego se enfrió a temperatura ambiente, se diluyó con MeOH y se purificó mediante HPLC preparativa. Las fracciones que contenían el producto previsto se combinaron y concentraron a presión reducida para obtener ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1-(terc-butoxicarbonil)piperidin-3-il)metilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico (24 mg, 0.031 mmol, 56 % de rendimiento en 2 etapas) como una película transparente e incolora. LCMS: m/e 727.7 $(M+H)^+$, 2.00 min (método 2). ^{1}H NMR (500 MHz, *Cloroformo-d*) δ ppm 7.98 (d, *J*= 7.93 Hz, 2 H), 7.21 (d, *J*= 7.93 Hz, 2 H), 5.29 (d, *J*= 5.49 Hz, 1 H), 4.70 (br. s., 1 H), 4.58 (br. s., 1 H), 3.82-4.51 (m, 5 H), 1.68 (s, 3 H), 1.47 (d, *J*= 4.58 Hz, 9 H), 1.10 (d, *J*= 7.93 Hz, 3 H), 0.98 (br. s., 6 H), 0.93 (s, 3 H), 0.92 (s, 3 H), 0.90-2.85 (m, 30 H).

Ejemplo 175

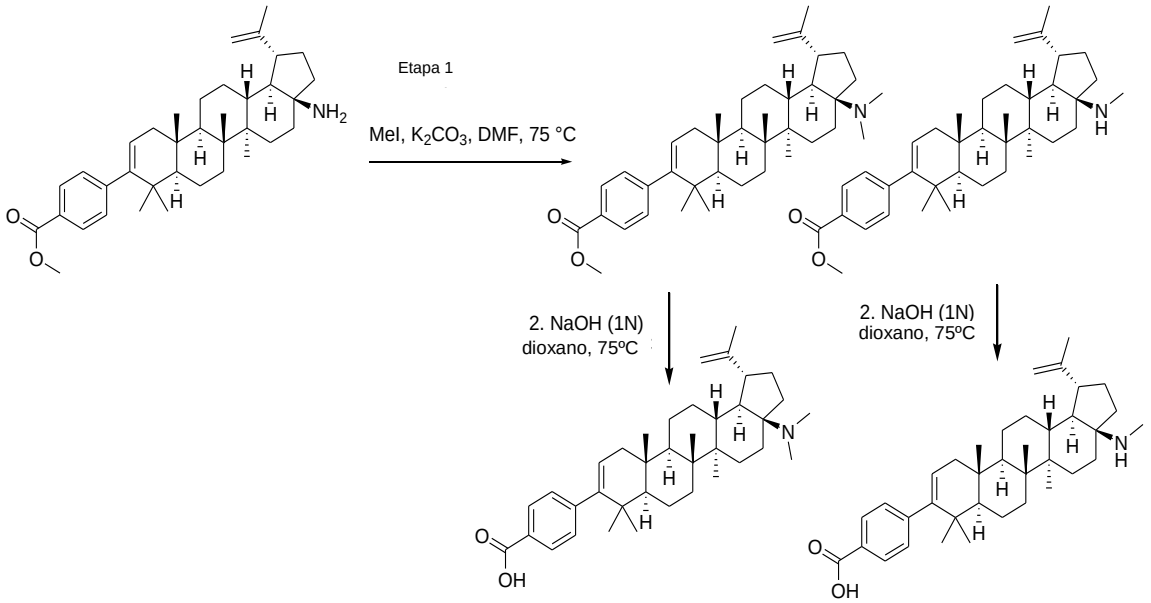
Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(piperidin-3-ilmetilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



A una solución de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((1-(terc-butoxicarbonil)piperidin-3-il)metilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico (0.019 g, 0.026 mmol) en diclorometano (1 mL), se agregó TFA (0.25 mL, 3.24 mmol). La mezcla se agitó a temperatura ambiente durante 1.75 h y luego se concentró a presión reducida. El residuo se purificó mediante HPLC preparativa. Las fracciones que contenían el producto previsto se combinaron y concentraron a presión reducida para obtener ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(piperidin-3-ilmetilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico (14.2 mg, 0.021 mmol, 81 % de rendimiento) como un sólido blanco. LCMS: m/e 627.6 $(M+H)^+$, 1.50 min (método 2).

Ejemplos 176 y 177

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(metilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico y ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(dimetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



Etapa 1. A un vial sellable que contenía 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo,

HCl (1.0 g, 1.72 mmol), se agregó carbonato de potasio (0.48 g, 3.45 mmol). La mezcla se diluyó con DMF (15 mL), y se agregó yoduro de metilo (323 mL, 3.45 mmol). Se selló el vial, y se calentó la mezcla a 75 °C durante 4 h; luego, se enfrió a temperatura ambiente. Se abrió el vial al aire y se agitó a temperatura ambiente durante la noche. La mezcla se diluyó con 20 mL de tiosulfato de sodio acuoso saturado. Se formaron sólidos que se recolectaron mediante filtración y se lavaron con agua. El residuo se purificó mediante cromatografía instantánea en gel de sílice mediante un gradiente de 0-25 % de acetato de etilo en hexanos con la adición de 0.1 % de hidróxido de amonio a la mezcla. Se recuperaron dos aislados principales de la columna. El producto menos polar, 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(dimetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (0.247 g, 0.405 mmol, 23.5 % de rendimiento) se recuperó como una espuma blanca. El aislado más polar, 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(metilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (0.5 g, 0.807 mmol, 46.8 % de rendimiento), se recuperó como

una sólido blanco. LCMS del aislado menos polar: m/e 572.6 $(M+H)^+$, 2.03 min (método 2). ^{1}H NMR (400MHz, *Cloroformo-d*) δ = 7.96-7.92 (m, 2H), 7.23-7.19 (m, 2H), 5.31-5.29 (m, 1H), 4.71 (d, *J*= 2.0 Hz, 1H), 4.61 (dd, *J*= 2.3, 1.3 Hz, 1H), 3.92 (s, 3H), 2.86 (td, *J*= 11.2, 6.1 Hz, 1H), 2.34-2.24 (m, 7H), 2.12 (dd, *J*= 17.1, 6.5 Hz, 1H), 2.04-1.80 (m, 5H), 1.70 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H), 0.94 (s, 3H), 0.94 (s, 3H), 1.74-0.85 (m, 15H). LCMS del aislado más polar: m/e 558.6 $(M+H)^+$, 2.04 min (método 2). ^{1}H NMR (400MHz, *Cloroformo-d*) δ = 7.93 (d, *J*= 8.0 Hz, 2H), 7.20 (d, *J*= 8.3 Hz, 2H), 5.30 (dd, *J*= 6.1, 1.6 Hz, 1H), 4.72 (d, *J*= 2.0 Hz, 1H), 4.59 (s, 1H), 3.92 (s, 3H), 2.60 (td, *J*= 10.9, 5.8 Hz, 1H), 2.24 (s, 3H), 2.11 (dd, *J*= 17.2, 6.1 Hz, 1H), 2.03-1.91 (m, 2H), 1.88-1.79 (m, 2H), 1.09 (s, 3H), 1.00 (s, 3H), 0.99 (s, 3H), 0.94 (s, 3H), 0.93 (s, 3H), 1.69-0.91 (m, 20H).

Etapa 2. La saponificación de los aislados se realizó de manera independiente.

Ejemplo 176: Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(metilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, HCl.

A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(metilamino)-1-(prop-1-en-2-il)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (88 mg, 0.158 mmol) en 1,4-dioxano (3 mL), se agregó NaOH (1M) (1 mL, 1.000 mmol). La mezcla se calentó a 75 °C durante 17 h; luego, se enfrió a temperatura ambiente y se acidificó con 3 mL de HCl 1N. Luego del reposo, se formaron sólidos, se recolectaron mediante filtración y se lavaron con agua. Los sólidos se disolvieron y se purificaron mediante cromatografía instantánea con gradiente de 0-40 % de metanol en acetato de etilo y una columna de gel de sílice Thomson de 25 g. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida; luego, se volvieron a disolver en diclorometano y metanol, y se filtraron a través de un tapón de Celite. El filtrado se concentró a presión reducida para obtener ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(metilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, HCl (40 mg, 0.065 mmol, 41 % de rendimiento) como un sólido blanco. LCMS: m/e 544.5 $(M+H)^+$, 1.79 min (método 2). ^{1}H NMR (500MHz, *Ácido acético* d_4) δ = 8.01 (d, *J*= 8.2 Hz, 2H), 7.27 (d, *J*= 8.2 Hz, 2H), 5.34 (d, *J*= 4.6 Hz, 1H), 4.84 (s, 1H), 4.71 (s, 1H), 2.85-2.77 (m, 1H), 2.74 (s, 3H), 1.75 (s, 3H), 1.16 (s, 3H), 1.10 (s, 3H), 1.06 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H),

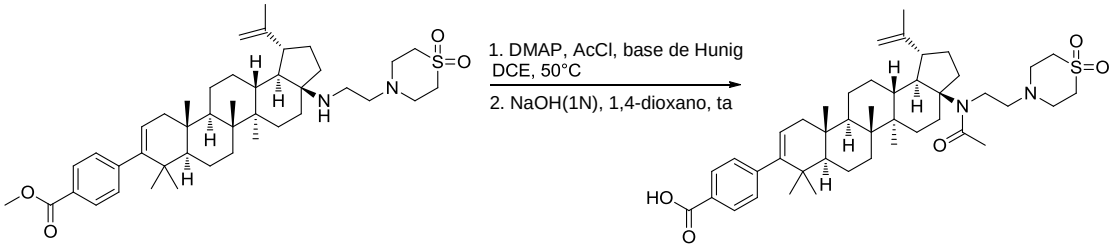
2.24-0.95 (m, 22H).

Ejemplo 177: Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(dimetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico. A una suspensión de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(dimetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo, HCl (100 mg, 0.164 mmol) en 1,4-dioxano (3 mL), se agregó NaOH 1N (1 mL, 1.000 mmol), y la mezcla se calentó a 70 °C. Después de 3.75 h, la mezcla se enfrió a temperatura ambiente y se diluyó con 2 mL de MeOH, y luego, se agregó HCl 1N (6 mL). Los sólidos que se formaron se recolectaron mediante filtración y se lavaron con agua. Los sólidos se disolvieron en dioxano y metanol y se purificaron mediante HPLC preparativa. Las fracciones que contenían el producto previsto se combinaron y concentraron a presión reducida para obtener ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(dimetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico (45 mg, 0.077 mmol, 46,6 % de rendimiento) como un sólido blanco. LCMS: m/e 558.3 $(M+H)^+$, 2.28 min (método 11). ^{1}H NMR (500 MHz,

Ácido acético d_4) δ ppm 8.04 (2 H, d, *J*= 8.2 Hz), 7.30 (2 H, d, *J*= 8.2 Hz), 5.37 (1 H, d, *J*= 4.9 Hz), 4.92 (1 H, s), 4.77 (1 H, s), 3.08 (7 H, br. s.), 1.80 (3 H, s), 1.22 (3 H, s), 1.18 (3 H, s), 1.09 (3 H, s), 1.02 (3 H, s), 1.00 (3 H, s), 0.98-2.46 (22 H, m).

Ejemplo 178

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(acetil(2-(1,1-dioxido-4-tiomorfolinil)etil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(acetil(2-(1,1-dioxido-4-tiomorfolinil)etil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(((1,1-dioxido-

4-tiomorfolinil)acetil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (0.05 g, 0.071 mmol) en dicloroetano (1 mL) y base de Hunig (0.062 mL, 0.355 mmol), se agregó cloruro de acetilo (0.020 mL, 0.284 mmol). La mezcla se calentó a 50 °C. Después de calentar la mezcla durante 71.25 h, la mezcla se enfrió a temperatura ambiente, se cargó directamente en una columna de gel de sílice Thomson de 12 g y se purificó mediante cromatografía instantánea Biotage con un gradiente de 0-5 % de MeOH en diclorometano. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida para obtener 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(acetil(2-(1,1-dioxido-4-tiomorfolinil)etil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (40 mg, 0.054 mmol, 75 %) como una película transparente e incolora. LCMS: m/e 747.5 $(M+H)^+$, 2.26 min (método 2).

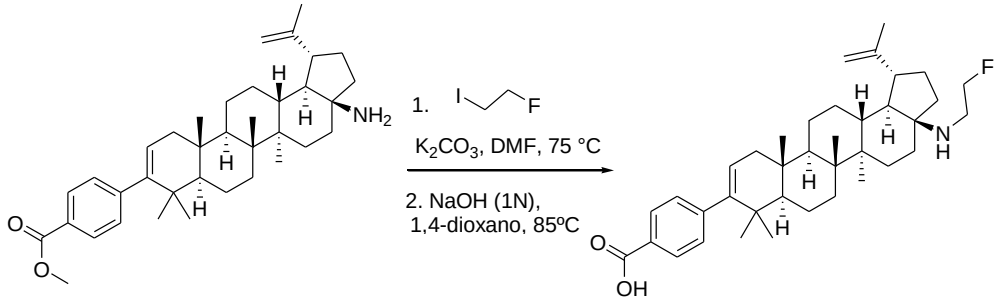
Etapa 2. A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(acetil(2-(1,1-dioxido-4-tiomorfolinil)etil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (40 mg, 0.054 mmol) en 1,4-dioxano (1 mL), se agregó NaOH (1N) (0.27 mL, 0.27 mmol). La mezcla se agitó a temperatura ambiente durante 16.5 h; luego, se purificó directamente mediante HPLC preparativa. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida para obtener ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(acetil(2-(1,1-dioxido-4-tiomorfolinil)etil)amino)-1-isopropenil-5a,5b,8,8,11a-pentametil-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico (14 mg, 0.018 mmol, 33 %) como un sólido blanco. LCMS: m/e 733.5 $(M+H)^+$, 1.96 min (método 2). ^{1}H NMR (400MHz, *Cloroformo-d*) δ = 7.99 (d, *J*= 7.8 Hz, 2H), 7.22 (d, *J*= 7.8 Hz, 2H), 5.23 (d, *J*= 4.0 Hz, 1H), 4.85 (br. s., 1H), 4.68 (br. s., 1H), 3.65 (br. s., 2H), 3.40-3.04 (m, 8H), 2.97-2.46 (m, 4H), 1.74 (s, 3H), 1.27 (s, 3H), 1.03-0.98 (m, 9H), 0.95 (br. s., 3H), 0.89 (br. s., 3H), 2.20-0.71 (m, 21H).

Ejemplo 179

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoroetil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoroetil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

A un vial sellable que contenía 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo, HCl (0.075 g, 0.129 mmol), se agregó carbonato de potasio (0.036 g, 0.258 mmol). La mezcla se diluyó con DMF (1 mL), y se agregó 1-fluoro-2-yodoetano (0.032 ml, 0.388 mmol). El vial se selló, y la mezcla se calentó a 75 °C durante 26 h y luego se enfrió a temperatura ambiente. La mezcla se diluyó con 3 mL de tiosulfato de sodio acuoso saturado y se extrajo con diclorometano (3 x 4 mL). Las capas orgánicas combinadas se secaron con sulfato de sodio, el agente de secado se

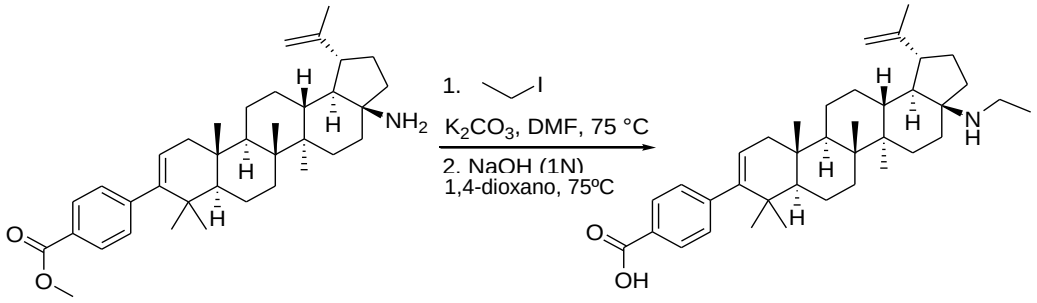
eliminó por filtración, y el filtrado se concentró a presión reducida. El residuo se disolvió en tolueno, se cargó en una columna de gel de sílice Thomson de 12 g y se purificó mediante cromatografía instantánea Biotage con un gradiente de 0-15 % de acetato de etilo en hexanos con la adición de 0.1 % de hidróxido de amonio a la mezcla. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida para obtener 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoroetil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (0.062 g, 0.103 mmol, 80 % de rendimiento) como una espuma blanca. LCMS: m/e 590.6 $(M+H)^+$, 2.05 min (método 2). ^{1}H NMR (400 MHz, *cloroformo-d*) δ 7.94 (d, *J*= 8.53 Hz, 2H), 7.21 (d, *J*= 8.28 Hz, 2H), 5.30 (dd, *J*= 2.01, 6.27 Hz, 1H), 4.73 (d, *J*= 2.01 Hz, 1H), 4.58-4.64 (m, 2H), 4.50 (t, *J*= 4.89 Hz, 1H), 3.92 (s, 3H), 2.57-2.85 (m, 3H), 2.11 (dd, *J*= 6.40, 17.19 Hz, 1H), 1.71 (s, 3H), 1.10 (s, 3H), 1.00 (s, 3H), 0.99 (s, 3H), 0.94 (s, 3H), 0.94 (s, 3H), 0.86-2.05 (m, 21H).

Etapa 2. A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoroetil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de

metilo (0.059 g, 0.100 mmol) en 1,4-dioxano (2 mL), se agregó NaOH (1N) (0.5 mL, 0.500 mmol). La mezcla se calentó a 85 °C durante 15.25 h, se enfrió a temperatura ambiente; luego, se diluyó con metanol y 1,4-dioxano y se purificó mediante HPLC preparativa. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida para obtener ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-fluoroetil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico (29.2 mg, 0.048 mmol, 48.2 % de rendimiento) como un sólido blanco. LCMS: m/e 576.6 $(M+H)^+$, 1.74 min (método 2). ^{1}H NMR (400 MHz, *Ácido acético* d_4) δ 7.99 (d, *J*= 8.53 Hz, 2H), 7.26 (d, *J*= 8.28 Hz, 2H), 5.33 (d, *J*= 4.77 Hz, 1H), 4.73-4.99 (m, 3H), 4.70 (s, 1H), 3.41-3.73 (m, 2H), 2.83-2.94 (m, 1H), 1.73 (s, 3H), 1.19 (s, 3H), 1.11 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.82-2.27 (m, 22H).

Ejemplo 180

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(etilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(etilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

A un vial sellable que contenía 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo, HCl (0.075 g, 0.129 mmol), se agregó carbonato de potasio (0.036 g, 0.258 mmol). La mezcla se diluyó con DMF (1 mL), y se agregó yodoetano (0.031 mL, 0.388 mmol). La mezcla se calentó a 75 °C durante 23 h; luego, se enfrió a temperatura ambiente. La mezcla se diluyó con 1 mL de DMF, y se agregó yodoetano (0.031 mL, 0.388 mmol) adicional a la mezcla. El vial se selló y se calentó a 75 °C durante 24 h; luego, se concentró a presión reducida y se adsorbió en gel de sílice. La mezcla se purificó mediante cromatografía

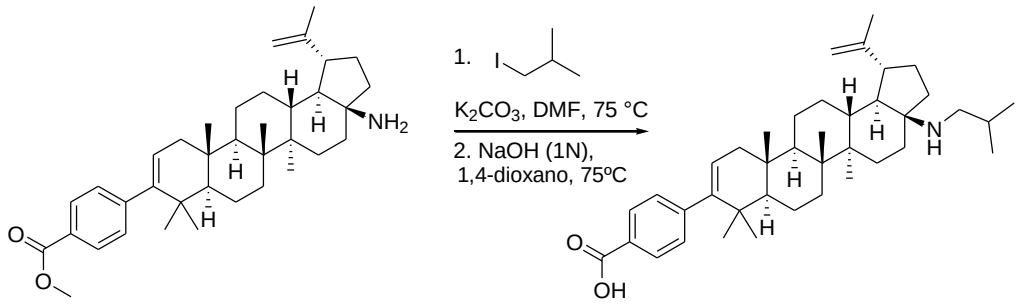
instantánea con gradiente de 0-25 % de EtOAc en hexanos, con la adición de 0.1 % de hidróxido de amonio y una columna de gel de sílice Thomson de 12 g. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida para obtener 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(etilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (0.039 g, 0.065 mmol, 50.1 % de rendimiento) como una espuma blanca. LCMS: m/e 572.7 $(M+H)^+$, 2.16 min (método 2). ^{1}H NMR (400 MHz, *cloroformo-d*) δ 7.94 (d, *J*= 8.28 Hz, 2H), 7.21 (d, *J*= 8.53 Hz, 2H), 5.30 (dd, *J*= 1.76, 6.27 Hz, 1H), 4.73 (d, *J*= 2.51 Hz, 1H), 4.59 (dd, *J*= 1.38, 2.38 Hz, 1H), 3.92 (s, 3H), 2.62 (dt, *J*= 5.40, 10.98 Hz, 1H), 2.38-2.53 (m, 2H), 2.11 (dd, *J*= 6.40, 17.19 Hz, 1H), 1.88-2.03 (m, 3H), 1.83 (dd, *J*= 7.78, 12.55 Hz, 1H), 1.70 (s, 3H), 1.10 (s, 3H), 1.11 (t, *J*= 7.03 Hz, 3H), 0.99 (s, 6H), 0.94 (s, 3H), 0.94 (s, 3H), 0.91-1.74 (m, 17H).

Etapa 2. A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(etilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (0.037 g, 0.065 mmol) en 1,4-dioxano (1.5 mL), se agregó NaOH

(1 N) (0.3 mL, 0.300 mmol). La mezcla se calentó a 75 °C durante 18.5 h; luego, se enfrió a temperatura ambiente, se diluyó con metanol y 1,4-dioxano, se filtró a través de un tapón de lana de vidrio y se purificó mediante HPLC preparativa. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida para obtener ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(etilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico (0.023 g, 0.040 mmol, 61.2 % de rendimiento) como un sólido blanco. LCMS: m/e 558.6 $(M+H)^+$, 1.77 min (método 2). ^{1}H NMR (400 MHz, *Ácido acético* d_4) δ 7.99 (d, *J*= 8.53 Hz, 2H), 7.26 (d, *J*= 8.28 Hz, 2H), 5.33 (d, *J*= 4.52 Hz, 1H), 4.82 (s, 1H), 4.69 (s, 1H), 3.23 (q, *J*= 7.11 Hz, 2H), 2.81-2.92 (m, 1H), 1.72 (s, 3H), 1.40 (t, *J*= 7.15 Hz, 3H), 1.19 (s, 3H), 1.09 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.83-2.24 (m, 22H).

Ejemplo 181

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(isobutilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(isobutilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo. A un vial sellable que contenía 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo, HCl (0.075 g, 0.129 mmol), se agregó carbonato de potasio (0.036 g, 0.258 mmol). La mezcla se diluyó con DMF (1 mL), y se agregó yoduro de isobutilo (0.045 mL, 0.388 mmol). El vial se selló, y la mezcla se calentó a 75 °C durante 23 h; luego, la mezcla se enfrió a temperatura ambiente. LC/MS mostró la información del producto previsto, pero aún había material de inicio. Se agregó más yoduro de isobutilo (0.045 mL, 0.388 mmol) a la mezcla, y el vial se selló y se calentó a 75 °C durante 48 h. La mezcla se enfrió a temperatura ambiente;

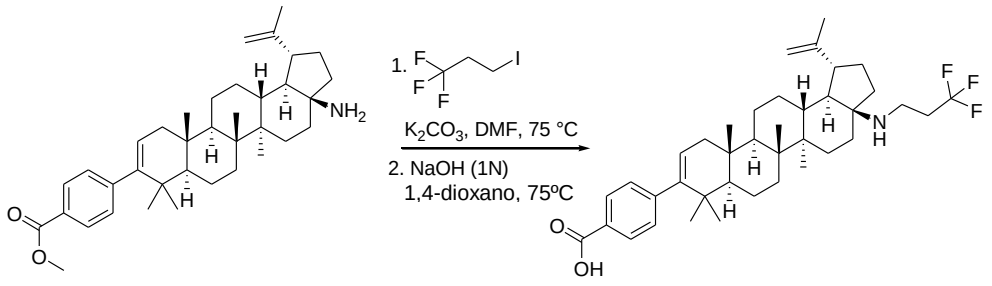
luego se diluyó con 5 mL de agua. Los sólidos que se formaron se recolectaron mediante filtración; luego, se lavaron con agua para obtener el producto previsto, 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(isobutilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (53 mg, 0.075 mmol, 58.1 % de rendimiento) como un sólido amarillo claro. El producto crudo se usó en la siguiente etapa sin purificación adicional. LCMS: m/e 600.6 $(M+H)^+$, 2.14 min (método 2).

Etapa 2. A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(isobutilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (52 mg, 0.087 mmol) en 1,4-dioxano (1.5 mL), se agregó NaOH (1N) (0.3 mL, 0.300 mmol). La mezcla se calentó a 75 °C durante 67 h; luego, se enfrió a temperatura ambiente. La mezcla se diluyó con 1,4-dioxano y metanol, se filtró a través de un tapón de lana de vidrio y se purificó mediante HPLC preparativa. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida para obtener ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(isobutilamino)-

5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico (25.2 mg, 0.041 mmol, 47.1 % de rendimiento) como un sólido blanco. LCMS: m/e 586.6 $(M+H)^+$, 1.85 min (método 2). ^{1}H NMR (400 MHz, *Ácido acético d4*) δ 8.00 (d, *J*= 8.28 Hz, 2H), 7.26 (d, *J*= 8.28 Hz, 2H), 5.33 (d, *J*= 4.52 Hz, 1H), 4.81 (s, 1H), 4.69 (s, 1H), 3.15 (dd, *J*= 5.02, 12.05 Hz, 1H), 2.88-2.98 (m, 1H), 2.78 (dd, *J*= 9.03, 11.80 Hz, 1H), 1.72 (s, 3H), 1.22 (s, 3H), 1.10 (s, 3H), 1.09 (d, *J*= 6.78 Hz, 3H), 1.06 (s, 3H), 1.01 (d, *J*= 6.78 Hz, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.83-2.31 (m, 23H).

Ejemplo 182

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-((3,3,3-trifluoropropil)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



Etapa 1. Preparación de 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-((3,3,3-trifluoropropil)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

A un vial sellable que contenía 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo, HCl (0.075 g, 0.129 mmol), se agregó carbonato de potasio (0.036 g, 0.258 mmol). La mezcla se diluyó con DMF (1 mL), y se agregó 1-yodo-3,3,3-trifluoropropano (0.045 mL, 0.388 mmol). El vial se selló, y la mezcla se calentó a 75 °C durante 23 h; luego se enfrió a temperatura ambiente. LC/MS mostró una mezcla de material de inicio y producto. Se agregaron 0.045 mL adicionales de 1-yodo-3,3,3-trifluoropropano, y la mezcla se calentó a 75 °C durante 48 h; luego, se enfrió a temperatura ambiente. LC/MS mostró una mayor progresión, pero la reacción aún estaba incompleta. Se agregaron 0.045 mL adicionales de 1-yodo-3,3,3-trifluoropropano, y la mezcla se calentó a 75 °C durante 71 h; luego, se enfrió a temperatura ambiente y se concentró a presión reducida. La mezcla se adsorbió en gel de sílice y se purificó mediante cromatografía instantánea con un gradiente

de 0-15 % de EtOAc en hexanos con la adición de 0.1 % de hidróxido de amonio a la mezcla y una columna de gel de sílice Thomson de 12 g. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida para obtener 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-((3,3,3-trifluoropropil)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (0.032 g, 0.044 mmol, 34.1 % de rendimiento) como una espuma blanca. LCMS: m/e 640.6 $(M+H)^+$, 2.15 min (método 2). ^{1}H NMR (500 MHz, *Cloroformo-d*) δ 7.92 (d, *J*= 8.24 Hz, 2H), 7.19 (d, *J*= 8.24 Hz, 2H), 5.28 (dd, *J*= 1.53, 6.10 Hz, 1H), 4.70 (d, *J*= 1.83 Hz, 1H), 4.59 (s, 1H), 3.90 (s, 3H), 2.60-2.73 (m, 2H), 2.56 (dt, *J*= 5.34, 10.91 Hz, 1H), 2.21-2.32 (m, 2H), 2.09 (dd, *J*= 6.41, 17.09 Hz, 1H), 1.68 (s, 3H), 1.07 (s, 3H), 0.98 (s, 6H), 0.92 (s, 3H), 0.92 (br. s., 3H), 0.84-2.01 (m, 21H).

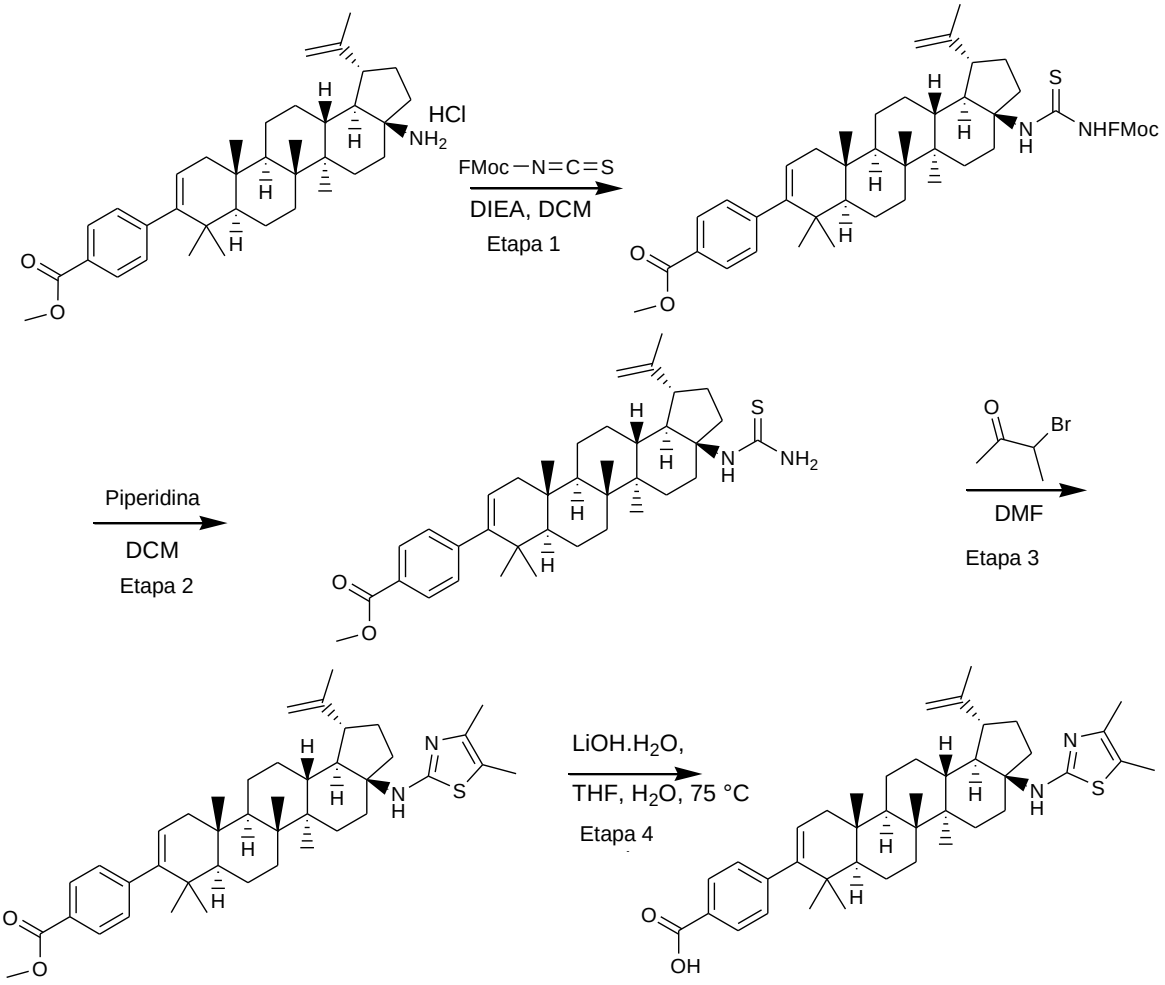
Etapa 2. A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-((3,3,3-trifluoropropil)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (0.032 g, 0.050 mmol) en 1,4-dioxano (1 mL), se

agregó NaOH (1N) (0.2 mL, 0.200 mmol). La mezcla se calentó a 75 °C durante 22.5 h; luego, se enfrió a temperatura ambiente. La mezcla se diluyó con metanol, se filtró a través de un tapón de lana de vidrio y se purificó mediante HPLC preparativa. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida para obtener ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-((3,3,3-trifluoropropil)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico (0.022 g, 0.033 mmol, 66.8 % de rendimiento) como un sólido blanco. LCMS: m/e 626.6 $(M+H)^+$, 1.87 min (método 2). ^{1}H NMR (400 MHz, *Ácido acético* d_4) δ7.99 (d, *J*= 8.28 Hz, 2H), 7.25 (d, *J*= 8.28 Hz, 2H), 5.33 (d, *J*= 4.77 Hz, 1H), 4.82 (s, 1H), 4.70 (s, 1H), 3.36-3.51 (m, 2H), 2.81-2.97 (m, 3H), 2.12-2.28 (m, 4H), 1.72 (s, 3H), 1.17 (s, 3H), 1.09 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.82-2.11 (m, 18H).

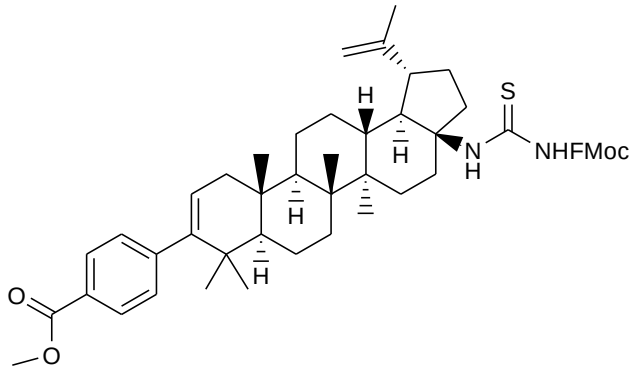
Ejemplo 183

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4,5-dimetiltiazol-2-ilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



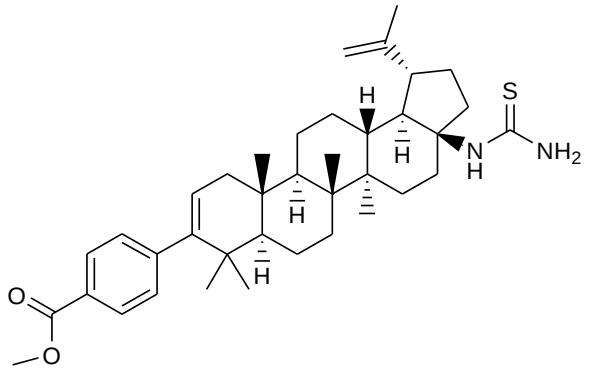
Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(((9H-fluoren-9-il)metoxi)carbonil)tioureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.



A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo, HCl (2 g, 3.45 mmol) en DCM (50 mL), se agregaron *N,N*-diisopropiletilamina (3.00 mL, 17.23 mmol) y Fmoc-isotioisocianato (1.939 g, 6.89 mmol). La mezcla de reacción se agitó a temperatura ambiente. Después de 3 h, la reacción se lavó con HCl 0.1 N (50 mL). La capa acuosa se extrajo con DCM (50 mL). La capa orgánica combinada se lavó con salmuera, se secó en $MgSO_4$, se filtró y se concentró hasta alrededor de 30 mL de DCM, y se trató con MeOH (100 mL). La mezcla se concentró para eliminar todo el DCM hasta que quedaron aproximadamente 50 mL de MeOH. El precipitado amarillo resultante se filtró y se lavó con MeOH. El producto sólido se guardó, y el filtrado líquido se concentró para producir más precipitación. El sólido resultante se aisló mediante filtración y se lavó con MeOH.

El producto sólido combinado se secó en un horno al vacío a 50 °C para obtener 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(((9H-fluoren-9-il)metoxi)carbonil)tioureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (2.52 g, 3.05 mmol, 89 % de rendimiento) como un sólido amarillo. ^{1}H NMR (500MHz, *CLOROFORMO-d*) δ 9.84 (s, 1 H), 8.00 (s, 1 H), 7.95 (d, *J* = 8.2 Hz, 2 H), 7.82 (d, *J* = 7.6 Hz, 2 H), 7.64 (t, *J* = 8.2 Hz, 2 H), 7.49-7.44 (m, 2 H), 7.38 (tt, *J* = 1.5, 7.4 Hz, 2 H), 7.21 (d, *J* = 8.5 Hz, 2 H), 5.33-5.27 (m, 1 H), 4.79 (s, 1 H), 4.67 (s, 1 H), 4.58-4.53 (m, 2 H), 4.29 (t, *J* = 6.9 Hz, 1 H), 3.93 (s, 3 H), 3.39 (d, *J* = 13.7 Hz, 1 H), 3.23 (dd, *J* = 8.2, 12.8 Hz, 1 H), 2.50 (dt, *J* = 5.3, 10.8 Hz, 1 H), 2.13 (dd, *J* = 6.4, 17.1 Hz, 1 H), 1.98-1.88 (m, 1 H), 1.87-1.77 (m, 3 H), 1.74 (s, 3 H), 1.70 (d, *J* = 17.4 Hz, 1 H), 1.54-1.42 (m, 8 H), 1.41-1.29 (m, 3 H), 1.24 (d, *J* = 10.4 Hz, 1 H), 1.19-1.10 (m, 2 H), 1.05 (s, 3 H), 1.00 (s, 6 H), 0.94 (s, 6 H).

Etapa 2. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-tioureido-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

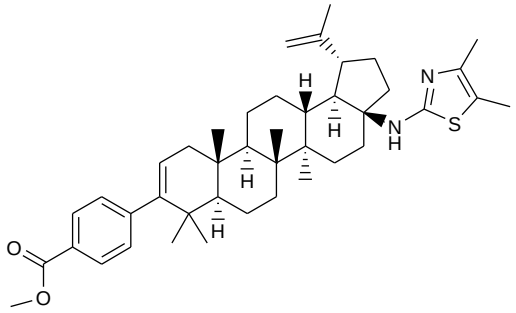


A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(3-(((9H-fluoren-9-il)metoxi)carbonil)tioureido)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (2.51 g, 3.04 mmol) en DCM (30 mL), se agregó piperidina (1.502 mL, 15.21 mmol). La mezcla de reacción marrón resultante se agitó a temperatura ambiente durante 5 h. La reacción se concentró y se trituró con MeOH para producir un producto sólido blanco y aducto de fulveno. Luego, este material se volvió a disolver en DCM caliente y se dejó enfriar a temperatura ambiente. El precipitado blanco resultante se filtró y se lavó con DCM frío. El filtrado líquido se concentró, y se filtró más precipitado blanco. El producto sólido blanco combinado se secó en un horno al vacío. El filtrado líquido se concentró y se cargó en una columna de SiO_2 (90 g), y se eluyó con DCM (1L) para eliminar el subproducto de la mancha superior; luego, el producto

deseado se eluyó con 97:3 de DCM:MeOH. Después de secarlo en un horno al vacío, se combinó todo el producto sólido para obtener 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-tioureido-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (1.7 g, 2.82 mmol, 93 % de rendimiento) como un sólido blanco. LCMS: m/e 603.5 $(M+H)^+$, 2.51min (método 1). ^{1}H NMR (500MHz, *CLOROFORMO-d*) δ 7.94 (d, *J* = 7.9 Hz, 2 H), 7.28 (s, 1 H), 7.21 (d, *J* = 7.9 Hz, 2 H), 6.07 (br. s., 1 H), 5.94 (br. s., 1 H), 5.34-5.28 (m, 2 H), 4.78 (s, 1 H), 4.68 (br. s., 1 H), 3.92 (s, 3 H), 2.64-2.55 (m, 1 H), 2.17-2.02 (m, 2 H), 1.85-1.74 (m, 3 H), 1.71 (s, 3 H), 1.67 (br. s., 1 H), 1.60-1.38 (m, 10 H), 1.35-1.35 (m, 1 H), 1.27-1.17 (m, 2 H), 1.13 (s, 4 H), 1.02 (s, 3 H), 1.00 (s, 3 H), 0.95 (br. s., 3 H), 0.94 (br. s., 3 H), 0.91-0.90 (m, 1 H). ^{13}C NMR (126MHz, *CLOROFORMO-d*) δ 182.0, 167.4, 148.8, 148.4, 146.4, 130.2, 128.6, 128.0, 124.0, 111.0, 66.8, 53.5, 53.0, 52.1, 50.3, 49.5, 46.8, 42.0, 41.8, 40.6, 37.9, 37.6, 36.4, 34.2, 33.5, 29.7, 29.5, 29.5, 27.6, 25.1, 21.3, 21.1, 19.8, 19.4, 16.5, 15.9, 14.6.

Etapa 3. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4,5-dimetiltiazol-2-ilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

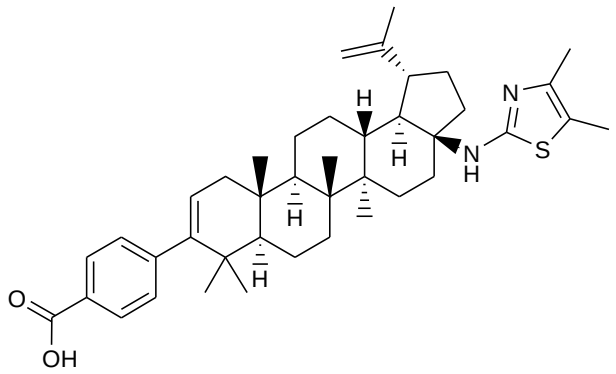
octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.



A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-tioureido-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (150 mg, 0.249 mmol) en DMF (5 mL), se agregaron *N,N*-diisopropiletilamina (0.173 mL, 0.995 mmol) y 3-bromobutan-2-ona (56.4 mg, 0.373 mmol). La mezcla de reacción se agitó a temperatura ambiente. Después de 18 h, la mezcla de reacción se vertió en un embudo separador que contenía H_2O (10 mL) y se extrajo con EtOAc (50 mL). La capa orgánica se lavó con salmuera, se secó en $MgSO_4$, se filtró y se concentró hasta obtener un sólido blanco. El material se volvió a disolver en DCM (5 mL), y se agregó MeOH para realizar la precipitación. La mezcla se concentró para eliminar la mayor parte de DCM, y el precipitado blanco resultante se filtró, se lavó con MeOH frío y se secó en un horno al vacío para obtener 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4,5-dimetiltiazol-2-ilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-

en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (121 mg, 0.175 mmol, 70.5 % de rendimiento) como un sólido blanco. LCMS: m/e 655.3 $(M+H)^+$, 2.72 min (método 2). ^{1}H NMR (500MHz, *CLOROFORMO-d*) δ 7.95 (d, J = 8.2 Hz, 2 H), 7.21 (d, J = 8.2 Hz, 2 H), 5.31 (d, J = 4.6 Hz, 1 H), 4.76 (br. s., 1 H), 4.65 (s, 1 H), 3.93 (s, 3 H), 2.43 (d, J = 10.4 Hz, 1 H), 2.21 (s, 3 H), 2.15 (s, 3 H), 2.11 (d, J = 6.7 Hz, 1 H), 2.07-1.96 (m, 1 H), 1.80-1.65 (m, 6 H), 1.57-1.36 (m, 8 H), 1.35-1.27 (m, 2 H), 1.23 (d, J = 10.1 Hz, 1 H), 1.17-1.11 (m, 1 H), 1.09 (s, 3 H), 1.03 (s, 3 H), 1.00 (s, 3 H), 0.94 (s, 6 H).

Etapa 4. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4,5-dimetiltiazol-2-ilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, TFA.



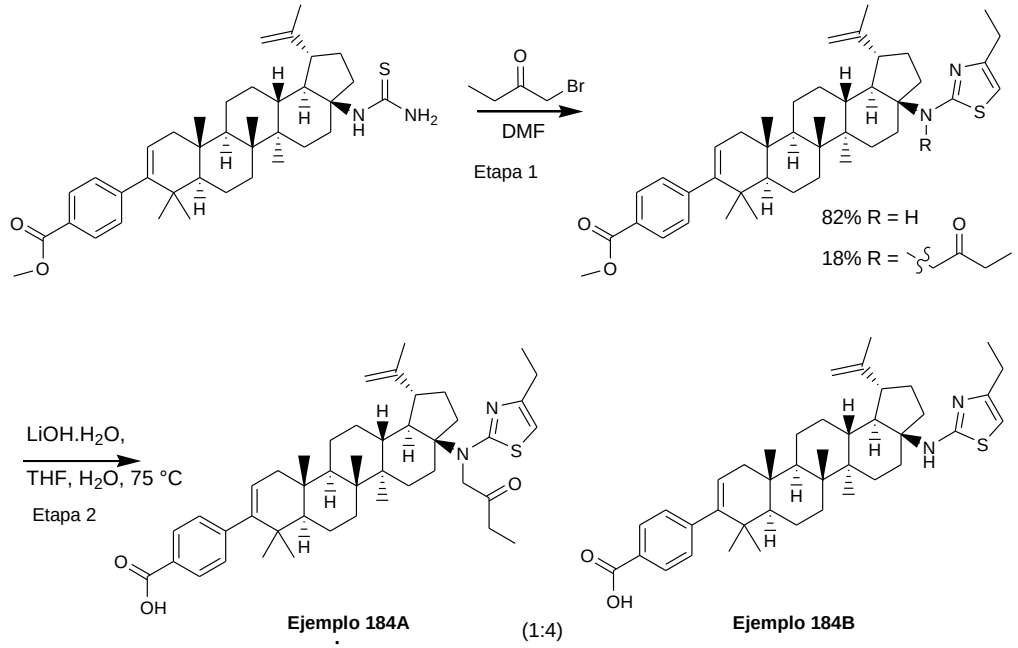
A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4,5-

dimetiltiazol-2-ilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (107 mg, 0.163 mmol) en THF (3 mL), se agregó una solución de hidróxido de litio monohidrato (20.57 mg, 0.490 mmol) en agua (1.000 mL). La reacción se calentó a 75 °C durante 6 h. La mezcla de reacción se concentró, se volvió a disolver en MeOH (2 mL) y THF (1 mL), se filtró y luego se inyectó (2 inyecciones) en HPLC de fase inversa para la purificación con el método 3 de HPLC preparativa, a fin de obtener ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4,5-dimetiltiazol-2-ilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, TFA (58.3 mg, 0.073 mmol, 44.4 % de rendimiento) como un sólido blanco. LCMS: m/e 641.3 $(M+H)^+$, 2.51 min (método 2). ^{1}H NMR (500MHz, *CLOROFORMO-d*) δ 10.10 (s, 1 H), 8.02 (d, *J* = 8.2 Hz, 2 H), 7.25 (d, *J* = 8.2 Hz, 2 H), 5.33 (d, *J* = 4.6 Hz, 1 H), 4.84 (s, 1 H), 4.69 (s, 1 H), 2.97 (dt, *J* = 5.2, 11.0 Hz, 1 H), 2.48 (d, *J* = 13.7 Hz, 1 H), 2.32-2.25 (m, 2 H), 2.23 (s, 3 H), 2.20 (s, 3 H), 2.16 (dd, *J* = 6.4, 17.1 Hz, 1 H), 2.03-1.89 (m, 1 H), 1.89-1.79 (m, 2 H), 1.74 (s, 3 H), 1.71 (br. s., 1 H), 1.60-1.34 (m, 11 H), 1.26-1.19 (m, 1 H), 1.12 (d, *J* = 13.4 Hz, 1 H), 1.06 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.96 (s, 3 H), 0.94 (s, 3 H). ^{13}C NMR (126MHz, *CLOROFORMO-*

d) δ 171.0, 164.9, 149.8, 148.9, 146.2, 132.4, 130.3, 129.2, 127.0, 124.4, 117.7, 111.4, 110.7, 68.1, 53.1, 50.3, 49.8, 45.4, 41.9, 40.8, 37.6, 36.5, 36.4, 33.8, 33.1, 29.6, 27.3, 25.3, 21.2, 19.9, 19.6, 16.5, 15.7, 14.5, 11.4, 10.8.

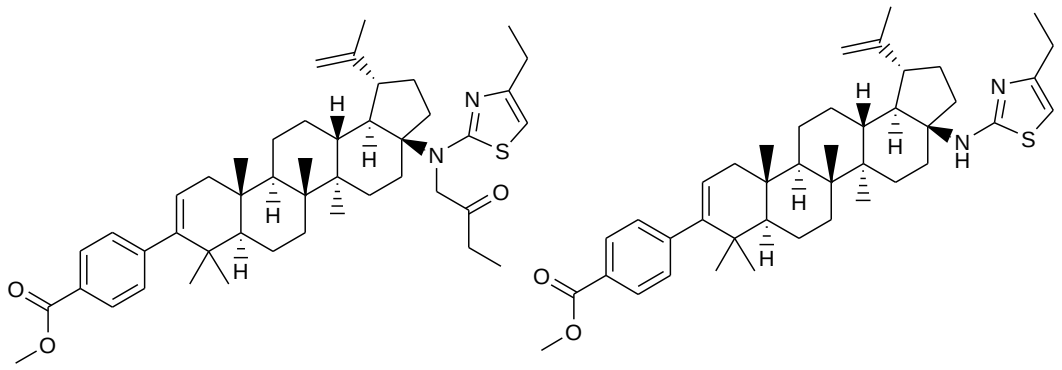
Ejemplos 184A y 184B

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((4-etiltiazol-2-il)(2-oxobutil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico y ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-etiltiazol-2-ilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



Etapa 1. Preparación de 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((4-etiltiazol-2-il)(2-oxobutil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo y 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-etiltiazol-2-ilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

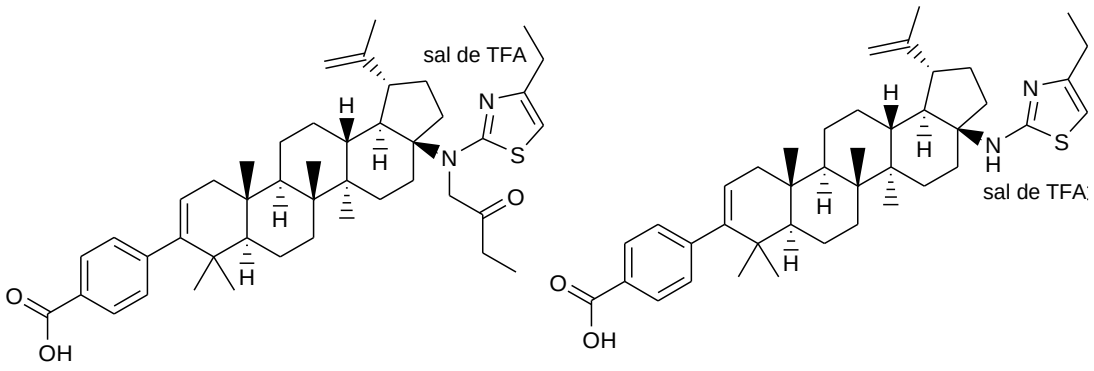


A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-tioureido-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (158 mg, 0.262 mmol) en DMF (3 mL), se agregaron *N,N*-diisopropiletilamina (0.183 mL, 1.048 mmol) y 1-bromobutan-2-ona (0.042 mL, 0.393 mmol). La mezcla de reacción se agitó a temperatura ambiente. Después de 16 h, la mezcla de reacción se vertió en H_2O (5 mL) y se extrajo con EtOAc (50 mL). La capa orgánica se lavó con salmuera, se secó en $MgSO_4$, se

filtró y se concentró. El material crudo se disolvió en DCM y se trató con MeOH para realizar la precipitación. La mezcla se concentró para eliminar todo el DCM, y el precipitado blanco resultante se filtró y se lavó con MeOH. El producto se secó en un horno al vacío para obtener una mezcla de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((4-etiltiazol-2-il)(2-oxobutil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo y 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-etiltiazol-2-ilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo como un sólido blanco en rendimiento cuantitativo (173 mg, 0.264 mmol). LC/MS: m/e 725.4 $(M+H)^+$, 2.70 min y m/e 655.3 $(M+H)^+$, 2.95 min (método 9), respectivamente. La HPLC analítica de fase inversa mostró una relación entre el producto principal a temperatura ambiente = 23.45 min (m/e 655,3 $(M+H)^+$) y el producto menor a temperatura ambiente = 26.86 min (m/e 725.4 $(M+H)^+$) de 82 %:18 % (con el método 1 de HPLC analítica).

Etapa 2. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((4-etiltiazol-2-il)(2-oxobutil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, TFA y ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-etiltiazol-2-ilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, TFA.



A una mezcla de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((4-etiltiazol-2-il)(2-oxobutil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo y 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-etiltiazol-2-ilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo en THF (3 mL), se agregó una solución de Li. H O. H_2O (32.7 mg, 0.779 mmol) en agua (1.50 mL). La reacción se calentó a 75 °C durante 6 h. La mezcla de reacción se concentró, se volvió a disolver en MeOH (2 mL) y THF (1 mL), se filtró y

luego se inyectó (2 inyecciones) en HPLC de fase reversa para la purificación con el método 3 de HPLC preparativa, a fin de obtener ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((4-etiltiazol-2-il)(2-oxobutil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, TFA (22.3 mg, 0.027 mmol, 10.31 % de rendimiento) y ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-etiltiazol-2-ilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, TFA (91.7 mg, 0.118 mmol, 45.4 % de rendimiento), ambos como un sólido blanco.

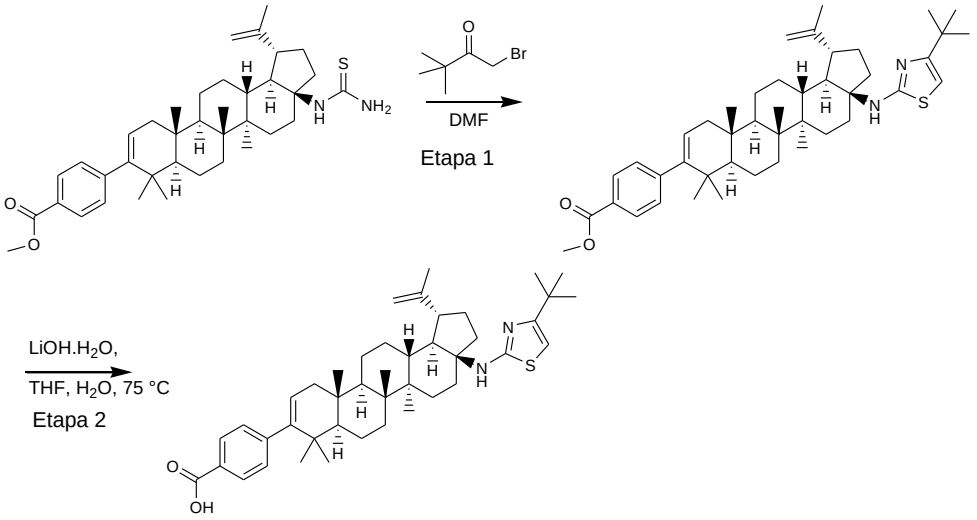
Ejemplo 184A: LC/MS: m/e 711.4 $(M+H)^+$, 2.45 min (método 11), ^{1}H NMR (500MHz, *CLOROFORMO-d*) δ 8.14 (br. s., 1 H), 7.97 (d, *J* = 7.9 Hz, 2 H), 7.21 (d, *J* = 8.2 Hz, 2 H), 6.56-6.45 (m, 1 H), 6.32 (s, 1 H), 5.26 (d, *J* = 5.2 Hz, 1 H), 5.16 (d, *J* = 19.5 Hz, 1 H), 4.84 (s, 1 H), 4.67 (br. s., 1 H), 3.11-2.98 (m, 1 H), 2.89-2.77 (m, 1 H), 2.73-2.61 (m, 2 H), 2.54-2.47 (m, 1 H), 2.43 (dd, *J* = 7.6, 16.2 Hz, 1 H), 2.30-2.22 (m, 1 H), 2.21-2.11 (m, 1 H), 2.11-1.98 (m, 2 H), 1.95-1.87 (m, 1 H), 1.71 (s, 3 H), 1.63 (d, *J* = 16.2 Hz, 2 H), 1.51 (d, *J* = 11.0 Hz, 2 H), 1.48-1.37 (m, 6 H), 1.34-1.25 (m, 6 H), 1.23-1.19 (m, 1 H), 1.16 (t, *J* = 7.2 Hz, 3

H), 1.11 (d, *J* = 10.7 Hz, 1 H), 1.00 (br. s., 3 H), 0.99 (br. s., 3 H), 0.96 (br. s., 6 H), 0.95 (br. s., 2 H). ^{13}C NMR (126MHz, *CLOROFORMO-d*) δ 203.2, 170.6, 167.1, 149.4, 148.6, 146.3, 144.3, 130.2, 129.1, 127.8, 124.6, 110.7, 100.1, 70.7, 55.2, 53.0, 50.7, 49.4, 44.3, 42.0, 41.8, 40.7, 37.6, 36.4, 36.3, 33.6, 33.4, 32.7, 29.6, 29.4, 27.3, 27.2, 25.2, 21.5, 21.2, 20.7, 19.8, 19.7, 16.5, 15.5, 14.5, 10.8, 7.3.

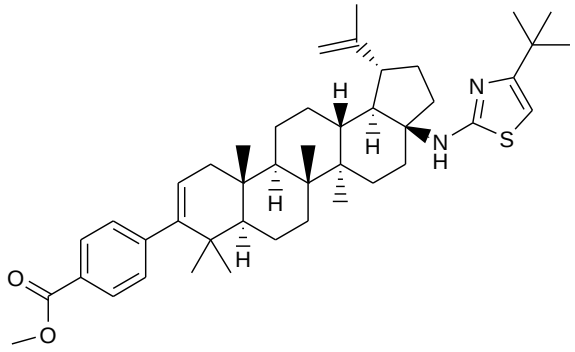
Ejemplo 184B: LC/MS: m/e 641.3 $(M+H)^+$, 2.51 min (método 11), ^{1}H NMR (500MHz, *CLOROFORMO-d*) δ 10.17 (s, 1 H), 8.02 (d, *J* = 8.2 Hz, 2 H), 7.25 (d, *J* = 8.2 Hz, 2 H), 6.07 (s, 1 H), 5.33 (d, *J* = 4.6 Hz, 1 H), 4.85 (s, 1 H), 4.70 (s, 1 H), 2.97 (dt, *J* = 5.0, 11.1 Hz, 1 H), 2.71 (dq, *J* = 0.9, 7.5 Hz, 2 H), 2.53-2.45 (m, 1 H), 2.32 (dd, *J* = 7.8, 13.0 Hz, 1 H), 2.26 (dt, *J* = 2.9, 12.1 Hz, 1 H), 2.16 (dd, *J* = 6.3, 17.2 Hz, 1 H), 2.05-1.92 (m, 1 H), 1.90-1.79 (m, 2 H), 1.74 (s, 3 H), 1.69 (d, *J* = 16.8 Hz, 1 H), 1.60-1.35 (m, 11 H), 1.30 (t, *J* = 7.6 Hz, 3 H), 1.23 (dd, *J* = 4.1, 9.6 Hz, 1 H), 1.13 (d, *J* = 13.1 Hz, 1 H), 1.06 (s, 3 H), 1.03 (s, 3 H), 1.01 (s, 3 H), 0.96 (s, 3 H), 0.95 (s, 3 H). ^{13}C NMR (126MHz, *CLOROFORMO-d*) δ 171.5, 167.1, 163.3, 163.0, 149.8, 148.8, 146.2, 144.6, 130.3, 129.3, 127.1, 124.4, 117.5, 115.2, 110.8, 98.3, 68.3, 53.1, 50.3, 49.7, 45.4, 41.9, 40.8, 37.6, 36.5, 36.4, 33.8, 32.8, 29.6, 27.3, 27.1, 25.3, 21.7, 21.2, 19.8, 19.6, 16.5, 15.7, 14.5, 11.8.

Ejemplo 185

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-terc-butiltiazol-2-ilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-terc-butiltiazol-2-ilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato.

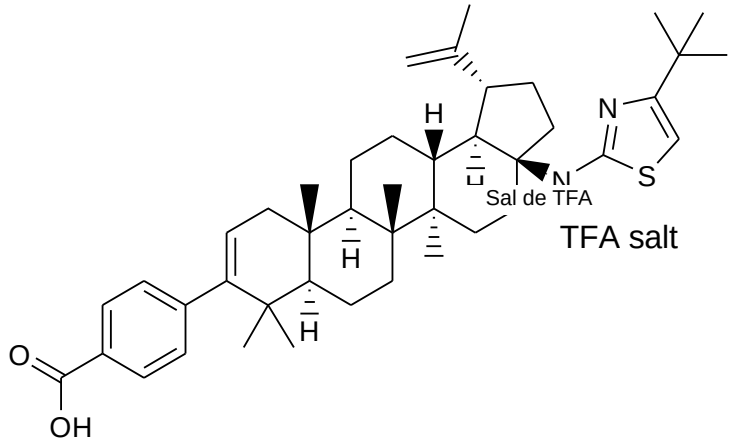


A una solución de 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-tioureido-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (150 mg, 0.249 mmol) en DMF (3 mL), se agregaron *N,N*-diisopropiletilamina (0.217 mL, 1.244 mmol) y 1-bromopinacolona (0.056 mL, 0.373 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. Después de 18 h, la mezcla de reacción se vertió en un embudo separador que contenía H_2O (5 mL) y se extrajo con EtOAc (50 mL). La capa orgánica se lavó con salmuera, se secó en $MgSO_4$, se filtró y se concentró hasta obtener un sólido blanco. El material se volvió a disolver en DCM (3 mL), se agregó lavado de MeOH y se concentró para eliminar la mayor parte de DCM. El precipitado blanco resultante se filtró, se lavó con MeOH frío y se secó en un horno al vacío para obtener 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-terc-butiltiazol-2-ilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (154.0 mg, 0.225 mmol, 91 % de rendimiento) como un sólido blanco. LC/MS: m/e 683.4 $(M+H)^+$, 2.88 min (método 11). ^1H NMR (500MHz, *CLOROFORMO-d*) δ 7.95 (d, *J* = 8.2 Hz, 2 H), 7.22 (d, *J* = 8.2 Hz, 2 H), 6.06 (s, 1 H), 5.31 (d, *J* = 4.6 Hz, 1 H), 4.88 (s, 1 H), 4.77 (s, 1 H), 4.66 (s, 1 H), 3.93 (s, 3

H), 2.72 (d, J = 13.7 Hz, 1 H), 2.68-2.62 (m, 1 H), 2.55 (dd, J = 8.1, 12.7 Hz, 1 H), 2.13 (dd, J = 6.4, 17.1 Hz, 1 H), 2.07-1.98 (m, 1 H), 1.92-1.83 (m, 1 H), 1.82-1.76 (m, 1 H), 1.74 (s, 3 H), 1.73-1.66 (m, 2 H), 1.61 (s, 1 H), 1.57-1.49 (m, 3 H), 1.49-1.40 (m, 4 H), 1.40-1.31 (m, 3 H), 1.29 (s, 9 H), 1.27-1.21 (m, 1 H), 1.18-1.12 (m, 1 H), 1.10 (s, 3 H), 1.04 (s, 3 H), 1.01 (s, 3 H), 0.95 (s, 6 H).

Etapa 2. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-terc-butiltiazol-2-ilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, TFA.



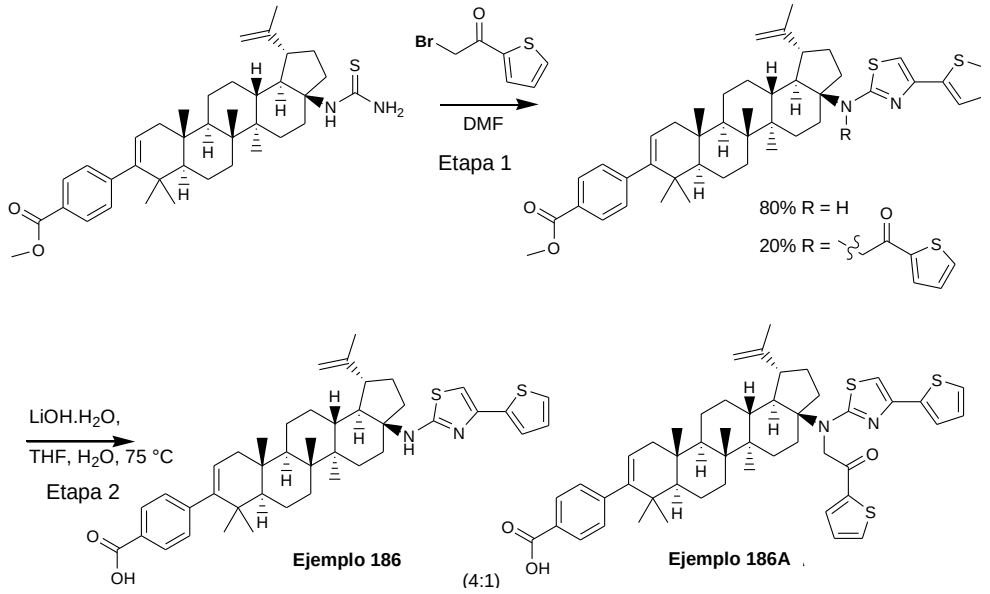
A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-terc-butiltiazol-2-ilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-

1H-ciclopenta[a]crisen-9-il)benzoato de metilo (139 mg, 0.204 mmol) en THF (3 mL), se agregó una solución de hidróxido de litio monohidrato (25.6 mg, 0.611 mmol) en agua (1 mL). La reacción se calentó a 75 °C durante 6 h. La mezcla de reacción se concentró, se volvió a disolver en MeOH (2 mL) y THF (1 mL), se filtró y luego se inyectó (2 inyecciones) en HPLC de fase inversa para la purificación con el método 3 de HPLC preparativa, a fin de obtener ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(4-terc-butiltiazol-2-ilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, TFA (49.3 mg, 0.059 mmol, 28.8 % de rendimiento) como un sólido blanco. LC/MS: m/e 669.4 $(M+H)^+$, 2.61 min (método 11). ^{1}H NMR (500MHz, *CLOROFORMO-d*) δ 8.02 (d, *J* = 7.9 Hz, 2 H), 7.25 (d, *J* = 8.2 Hz, 2 H), 6.05 (s, 1 H), 5.33 (d, *J* = 4.9 Hz, 1 H), 4.86 (s, 1 H), 4.70 (s, 1 H), 3.52 (s, 1 H), 3.03 (dt, *J* = 5.0, 10.9 Hz, 1 H), 2.54 (d, *J* = 14.0 Hz, 1 H), 2.34 (dd, *J* = 8.1, 12.7 Hz, 1 H), 2.31 – 2.22 (m, 1 H), 2.16 (dd, *J* = 6.3, 17.2 Hz, 1 H), 2.09 – 1.96 (m, 1 H), 1.92 – 1.80 (m, 2 H), 1.75 (s, 3 H), 1.69 (d, *J* = 16.8 Hz, 1 H), 1.58 (br. S., 1 H), 1.53 – 1.42 (m, 8 H), 1.39 (s, 9 H), 1.28 (s, 2 H), 1.23 (d, *J* = 9.2 Hz, 2 H), 1.13 (d, *J* = 13.7 Hz, 1 H), 1.08 (s, 4 H), 1.04 (s, 3 H), 1.01 (s, 3 H), 0.95 (br. S., 3 H), 0.95 (br. S., 3 H). ^{13}C NMR (126MHz, *CLOROFORMO-d*) δ 170.9, 167.4, 151.7, 149.5, 148.3, 145.6, 129.9, 128.8, 126.5, 124.0, 110.5, 96.6, 68.0, 52.7, 50.0, 49.3, 44.9, 41.5, 41.5,

40.3, 37.2, 36.1, 36.0, 33.5, 33.4, 32.3, 29.2, 29.2, 28.5, 27.0, 26.8, 24.9, 20.8, 20.7, 19.4, 19.3, 16.1, 15.4, 14.1.

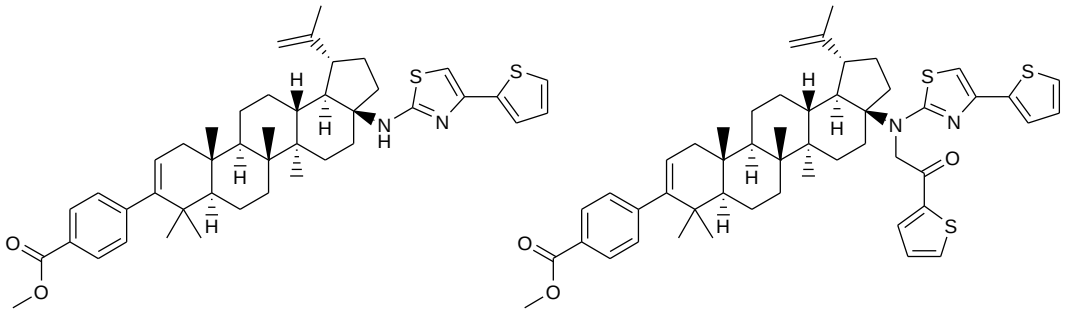
Ejemplo 186

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(4-(tiofen-3-il)tiazol-2-ilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico y ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-oxo-2-(tiofen-3-il)etil)(4-(tiofen-3-il)tiazol-2-il)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-

pentametil-1-(prop-1-en-2-il)-3a-(4-(tiofen-3-il)tiazol-2-ilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo y 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-oxo-2-(tiofen-3-il)etil)(4-(tiofen-3-il)tiazol-2-il)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

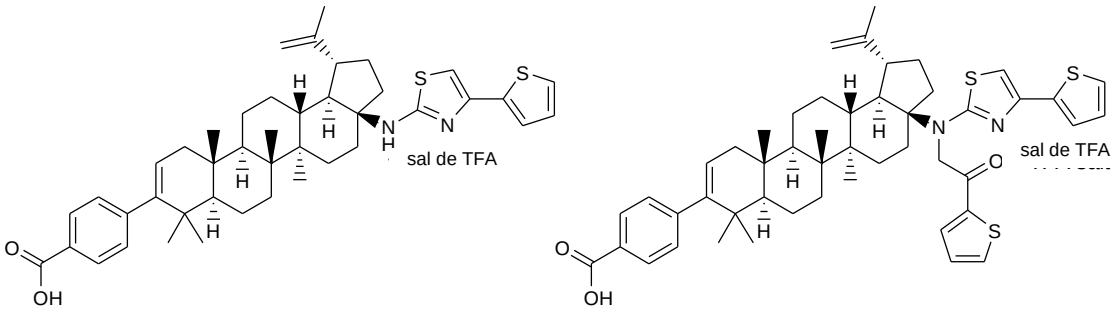


A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-tioureido-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (150 mg, 0.249 mmol) en DMF (3 mL), se agregaron *N,N*-diisopropiletilamina (0.217 mL, 1.244 mmol) y 2-bromo-1-(tiofen-3-il)etanona (77 mg, 0.373 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. Después de 18 h, la mezcla de reacción se vertió en un embudo separador que contenía H_2O (5 mL) y se extrajo con EtOAc (50

mL). La capa orgánica se lavó con salmuera, se secó en $MgSO_4$, se filtró y se concentró hasta obtener un sólido blanco. El material se volvió a disolver en DCM (3 mL). Se agregó MeOH, y la mezcla se concentró para eliminar la mayor parte de DCM. El precipitado blanco resultante se filtró, se lavó con MeOH frío y se secó en un horno al vacío para obtener una mezcla 4:1 (según se determinó mediante integración de HPLC) de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(4-(tiofen-3-il)tiazol-2-ilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo y 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-oxo-2-(tiofen-3-il)etil)(4-(tiofen-3-il)tiazol-2-il)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (134 mg, 82 % de rendimiento) como un sólido blanco. LC/MS: m/e 709.3 $(M+H)^+$, 3.62 min and m/e 833.3 $(M+H)^+$, 2.63 min (método 9), respectivamente. La HPLC analítica de fase inversa mostró una relación entre el producto principal a temperatura ambiente = 16.04 min (m/e 709.3 $(M+H)^+$) y el producto menor a temperatura ambiente = 15.42 min (m/e 833.3 $(M+H)^+$) de 80 %:20 % (con el método 2 de HPLC analítica).

Etapa 2. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-

pentametil-1-(prop-1-en-2-il)-3a-(4-(tiofen-3-il)tiazol-2-ilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, TFA y ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-oxo-2-(tiofen-3-il)etil)(4-(tiofen-3-il)tiazol-2-il)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, TFA.



A una mezcla de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(4-(tiofen-3-il)tiazol-2-ilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (119.36 mg, 0.168 mmol) y 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-oxo-2-(tiofen-3-il)etil)(4-(tiofen-3-il)tiazol-2-il)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (29.84 mg, 0.036 mmol) en THF (3 mL), se agregó una solución de hidróxido de litio monohidrato (25.4 mg, 0.606 mmol) en agua (1 mL). La reacción se calentó a 75 °C durante 6 h. La mezcla de reacción se concentró, se volvió a disolver en MeOH (2 mL) y THF (1 mL), se filtró y luego se inyectó (2 inyecciones) en HPLC de fase inversa para la purificación con el método 3 de HPLC preparativa, a fin de obtener ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(4-(tiofen-3-il)tiazol-2-ilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, TFA (110.7 mg, 0.134 mmol, 80 % de rendimiento) y ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-oxo-2-(tiofen-3-il)etil)(4-(tiofen-3-il)tiazol-2-il)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, TFA (13.4 mg, 0.016 mmol, 9.52 % de rendimiento).

Ejemplo 186: LC/MS: m/e 695.3 $(M+H)^+$, 2.92 min (método 11). ^{1}H NMR (500MHz, *CLOROFORMO-d*) δ 8.12 (br. s., 1 H), 8.03 (d, J = 8.2 Hz, 2 H), 7.42-7.39 (m, 1 H), 7.38-7.36 (m, 1 H), 7.25 (d, J = 8.2 Hz, 2 H), 6.52

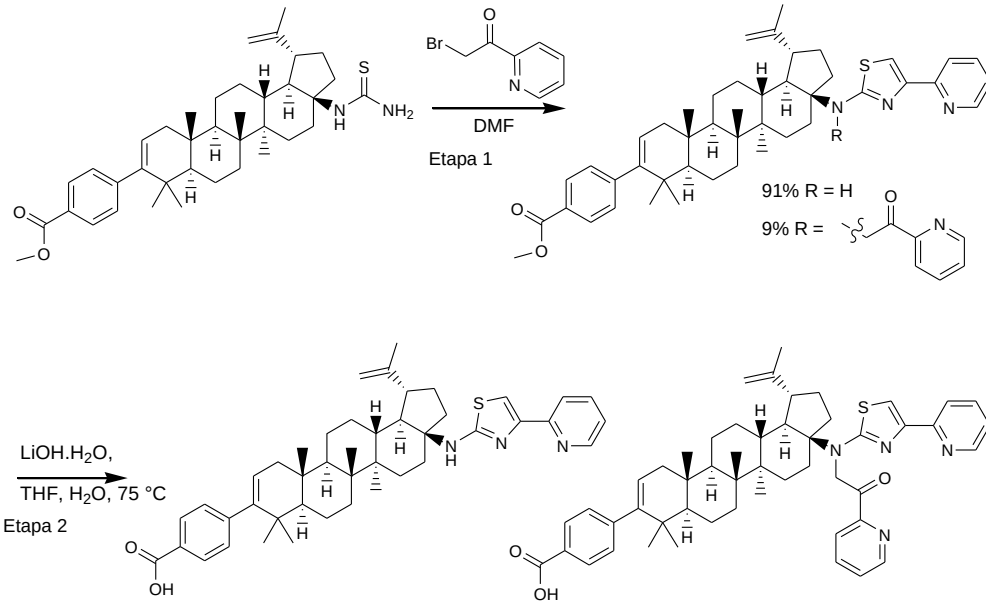
(s, 1 H), 5.33 (d, J = 4.6 Hz, 1 H), 4.86 (s, 1 H), 4.71 (s, 1 H), 3.04 (dt, J = 5.0, 11.1 Hz, 1 H), 2.58 (d, J = 14.0 Hz, 1 H), 2.39 (dd, J = 7.9, 12.8 Hz, 1 H), 2.33-2.25 (m, 1 H), 2.15 (dd, J = 6.4, 17.1 Hz, 1 H), 2.06-1.98 (m, 1 H), 1.92-1.82 (m, 2 H), 1.76 (s, 3 H), 1.70 (d, J = 17.1 Hz, 1 H), 1.64-1.56 (m, 1 H), 1.55-1.47 (m, 5 H), 1.46-1.37 (m, 5 H), 1.23 (d, J = 10.1 Hz, 1 H), 1.15 (d, J = 13.1 Hz, 1 H), 1.06 (s, 3 H), 1.05 (s, 3 H), 0.99 (s, 3 H), 0.95 (s, 3 H), 0.94 (s, 3 H). ^{13}C NMR (126MHz, *CLOROFORMO-d*) δ 171.2, 167.1, 163.3, 149.3, 148.5, 145.9, 129.9, 128.8, 127.0, 126.9, 124.7, 124.4, 123.9, 117.4, 115.1, 110.4, 98.1, 68.0, 52.6, 50.0, 49.3, 45.0, 41.6, 41.5, 40.4, 37.2, 36.2, 36.0, 33.4, 32.6, 29.2, 29.2, 27.0, 26.9, 24.9, 20.8, 19.5, 19.2, 16.1, 15.3, 14.1.

Ejemplo 186A: LC/MS: m/e 818.4 $(M+H)^+$, 2.50 min (método 11).

Ejemplos 187 y 187A

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(4-(piridin-2-il)tiazol-2-ilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico y ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-

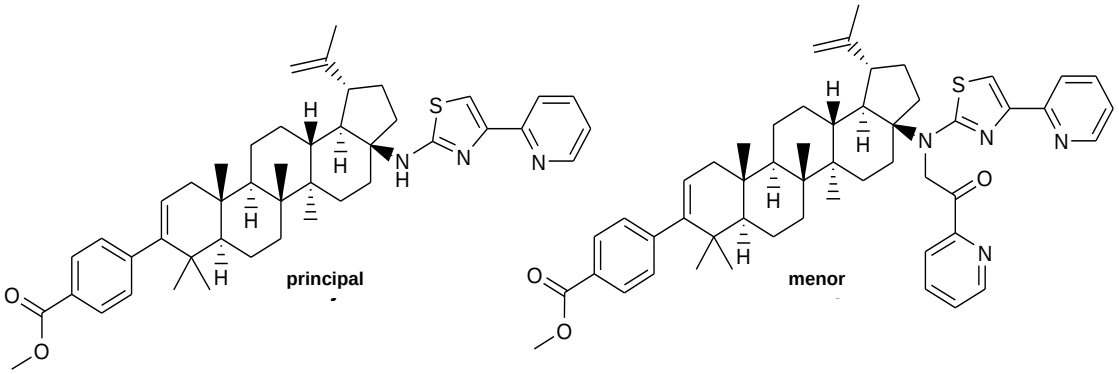
5a,5b,8,8,11a-pentametil-3a-((2-oxo-2-(piridin-2-il)etil)(4-(piridin-2-il)tiazol-2-il)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



Ejemplo 187 (7:1) **Ejemplo 187A**

Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(4-(piridin-2-il)tiazol-2-ilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo y 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-oxo-2-(piridin-2-il)etil)(4-(piridin-2-il)tiazol-2-il)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

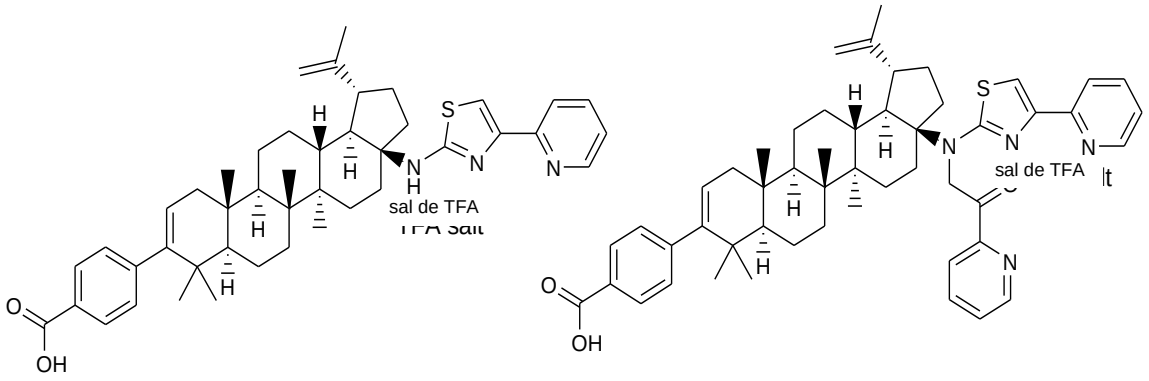


A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-tioureido-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (150 mg, 0.249 mmol), se agregaron *N,N*-diisopropiletilamina (0.217 mL, 1.244 mmol) y 2-bromo-1-(piridin-2-il)etanona, bromhidrato (116 mg, 0.373 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche. Después de 18 h, la mezcla de reacción se vertió en un embudo separador que contenía H_2O (5 mL) y se extrajo con EtOAc (50 mL). La capa orgánica se lavó con salmuera, se secó en $MgSO_4$, se filtró y se concentró hasta obtener un sólido marrón. El material se volvió a disolver en DCM (3 mL), se agregó MeOH, y la mezcla resultante se concentró para eliminar la mayor parte de DCM. El precipitado blanco resultante se filtró, se lavó con MeOH frío y se secó en un horno al vacío para obtener una mezcla 91:9 (según se determinó mediante integración de HPLC) de 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(4-(piridin-2-il)tiazol-2-ilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo y 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-oxo-2-(piridin-2-il)etil)(4-(piridin-2-il)tiazol-2-il)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (137 mg, 76.57 % de rendimiento) como un sólido marrón. LC/MS: m/e 704.3 $(M+H)^+$, 3.72 min y m/e 823.4 $(M+H)^+$, 2.56 min (método 9), respectivamente. La HPLC analítica de fase inversa mostró una relación entre el producto principal a temperatura ambiente = 22.43 min (m/e 704.3 $(M+H)^+$) y el producto menor a temperatura ambiente = 23.61 min (m/e 823.4 $(M+H)^+$) de 91 %:9 % (con el método 1 de HPLC analítica).

Etapa 2. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(4-(piridin-2-il)tiazol-2-ilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, TFA y ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-oxo-2-(piridin-2-il)etil)(4-(piridin-2-il)tiazol-2-il)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, TFA.



A una mezcla de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(4-(piridin-2-il)tiazol-2-ilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (117.66 mg, 0.167 mmol) y 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-oxo-2-(piridin-2-il)etil)(4-(piridin-2-il)tiazol-2-il)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (19.6 mg, 0.024 mmol) en THF (3 mL), se agregó una solución de hidróxido de litio monohidrato (25.2 mg, 0.602 mmol) en agua (1 mL). La reacción se calentó a 75 °C durante 6 h. La mezcla de reacción se concentró, se volvió a disolver en MeOH (2 mL) y THF (1 mL), se filtró y se inyectó en HPLC de fase inversa para la purificación con el método 3 de HPLC preparativa, a fin de obtener ácido 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(4-(piridin-2-il)tiazol-2-ilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, TFA (70.2 mg, 0.085 mmol, 50.7 % de rendimiento) y ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-oxo-2-(piridin-2-il)etil)(4-(piridin-2-il)tiazol-2-il)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, TFA (10.3 mg, 0.011 mmol, 6.86 % de rendimiento).

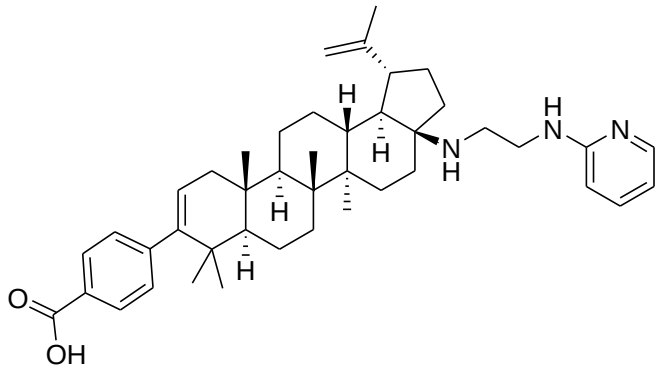
Ejemplo 187: LC/MS: m/e 690.3 $(M+H)^+$, 2.53 min (método 11). ^{1}H NMR (500MHz, *CLOROFORMO-d*) δ 9.67 (br. s., 1 H), 8.73 (td, *J* = 0.9, 5.0 Hz, 1 H), 8.14 (d, *J* = 7.9 Hz, 1 H), 8.02 (d, *J* = 8.2 Hz, 2 H), 7.96 (dt, *J* = 1.7, 7.9 Hz, 1 H), 7.42 (s, 1 H), 7.40 (ddd, *J* = 0.9, 4.9, 7.6 Hz, 1 H), 7.25 (d, *J* = 8.5 Hz, 2 H), 5.33 (d, *J* = 4.6 Hz, 1 H), 4.86 (s, 1 H), 4.71 (s, 1 H), 2.99 (dt, *J* = 4.9, 11.0 Hz, 1 H), 2.64-2.58 (m, 1 H), 2.41 (dd, *J* = 8.1, 12.7 Hz, 1 H), 2.23 (dt, *J* = 3.1, 12.1 Hz, 1 H), 2.16 (dd, *J* = 6.3, 17.2 Hz, 1 H), 2.06-2.00 (m, 1 H), 1.90 (t, *J* = 11.7 Hz, 1 H), 1.85 (d, *J* = 12.5 Hz, 1 H), 1.76 (s, 3 H), 1.70 (d, *J* = 17.1 Hz, 1 H), 1.64-1.55 (m, 1 H), 1.55-1.39 (m, 9 H), 1.30-1.21 (m, 1 H), 1.17 (d, *J* = 13.1 Hz, 1 H), 1.08 (s, 3 H), 1.06 (s, 3 H), 1.01 (s, 3 H), 0.95 (s, 3 H), 0.95 (s, 3 H). ^{13}C NMR

(126MHz, *CLOROFORMO-d*) δ 170.8, 167.4, 149.3, 148.4, 146.3, 145.9, 141.1, 138.6, 129.9, 128.8, 126.8, 123.9, 123.9, 121.2, 110.4, 104.8, 77.3, 68.1, 52.6, 49.9, 49.3, 45.2, 41.6, 41.5, 40.4, 37.2, 36.5, 36.0, 33.3, 32.7, 29.2, 29.2, 26.9, 24.9, 20.8, 19.4, 19.2, 16.1, 15.4, 14.2.

Ejemplo 187A: LC/MS: m/e 809.5 $(M+H)^+$, 2.38 min (método 11).

Ejemplo 188

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(2-(piridin-2-ilamino)etilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



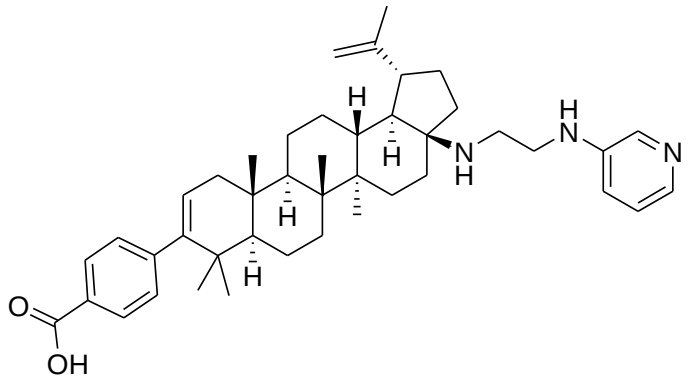
En un vial 1 dram en nitrógeno se combinaron (2R)-1-[(1R)-1-[bis(1,1-dimetiletil)fosfino]etil]-2-(diciclohexilfosfino)ferroceno (CAS# 158923-11-6) (2.101 mg, 3.79 µmol), acetato de paladio(II) (0.851 mg, 3.79 µmol) y DME seco (0.5 ml). El contenido del vial se agitó durante 10

min, y luego se agregó de una sola vez a una mezcla separada de 2-bromopiridina (0.012 g, 0.076 mmol), ter-butóxido de sodio (0.032 g, 0.333 mmol) en DME seco (0.5 mL) contenido en un vial 1 dram separado. La mezcla resultante se dejó agitar por poco tiempo (1 min) antes de agregar TBDMSCl (0.025 g, 0.167 mmol). El vial se agitó por poco tiempo, y se agregó en una porción sal de bis HCI de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-aminoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo sólido (0.050 g, 0.076 mmol). La adición final dio como resultado una exotermia leve. La mezcla se calentó a 110 °C durante 15 min. LCMS indicó un consumo esencialmente completo del material de inicio. A la mezcla se agregó agua (0.5 mL) y metanol (1.5 mL), y la mezcla resultante se agitó durante 2 días. La purificación de la mezcla cruda mediante HPLC preparativa de fase inversa con el método 6 de HPLC preparativa produjo el compuesto del título (0.0092 g, 13.1 % de rendimiento) como sal de bis-TFA en forma de polvo beige. LCMS: m/e 650.4 $(M+H)^+$, 3.76 min (método 16). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 8.01 (d, *J*= 4.9 Hz, 1H), 7.95-7.88 (m, *J*= 8.2 Hz, 2H), 7.72 (t, *J*= 7.3 Hz, 1H), 7.23-7.16 (m, *J*= 8.2 Hz, 2H), 6.92 (d, *J*= 8.2 Hz, 1H), 6.85 (t, *J*= 6.3 Hz, 1H), 5.29 (d, *J*= 4.9 Hz, 1H),

4.86 (s, 1H), 4.74 (br. s., 1H), 3.90-3.72 (m, 2H), 3.23-3.14 (m, 1H), 2.78-2.67 (m, 1H), 2.17-2.04 (m, 2H), 2.03-1.82 (m, 5H), 1.73 (s, 3H), 1.71-1.66 (m, 1H), 1.65-1.46 (m, 6H), 1.45-1.22 (m, 9H), 1.21-1.09 (m, 1H), 1.06 (s, 3H), 0.99 (br. s., 3H), 0.98 (br. s., 3H), 0.94 (s, 3H), 0.93 (br. s., 3H), 0.91-0.84 (m, *J*= 6.7, 3.4 Hz, 1H).

Ejemplo 189

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(2-(piridin-3-ilamino)etilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



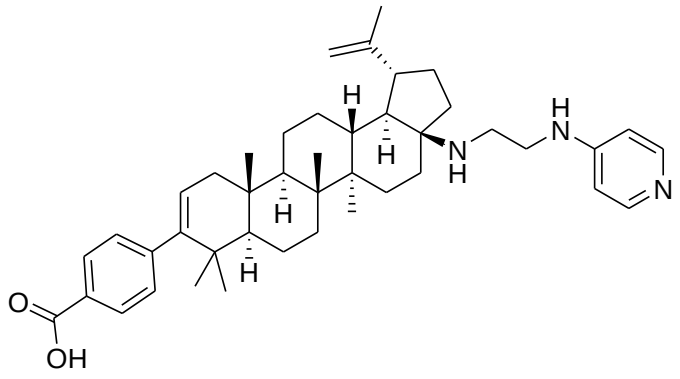
En un vial 1 dram en nitrógeno se combinaron (2R)-1-[(1R)-1-[bis(1,1-dimetiletil)fosfino]etil]-2-(diciclohexilfosfino)ferroceno (CAS# 158923-11-6) (2.101 mg, 3.79 µmol), acetato de paladio(II) (0.851 mg, 3.79 µmol) y DME seco (0.5 ml). El contenido del vial se agitó durante 10 min, y luego se agregó de una sola vez a una mezcla separada

de 3-bromopiridina (0.014 g, 0.091 mmol) y ter-butóxido de sodio, solución 2.0 M en THF (0.167 mL, 0.333 mmol) en DME seco (0.333 mL) contenido en un vial 1 dram separado. La mezcla resultante se dejó agitar por poco tiempo (1 min) antes de agregar en una porción de sal de bis HCl de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-aminoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo sólido (0.050 g, 0.076 mmol). La mezcla se calentó a 110 °C durante la noche. A la mezcla se agregó hidróxido de litio monohidrato (6.4 mg, 0.152 mmol) con agua (0.2 mL) y metanol (0.5 mL), y la mezcla resultante se agitó durante 4 días. La purificación de la mezcla cruda mediante HPLC preparativa de fase inversa con el método 7 de HPLC preparativa produjo el compuesto del título (0.0407 g, 57.5% de rendimiento) como sal de bis-TFA en forma de polvo beige. LCMS: m/e 650.4 $(M+H)^+$, 2.26 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 8.26 (d, *J*= 2.4 Hz, 1H), 8.02 (d, *J*= 4.9 Hz, 1H), 7.94-7.87 (m, *J*= 8.2 Hz, 2H), 7.77 (dd, *J*= 8.9, 1.5 Hz, 1H), 7.67 (dd, *J*= 8.9, 5.2 Hz, 1H), 7.22-7.14 (m, 2H), 5.28 (dd, *J*= 6.3, 1.7 Hz, 1H), 4.82 (s, 1H), 4.74 (s, 1H), 3.89-3.78 (m, 1H), 3.70 (dt, *J*= 14.6, 4.5 Hz, 1H), 3.30-3.23 (m, 2H), 2.85 (td, *J*= 11.1, 5.5 Hz, 1H), 2.21-2.05 (m, 3H), 2.03-1.94 (m, 2H), 1.94-1.85 (m, 1H),

1.85-1.76 (m, 1H), 1.72 (s, 3H), 1.70-1.64 (m, 1H), 1.64-1.51 (m, 3H), 1.51-1.44 (m, 3H), 1.43-1.20 (m, 6H), 1.19-1.08 (m, 2H), 1.07-1.04 (m, 3H), 1.04-1.00 (m, 3H), 0.99 (s, 3H), 0.95-0.88 (m, 7H).

Ejemplo 190

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(2-(piridin-4-ilamino)etilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

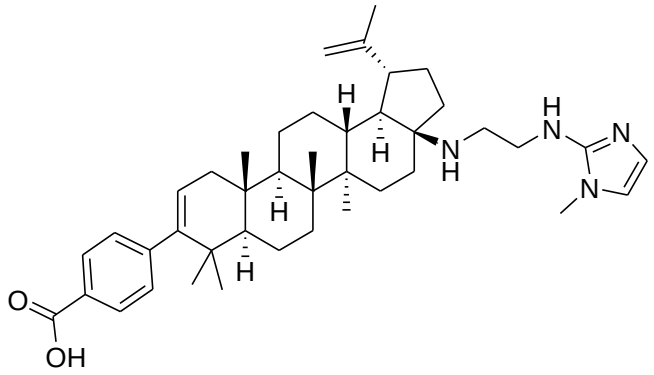


El compuesto del título se preparó de acuerdo con un procedimiento similar al descrito para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(2-(piridin-3-ilamino)etilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó clorhidrato de 4-bromopiridina (0.018

g, 0.091 mmol) en lugar de 3-bromopiridina, y 1.2 equivalentes adicionales de solución de ter-butóxido de sodio, solución 2.0 M en THF (para un total de 5.6 equivalentes, 0.212 mL, 0.424 mmol). El producto se aisló después de la purificación mediante HPLC preparativa de fase inversa con el método 7 de HPLC preparativa como una sal de bis-TFA sólida beige (74 mg, 54 % de rendimiento). LCMS: m/e 650.4 $(M+H)^+$, 3.85 min (método 16). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 8.19-7.97 (m, 2H), 7.91 (d, *J*= 8.2 Hz, 2H), 7.19 (d, *J*= 8.2 Hz, 2H), 7.06 (br. s., 2H), 5.28 (d, *J*= 4.6 Hz, 1H), 4.83 (s, 1H), 4.73 (s, 1H), 3.96-3.81 (m, 2H), 3.31-3.19 (m, 2H), 2.88-2.76 (m, 1H), 2.18-2.03 (m, 3H), 1.97 (dd, *J*= 10.4, 6.4 Hz, 3H), 1.83 (d, *J*= 12.5 Hz, 1H), 1.72 (s, 3H), 1.68 (br. s., 1H), 1.66-1.45 (m, 7H), 1.44-1.28 (m, 5H), 1.24 (d, *J*= 8.2 Hz, 1H), 1.18-1.11 (m, 1H), 1.09 (s, 3H), 1.06 (s, 3H), 1.01 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H).

Ejemplo 191

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(1-metil-1H-imidazol-2-ilamino)etilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

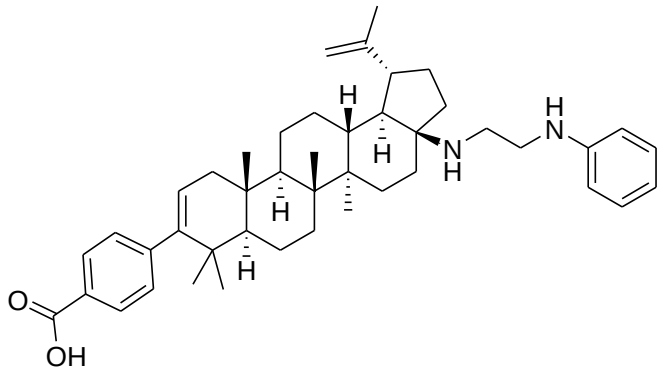


El compuesto del título se preparó de acuerdo con un procedimiento similar al descrito para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(2-(piridin-3-ilamino)etilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó 2-bromo-1-metil-1H-imidazol (0.015 g, 8.88 µL, 0.091 mmol) en lugar de 3-bromopiridina. Asimismo, no fue necesaria la adición de LiOH, agua y metanol para este ejemplo, debido a que la hidrólisis de ésteres ocurrió espontáneamente en el transcurso de la reacción de aminación. El producto se aisló después de la purificación mediante HPLC preparativa de fase inversa con el método 8 de HPLC preparativa como una sal de bis-TFA sólida beige (38.1 mg, 51.5% de rendimiento). LCMS: m/e 653.4 $(M+H)^+$, 3.88 min (método 16). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 7.91 (d, *J*= 8.2 Hz, 2H), 7.19 (d, *J*= 7.9 Hz, 2H), 6.86 (s, 1H), 6.83-6.79 (m, 1H), 5.28 (d, *J*=

5.5 Hz, 1H), 4.84 (s, 1H), 4.73 (s, 1H), 4.71 (br. s., 1H), 3.98-3.82 (m, 2H), 3.58 (s, 3H), 3.25 (br. s., 1H), 2.89-2.78 (m, 1H), 2.18-2.07 (m, 3H), 2.05-1.92 (m, 3H), 1.90-1.79 (m, 1H), 1.72 (s, 4H), 1.69 (br. s., 1H), 1.62-1.54 (m, 3H), 1.53-1.47 (m, 3H), 1.46-1.34 (m, 5H), 1.28-1.20 (m, 2H), 1.18-1.12 (m, 1H), 1.11 (s, 3H), 1.09-1.03 (m, 4H), 1.01 (s, 3H), 0.93 (br. s., 3H), 0.93 (br. s., 3H).

Ejemplo 192

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(fenilamino)etilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

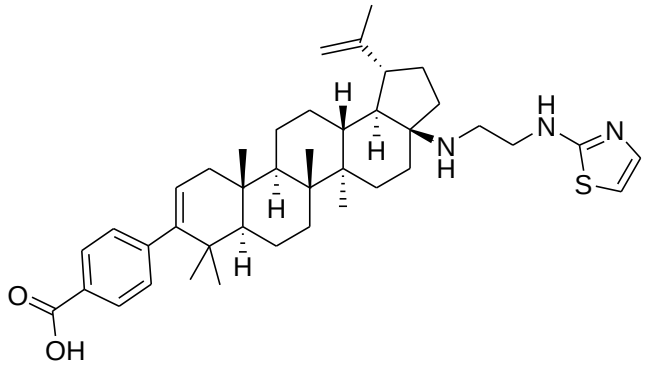


El compuesto del título se preparó de acuerdo con un procedimiento similar al descrito para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(2-(piridin-3-ilamino)etilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó bromobenceno (0.014 g, 9.58 µL, 0.091 mmol) en lugar de 3-bromopiridina. El producto se aisló después de la purificación mediante HPLC preparativa de fase inversa con el método 7 de HPLC preparativa como una sal de bis-TFA sólida beige (29.7 mg, 42 % de rendimiento). LCMS: m/e 649.4 $(M+H)^+$, 2.42 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 7.94-7.88 (m, *J*= 7.9 Hz, 2H), 7.22 (t, *J*= 7.8 Hz, 2H), 7.20-7.15 (m, *J*= 8.2 Hz, 2H), 6.82 (t, *J*= 7.3 Hz, 1H), 6.75 (d, *J*= 7.9 Hz, 2H), 5.27 (d, *J*= 5.5 Hz, 1H), 4.81 (s, 1H), 4.73 (s, 1H), 3.68-3.58 (m, 1H), 3.58-3.51 (m, 1H), 3.25-3.17 (m, 2H), 2.82 (td, *J*= 11.0, 5.2 Hz, 1H), 2.18-2.05 (m, 2H), 2.01-1.92 (m, 2H), 1.90 (br. s., 1H), 1.83-1.72 (m, 2H), 1.71 (s, 3H), 1.68 (d, *J*= 17.4 Hz, 1H), 1.64-1.46 (m, 6H), 1.45-1.30 (m, 5H), 1.27-1.11 (m, 4H), 1.10-1.02 (m, 2H), 1.02-0.99 (m, 6H), 0.98 (s, 3H), 0.93 (s, 3H), 0.91 (s, 3H).

Ejemplo 193

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(2-(tiazol-2-ilamino)etilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

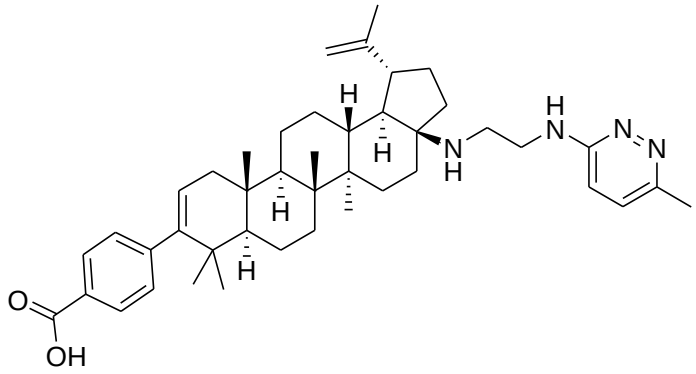


El compuesto del título se preparó de acuerdo con un procedimiento similar al descrito para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(2-(piridin-3-ilamino)etilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó 2-bromotiazol (0.015 g, 0.091 mmol) en lugar de 3-bromopiridina. El producto se aisló después de la purificación mediante HPLC preparativa de fase inversa con el método 7 de HPLC preparativa como una sal de bis-TFA sólida beige (12.8 mg, 18 % de rendimiento). LCMS: m/e 656.4 $(M+H)^+$, 2.38 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 7.91 (d, *J*= 8.2 Hz, 2H), 7.19 (d, *J*= 8.2 Hz, 2H), 7.08 (d, *J*= 3.7 Hz, 1H), 6.68 (d, *J*= 4.0 Hz, 1H), 5.28 (d, *J*= 4.6 Hz, 1H), 4.86 (s, 1H), 4.74 (br. s., 1H), 3.69 (dd, *J*= 9.9, 5.3 Hz, 1H), 3.43-3.36 (m, 1H), 2.13 (dd, *J*= 17.2, 6.3 Hz, 1H), 2.05 (d, *J*= 15.0 Hz, 1H), 2.01-1.79 (m, 6H), 1.73 (s, 4H), 1.70-1.46 (m, 8H), 1.46-1.27

(m, 6H), 1.27-1.22 (m, 2H), 1.22-1.10 (m, 2H), 1.07 (s, 3H), 1.04 (s, 3H), 1.00 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H).

Ejemplo 194

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(6-metilpiridazin-3-ilamino)etilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

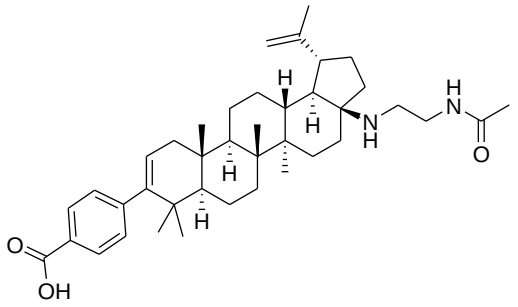


En un vial 1 dram en nitrógeno se combinaron (2R)-1-[(1R)-1-[bis(1,1-dimetiletil)fosfino]etil]-2-(diciclohexilfosfino)ferroceno (CAS# 158923-11-6) (2.52 mg, 4.55 µmol), acetato de paladio(II) (1.02 mg, 4.55 µmol) y DME seco (0.5 ml). El contenido del vial se agitó durante 10 min, y luego se agregó de una sola vez a una mezcla separada de 3-bromo-6-metilpiridazina (0.017 g, 0.100 mmol) y ter-butóxido de sodio, solución 2.0 M en THF (0.200 mL, 0.400 mmol) en DME seco (0.500 mL) contenido en un vial 1 dram separado. La mezcla resultante se dejó agitar por poco

tiempo (1 min) antes de agregar en una porción de sal de bis HCl de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-aminoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo sólido (0.060 g, 0.091 mmol). La mezcla se calentó a 110 °C durante la noche. La purificación iterativa de la mezcla cruda mediante HPLC preparativa de fase inversa primero con el método 9 de HPLC preparativa y luego la repurificación con el método 10 de HPLC preparativa produjeron el compuesto del título (0.0070 g, 8.3 % de rendimiento) como una sal de bis-TFA sólida vidriosa blanca. LCMS: m/e 665.5 $(M+H)^+$, 2.22 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 7.90 (d, *J*= 8.5 Hz, 2H), 7.49-7.42 (m, 1H), 7.32-7.23 (m, 1H), 7.18 (d, *J*= 8.2 Hz, 2H), 5.27 (dd, *J*= 6.0, 1.4 Hz, 1H), 4.88 (br. s., 1H), 4.72 (br. s., 1H), 3.94-3.84 (m, 1H), 3.84-3.73 (m, 1H), 3.26-3.13 (m, 1H), 2.84 (d, *J*= 12.5 Hz, 1H), 2.57 (s, 3H), 2.12 (dd, *J*= 16.9, 6.3 Hz, 1H), 2.05 (d, *J*= 15.6 Hz, 1H), 2.01-1.91 (m, 2H), 1.91-1.74 (m, 2H), 1.70 (s, 3H), 1.69-1.59 (m, 2H), 1.59-1.43 (m, 4H), 1.43-1.28 (m, 4H), 1.28-1.18 (m, 4H), 1.18-1.06 (m, 2H), 1.05 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 0.92 (s, 3H), 0.92-0.89 (m, 3H).

Ejemplo 195

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-(2-acetamidoetilamino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

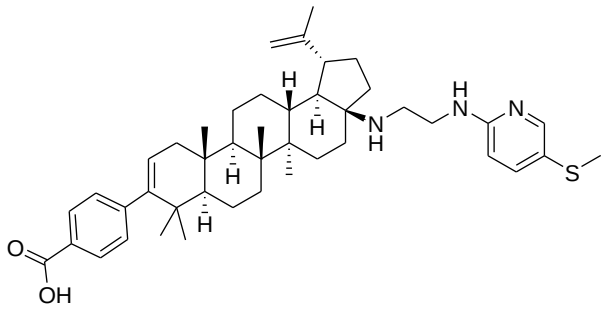


El compuesto del título se preparó de acuerdo con un procedimiento similar al descrito para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(6-metilpiridazin-3-ilamino)etilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó 4-bromopirimidina (0.016 g, 0.100 mmol) en lugar de 3-bromo-6-metilpiridazina. La reacción no produjo el producto deseado, sino que, en su lugar, produjo el subproducto del compuesto del título como el aislado principal. La purificación iterativa de la mezcla cruda mediante HPLC preparativa de fase inversa primero con el método 9 de HPLC preparativa y luego la repurificación con el método 10 de HPLC preparativa produjeron el compuesto del

título como una sal de mono-TFA sólida vidriosa blanca (7.5 mg, 9.6 % de rendimiento). LCMS: m/e 615.5 $(M+H)^+$, 2.42 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 8.18 (s, 1H), 7.94-7.84 (m, *J*= 8.2 Hz, 2H), 7.24-7.13 (m, *J*= 8.2 Hz, 2H), 5.27 (d, *J*= 4.6 Hz, 1H), 4.83 (s, 1H), 4.72 (br. s., 1H), 3.89 (s, 3H), 3.61 (br. s., 2H), 3.18 (br. s., 2H), 2.71 (td, *J*= 11.1, 6.3 Hz, 2H), 2.12-1.92 (m, 6H), 1.90-1.76 (m, 3H), 1.76-1.66 (m, 5H), 1.66-1.43 (m, 9H), 1.42-1.33 (m, 3H), 1.24 (br. s., 2H), 1.17 (s, 3H), 1.07 (s, 3H), 1.01 (s, 3H), 0.93 (s, 3H), 0.92 (br. s., 3H).

Ejemplo 196

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(5-(metiltio)piridin-2-ilamino)etilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

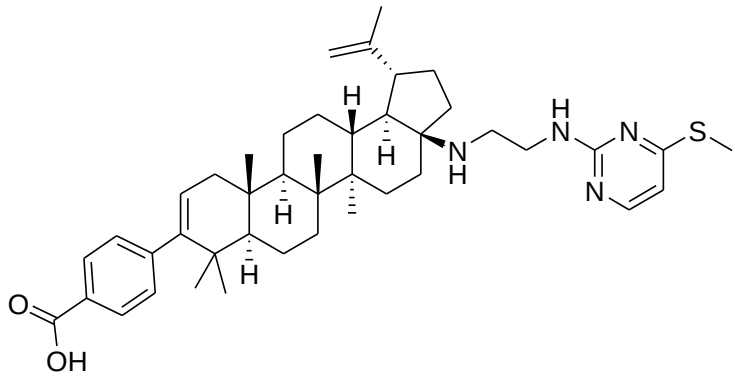


El compuesto del título se preparó de acuerdo con un procedimiento similar al descrito para la síntesis de

ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(6-metilpiridazin-3-ilamino)etilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó 2-bromo-5-(metiltio)piridina (0.020 g, 0.100 mmol) en lugar de 3-bromo-6-metilpiridazina. La purificación iterativa de la mezcla cruda mediante HPLC preparativa de fase inversa primero con el método 9 de HPLC preparativa y luego la repurificación con el método 10 de HPLC preparativa produjeron el compuesto del título como una sal de bis-TFA sólida vidriosa blanca (5.2 mg, 5.9 % de rendimiento). LCMS: m/e 696.5 $(M+H)^+$, 2.34 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 8.03 (d, *J*= 1.8 Hz, 1H), 7.93-7.88 (m, *J*= 8.2 Hz, 2H), 7.61-7.57 (m, 1H), 7.21-7.14 (m, *J*= 8.2 Hz, 2H), 6.71 (d, *J*= 8.9 Hz, 1H), 5.27 (dd, *J*= 6.1, 1.5 Hz, 1H), 4.87 (s, 1H), 4.75 (br. s., 1H), 4.72 (br. s., 1H), 3.80-3.72 (m, 1H), 3.72-3.63 (m, 1H), 3.18-3.09 (m, 1H), 2.72-2.64 (m, 1H), 2.39 (s, 3H), 2.11 (dd, *J*= 17.1, 6.4 Hz, 1H), 2.08-2.01 (m, 1H), 2.00-1.90 (m, 3H), 1.90-1.74 (m, 3H), 1.72 (s, 3H), 1.71-1.66 (m, 2H), 1.65-1.44 (m, 7H), 1.44-1.33 (m, 3H), 1.33-1.12 (m, 7H), 1.04 (s, 3H), 0.97 (s, 3H), 0.91 (br. s., 3H), 0.91 (br. s., 3H), 0.87 (s, 3H).

Ejemplo 197

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(4-(metiltio)pirimidin-2-ilamino)etilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

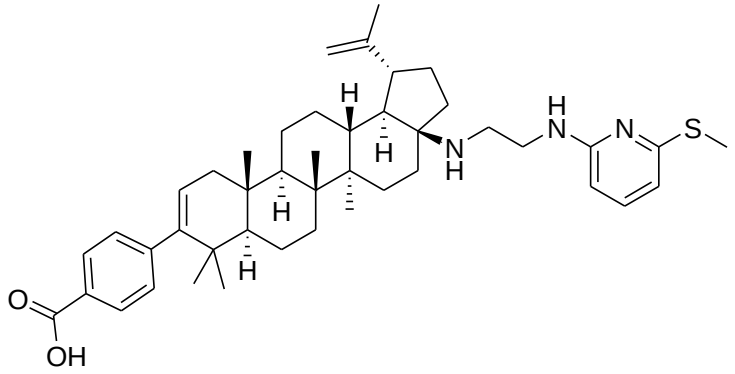


El compuesto del título se preparó de acuerdo con un procedimiento similar al descrito para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(6-metilpiridazin-3-ilamino)etilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó 2-cloro-4-(metiltio)pirimidina (0.016 g, 0.100 mmol) en lugar de 3-bromo-6-metilpiridazina. La purificación iterativa de la mezcla cruda mediante HPLC preparativa de fase inversa primero con el método 9 de HPLC preparativa y luego la repurificación con el método 10 de HPLC preparativa produjeron el compuesto del título como una sal de bis-TFA

sólida vidriosa blanca (12.0 mg, 14% de rendimiento). LCMS: m/e 697.5 $(M+H)^+$, 2.30 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 7.99-7.85 (m, 3H), 7.17 (d, *J*= 8.2 Hz, 2H), 6.75-6.63 (m, 1H), 5.26 (d, *J*= 4.6 Hz, 1H), 4.82 (s, 1H), 4.70 (br. s., 1H), 3.96 (s, 1H), 3.85 (br. s., 2H), 3.43-3.34 (m, 1H), 3.25 (br. s., 1H), 2.72 (br. s., 1H), 2.55 (s, 3H), 2.10 (dd, *J*= 17.1, 6.4 Hz, 1H), 2.04 (d, *J*= 15.3 Hz, 1H), 2.01-1.89 (m, 3H), 1.89-1.77 (m, 2H), 1.70 (s, 4H), 1.68-1.49 (m, 5H), 1.46 (d, *J*= 7.3 Hz, 3H), 1.42-1.18 (m, 7H), 1.18-1.06 (m, 2H), 1.03 (s, 3H), 0.97 (s, 3H), 0.95 (s, 3H), 0.92 (s, 3H), 0.91 (br. s., 3H).

Ejemplo 198

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(6-(metiltio)piridin-2-ilamino)etilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



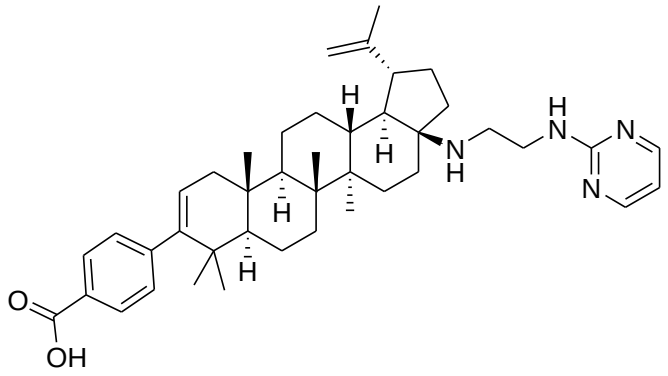
El compuesto del título se preparó de acuerdo con

un procedimiento similar al descrito para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(6-metilpiridazin-3-ilamino)etilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó 2-bromo-6-(metiltio)piridina (0.020 g, 0.100 mmol) en lugar de 3-bromo-6-metilpiridazina. La purificación iterativa de la mezcla cruda mediante HPLC preparativa de fase inversa primero con el método 9 de HPLC preparativa y luego la repurificación con el método 10 de HPLC preparativa produjeron el compuesto del título como una sal de bis-TFA sólida vidriosa blanca (10.3 mg, 12 % de rendimiento). LCMS: m/e 696.5 $(M+H)^+$, 2.34 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 7.95-7.85 (m, *J*= 8.2 Hz, 2H), 7.39 (t, *J*= 7.8 Hz, 1H), 7.20-7.12 (m, *J*= 8.2 Hz, 2H), 6.53 (d, *J*= 7.6 Hz, 1H), 6.37 (d, *J*= 7.9 Hz, 1H), 5.25 (d, *J*= 4.6 Hz, 1H), 4.85 (s, 1H), 4.72 (br. s., 1H), 3.96 (s, 1H), 3.78-3.59 (m, 2H), 3.28-3.13 (m, 2H), 2.95-2.83 (m, 1H), 2.49 (s, 3H), 2.08-1.86 (m, 6H), 1.78-1.69 (m, 4H), 1.69-1.52 (m, 5H), 1.52-1.31 (m, 6H), 1.31-1.07 (m, 7H), 1.01 (s, 3H), 0.95-0.83 (m, 9H), 0.57 (s, 3H).

Ejemplo 199

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-

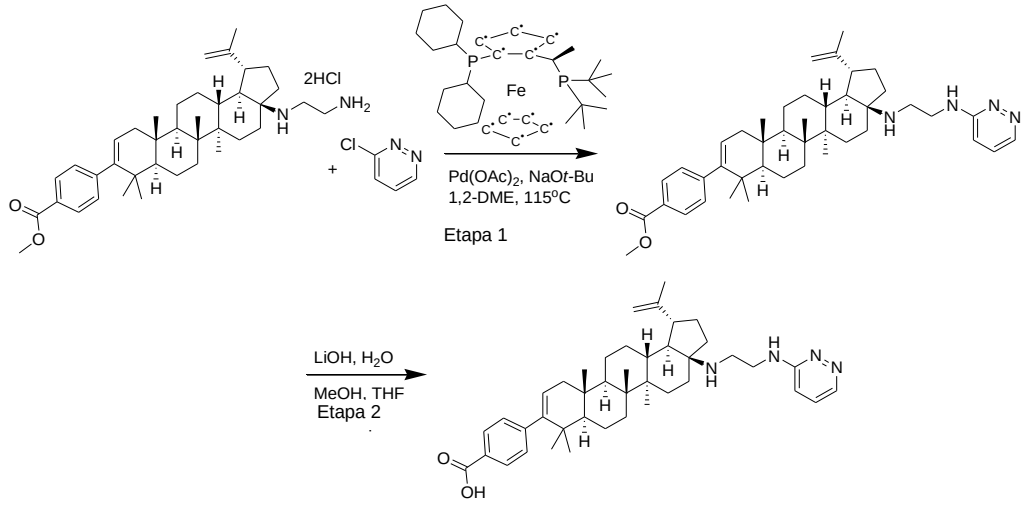
pentametil-1-(prop-1-en-2-il)-3a-(2-(pirmidin-2-ilamino)etilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



El compuesto del título se preparó de acuerdo con un procedimiento similar al descrito para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(6-metilpiridazin-3-ilamino)etilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó 2-bromopirimidina (0.016 g, 0.100 mmol) en lugar de 3-bromo-6-metilpiridazina. La purificación iterativa de la mezcla cruda mediante HPLC preparativa de fase inversa primero con el método 9 de HPLC preparativa y luego la repurificación con el método 10 de HPLC preparativa produjeron el compuesto del título como una sal de bis-TFA sólida vidriosa blanca (8.0 mg, 8.2 % de rendimiento). LCMS: m/e 651.5 $(M+H)^+$, 2.27 min (método 11).

Ejemplo 200

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(2-(piridazin-3-ilamino)etilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(2-(piridazin-3-ilamino)etilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

El compuesto del título se preparó de acuerdo con un procedimiento similar al descrito para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(6-metilpiridazin-3-

ilamino)etilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico, excepto que se usó 3-cloropiridazina (0.011 g, 0.100 mmol) en lugar de 3-bromo-6-metilpiridazina. La purificación de la mezcla cruda mediante HPLC preparativa de fase inversa con el método 9 de HPLC preparativa produjo el compuesto del título como una sal de bis-TFA sólida vidriosa blanca (4.9 mg, 6.0 % de rendimiento). LCMS: m/e 665.5 $(M+H)^+$, 2.40 min (método 11).

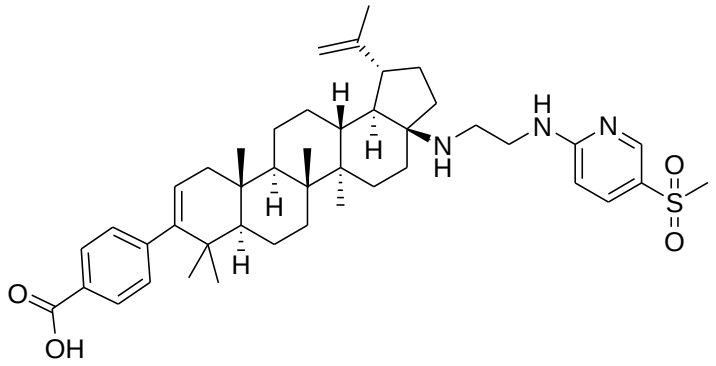
Etapa 2. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(2-(piridazin-3-ilamino)etilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

Una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(2-(piridazin-3-ilamino)etilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo e hidróxido de litio monohidrato (2.3 mg, 0.055 mmol) en una mezcla de agua (0.5 mL), THF (0.25 mL) y MeOH (0.25 mL) se agitó a temperatura ambiente durante 2.5 días. La purificación de la mezcla cruda mediante HPLC preparativa de

fase inversa con el método 10 de HPLC preparativa produjo el compuesto del título como una sal de bis-TFA sólida blanca (5.0 mg, 100 % de rendimiento). LCMS: m/e 651.5 $(M+H)^+$, 2.26 min (método 11).

Ejemplo 201

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(5-(metilsulfonil)piridin-2-ilamino)etilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



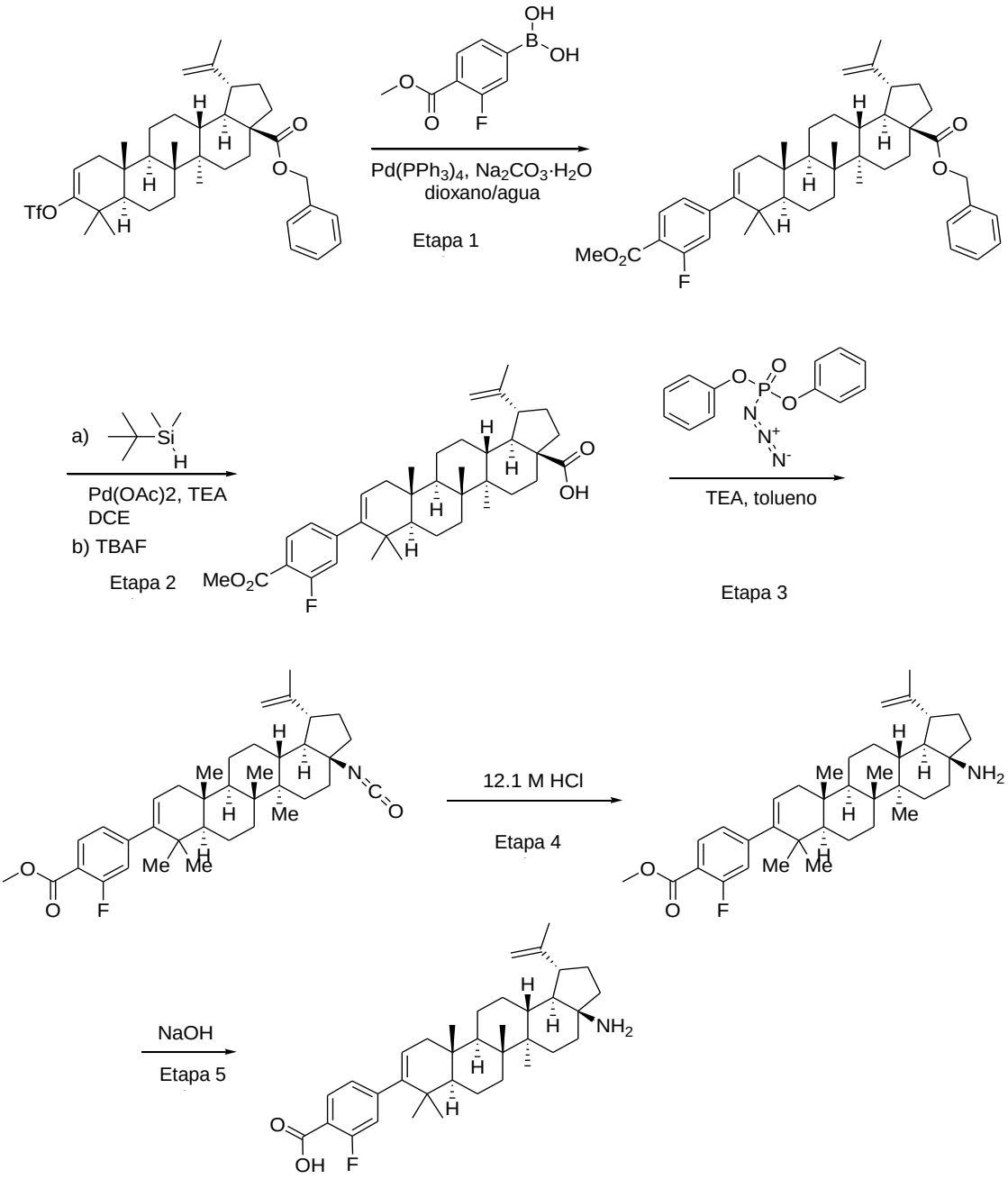
El compuesto del título se preparó de acuerdo con un procedimiento similar al descrito para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-(2-(piridazin-3-ilamino)etilamino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico,

excepto que se usó 2-bromo-5-(metilsulfonil)piridina (0.024 g, 0.100 mmol) en lugar de 3-cloropiridazina. La purificación de la mezcla cruda de la Etapa 2 mediante HPLC preparativa de fase inversa con el Método 10 de HPLC preparativa produjo el compuesto del título como una sal de bis-TFA sólida blancuzca (10.6 mg, 11.9 % de rendimiento en 2 etapas). LCMS: m/e 728.5 $(M+H)^+$, 2.22 min (método 11). ^{1}H NMR (500 MHz, 1:1 mezcla de *CDCl3* y *MeOD*, estabilización *MeOD*) δ ppm 8.61 (d, *J*= 1.8 Hz, 1H), 7.95-7.87 (m, 3H), 7.19 (d, *J*= 8.2 Hz, 2H), 6.80 (d, *J*= 8.9 Hz, 1H), 5.29 (d, *J*= 4.6 Hz, 1H), 4.90 (s, 1H), 4.82 (br. s., 1H), 3.96-3.85 (m, 1H), 3.85-3.71 (m, 1H), 3.42 (br. s., 1H), 3.37 (s, 3H), 3.27-3.18 (m, 1H), 3.10 (s, 3H), 2.70 (br. s., 1H), 2.14 (dd, *J*= 17.2, 6.3 Hz, 1H), 2.10-1.95 (m, 5H), 1.91-1.77 (m, 3H), 1.74 (s, 3H), 1.71 (d, *J*= 17.4 Hz, 2H), 1.65-1.47 (m, 6H), 1.47-1.34 (m, 3H), 1.34-1.11 (m, 6H), 1.06 (s, 3H), 1.00 (s, 3H), 0.94 (s, 6H), 0.93 (s, 3H).

Sección 6. Derivados del ácido F-benzoico

Ejemplo A1

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)-2-fluorobenzoico.



Etapa 1. Preparación de 9-(3-fluoro-4-(metoxicarbonil)fenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-carboxilato de (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-bencilo.

Una suspensión de 5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-9-(trifluorometilsulfoniloxi)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-carboxilato de (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-bencilo (4.0 g, 5.91 mmol), ácido 3-fluoro-4-(metoxicarbonil)fenilborónico (1.287 g, 6.50 mmol), carbonato de sodio monohidrato (2.198 g, 17.73 mmol) y $Pd(PPh_3)_4$ (0.205 g, 0.177 mmol) en 1,4-dioxano (24 mL) y agua (6 mL) se purgó con N_2, y la mezcla se calentó a reflujo. Después de 2 h de calentamiento, la mezcla se enfrió a temperatura ambiente. La mezcla se diluyó con agua (40 mL) y se extrajo con diclorometano (3 x 40 mL). Las capas orgánicas combinadas se secaron con Na_2SO_4. El agente de secado se retiró mediante filtración, y el filtrado se concentró a presión reducida. El residuo se disolvió en DCM y se filtró a través de una almohadilla de Celite y gel de sílice, y se lavó con una solución de 25 % de EtOAc en hexanos. El filtrado se concentró a presión reducida para obtener el compuesto del título (3.59 g, 5.27 mmol, 89 % de rendimiento) como una espuma gris oscura. El producto crudo se usó en la siguiente etapa sin purificación adicional. ^{1}H NMR (500 MHz, *CLOROFORMO-d*) δ ppm 7.80 (1 H, t, *J*= 7.8 Hz), 7.29-7.42 (5 H, m), 6.96 (1 H, d, *J*= 7.9 Hz), 6.91 (1 H, d, *J*= 11.9 Hz), 5.28-5.33 (1 H, m), 5.16 (1 H, d, *J*= 12.5 Hz), 5.09 (1 H, d, *J*= 12.2 Hz), 4.73 (1 H, s), 4.59 (1 H, br. s.),

3.92 (3 H, s), 3.03 (1 H, td, *J*= 10.8, 4.7 Hz), 2.20-2.33 (2 H, m), 2.09 (1 H, dd, *J*= 17.1, 6.4 Hz), 1.81-1.97 (2 H, m), 1.68 (3 H, s), 0.96 (3 H, s), 0.92 (3 H, s), 0.92 (3 H, s), 0.91 (3 H, s), 0.81 (3 H, s), 0.79-1.75 (17 H, m).

Etapa 2. Preparación de ácido (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(3-fluoro-4-(metoxicarbonil)fenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-carboxílico.

A una solución de 9-(3-fluoro-4-(metoxicarbonil)fenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-carboxilato de (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-bencilo (3.59 g, 5.27 mmol) en DCE (25 mL), se agregó TEA (1.176 mL, 8.44 mmol), *t*-butildimetilsilano (1.749 mL, 10.54 mmol) y acetato de paladio(II) (0.118 g, 0.527 mmol). La mezcla se purgó con N_2 y se calentó a 60 °C durante 1 h. La mezcla se enfrió a temperatura y se filtró a través de un tapón de Celite y gel de sílice (lavado con 25 % de EtOAc en hexanos). El filtrado se concentró a presión reducida. El residuo se diluyó con 25 mL de dioxano, y se agregó TBAF (75 % en agua) (2.76 g, 7.91 mmol). La mezcla se agitó durante 30 minutos a temperatura ambiente; luego, se diluyó con 50 mL de HCl 1N. Los sólidos que se formaron se recolectaron por filtración y se lavaron

con agua para obtener el compuesto del título (2.95 g, 4.99 mmol, 95 % de rendimiento) como un sólido blanco. ^{1}H NMR (400 MHz, *CLOROFORMO-d*) δ ppm 7.83 (1 H, t, *J*= 7.9 Hz), 6.90-7.00 (2 H, m), 5.34 (1 H, dd, *J*= 6.1, 1.6 Hz), 4.77 (1 H, d, *J*= 2.0 Hz), 4.64 (1 H, s), 3.94 (3 H, s), 3.04 (1 H, td, *J*= 10.7, 4.8 Hz), 2.24-2.34 (2 H, m), 2.13 (1 H, dd, *J*= 17.3, 6.3 Hz), 1.96-2.06 (2 H, m), 1.72 (3 H, s), 1.03 (3 H, s), 1.02 (3 H, s), 0.98 (3 H, s), 0.93-0.96 (6 H, m), 0.91-1.80 (17 H, m).

Etapa 3. Preparación de 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocianato-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

A una solución de ácido (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(3-fluoro-4-(metoxicarbonil)fenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-carboxílico (2.95 g, 4.99 mmol) en tolueno (50 mL) y TEA (1.39 mL, 9.99 mmol), se agregó difenil fosforazidata (1.614 mL, 7.49 mmol), y la mezcla se calentó a reflujo. Después de 3 h, la mezcla de reacción se concentró a presión reducida, se adsorbió en gel de sílice y se purificó mediante cromatografía instantánea con un gradiente de 0-10 % de EtOAc en hexanos para obtener

el compuesto del título como un sólido blanco. El material se usó en la siguiente etapa sin purificación adicional. ^{1}H NMR (500 MHz, *Cloroformo-d*) δ ppm 7.81 (1 H, t, *J*= 7.8 Hz), 6.96 (1 H, dd, *J*= 7.9, 1.5 Hz), 6.92 (1 H, dd, *J*= 11.9, 1.5 Hz), 5.31 (1 H, dd, *J*= 6.3, 1.7 Hz), 4.75 (1 H, s), 4.64 (1 H, s), 3.92 (3 H, s), 2.55 (1 H, td, *J*= 10.8, 5.8 Hz), 2.05-2.16 (2 H, m), 1.76-1.92 (4 H, m), 1.68 (3 H, s), 1.09-1.11 (3 H, m), 0.97 (3 H, s), 0.96 (3 H, s), 0.94 (3 H, s), 0.92 (3 H, s), 0.88-1.75 (16 H, m).

Etapa 4. Preparación de diclorhidrato de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)-2-fluorobenzoato de metilo.

A una solución de 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-isocianato-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo crudo (2.93 g, 4.99 mmol) en THF (35 mL), se agregó HCl 12N (10 mL, 121 mmol). Después de agitar la mezcla durante 24 h, la mezcla se diluyó con agua (100 mL) hasta que precipitaron sólidos. Los sólidos se recolectaron mediante filtración y se lavaron con agua para obtener el compuesto del título (2.75

g, 4.33 mmol, 87 % de rendimiento), como un sólido blancuzco que se usó en la siguiente etapa sin purificación adicional. LCMS: m/e 562 $(M+H)^+$, 1.96 min (método 2).

Etapa 5. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)-2-fluorobenzoico.

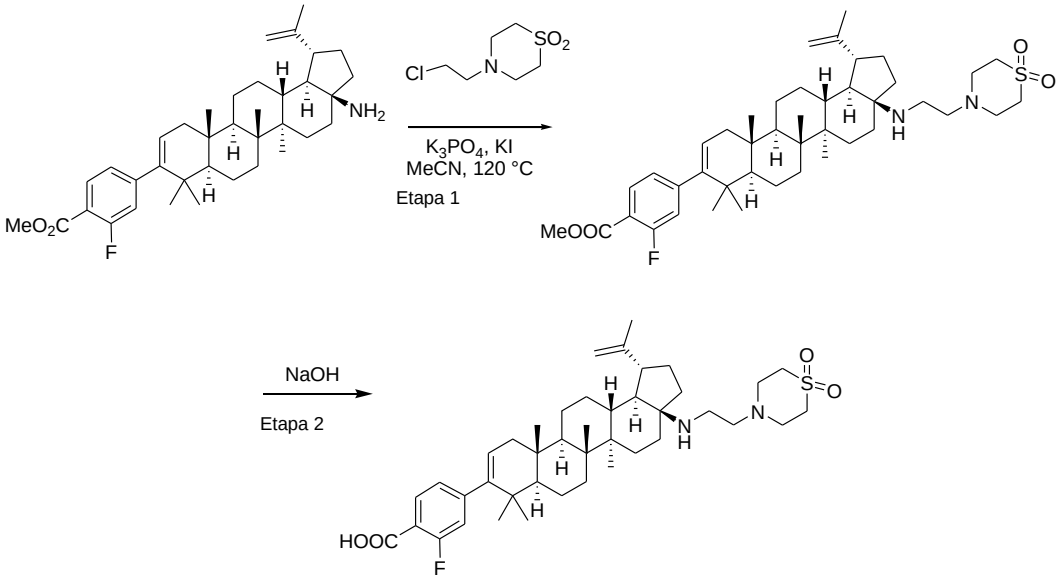
A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)-2-fluorobenzoato de metilo (100 mg, 0.178 mmol) en 1,4-dioxano (2 mL), se agregó NaOH 1N (0.890 mL, 0.890 mmol). Se formaron sólidos después de la adición de NaOH. La mezcla se calentó a 60 °C. Después de 20 minutos de calentamiento, la mezcla aún contenía sólidos. La mezcla también se diluyó con 1 mL de MeOH y 2 mL de dioxano; luego, se calentó a 60 °C durante la noche (los sólidos no se disolvieron completamente).

Después de 21 h de calentamiento, la mezcla se enfrió a temperatura ambiente. La mezcla se diluyó con 3 mL de agua, y los sólidos que permanecieron se recolectaron mediante filtración y se lavaron con agua y luego con éter para obtener ácido 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)-2-fluorobenzoico (67 mg, 0.113 mmol, 63.2 % de rendimiento) como un sólido blanco.. LCMS: m/e 548.4 $(M+H)^+$, 2.29 min (método 11).

Ejemplo A2

Preparación de ácido benzoico, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxido-4-tiomorfolinil)etil]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-1H-ciclopenta[a]crisen-9-il]-2-fluoro-, HCl



Etapa 1. Preparación de ácido benzoico, 4-

[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxido-4-tiomorfolinil)etil]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-1H-ciclopenta[a]crisen-9-il]-2-fluoro-, metiléster.

A un recipiente sellable que contenía 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)-2-fluorobenzoato de metilo, HCl (319 mg, 0.533 mmol) se agregó tiomorfolino, 4-(2-cloroetil)-, 1,1-dióxido, HCl (385 mg, 1.644 mmol), yoduro de potasio (240 mg, 1.446 mmol), ácido fosfórico y sal de potasio (500 mg, 2.356 mmol). La mezcla se diluyó con acetonitrilo (10 mL) y se purgó con N_2; luego el vial se selló y se calentó a 120 °C durante 115 h. La mezcla se enfrió a temperatura ambiente y se purificó directamente mediante cromatografía instantánea con un gradiente de 0-5 % de MeOH en DCM. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida para obtener el compuesto del título (0.308 g, 0.426 mmol, 80 % de rendimiento) como una espuma blancuzca. LCMS: m/e 723.5 $(M+H)^+$, 1.94 min (método 2).

Etapa 2. Preparación de ácido benzoico, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-

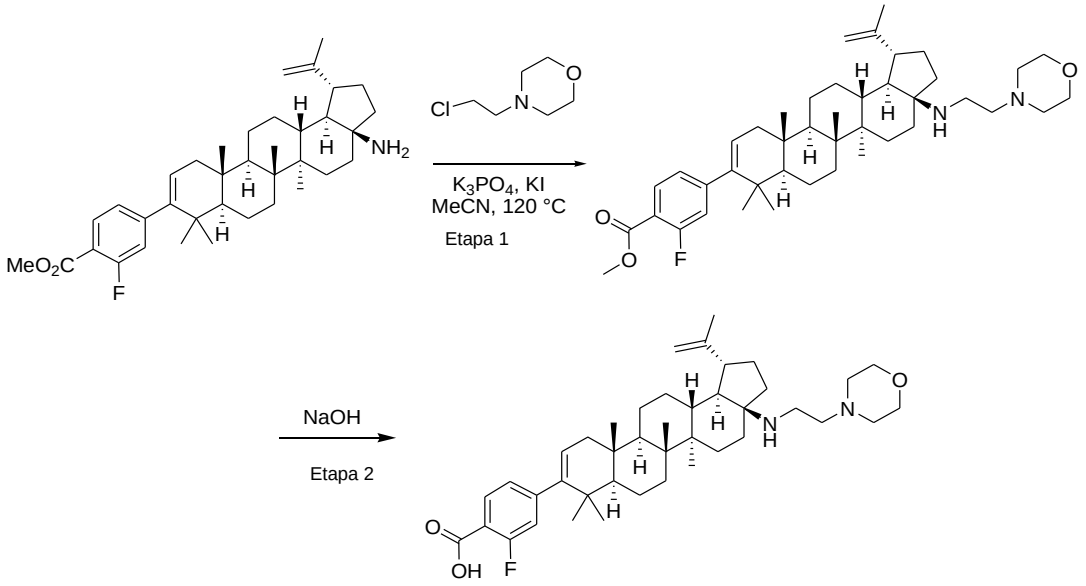
dioxido-4-tiomorfolinil)etil]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-1H-ciclopenta[a]crisen-9-il]-2-fluoro-, HCl.

A una solución de ácido benzoico, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxido-4-tiomorfolinil)etil]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-1H-ciclopenta[a]crisen-9-il]-2-fluoro-, metiléster (0.308g, 0.426 mmol) en 1,4-dioxano (5 mL), se agregó hidróxido de sodio 1 N (2.130 mL, 2.130 mmol). La mezcla se calentó a 70 °C durante 18 horas, luego se enfrió a temperatura ambiente. A la mezcla se agregó lentamente HCl 1N hasta que comenzaron a formarse sólidos. Los sólidos se recolectaron mediante filtración y se lavaron con agua para obtener ácido benzoico, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[2-(1,1-dioxido-4-tiomorfolinil)etil]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-1H-ciclopenta[a]crisen-9-il]-2-fluoro-, HCl como un sólido blancuzco (0.295g, 0.396 mmol, 93 % de rendimiento). LCMS: m/e 709.5 $(M+H)^+$, 1.66 min (método 2). ^{1}H NMR (500 MHz, *Ácido acético d4*) δ ppm 7.96 (1 H, t, *J*= 7.8 Hz), 7.09 (1 H, dd, *J*= 7.9, 1.5 Hz), 7.03 (1 H, d, *J*= 11.9 Hz), 5.43 (1 H, d, *J*= 4.6

Hz), 4.84 (1 H, s), 4.74 (1 H, s), 3.43-3.49 (1 H, m), 3.02-3.36 (11 H, m), 2.91-3.00 (1 H, m), 1.77 (3 H, s), 1.30 (3 H, s), 1.15 (3 H, s), 1.10 (3 H, s), 1.04 (3 H, s), 1.01 (3 H, s), 0.98-2.34 (22 H, m).

Ejemplo A3

Preparación de ácido 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-morfolinoetilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



Etapa 1. Preparación de 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-morfolinoetilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

A un recipiente sellable que contenía 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)-2-fluorobenzoato de metilo, HCl (0.1 g, 0.167 mmol), se agregó 4-(2-cloroetil)morfolina, HCl (0.093 g, 0.501 mmol), ácido fosfórico, sal de potasio (0.156 g, 0.735 mmol) y yoduro de potasio (0.075 g, 0.451 mmol). La mezcla se diluyó con acetonitrilo (3 mL), se purgó con N_2, y el vial se selló y se calentó a 120 °C. Después de calentar la mezcla durante 16 h, se enfrió a temperatura ambiente. El producto crudo se adsorbió en gel de sílice; luego, se purificó mediante cromatografía instantánea con una columna de gel de sílice Thomson de 12 g y un gradiente de 0-5 % de MeOH en DCM. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida para obtener 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-morfolinoetilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (77 mg, 0.114 mmol, 68.3 % de rendimiento) como una espuma blancuzca. LCMS: m/e 675.5 $(M+H)^+$, 1.91 min (método 2).

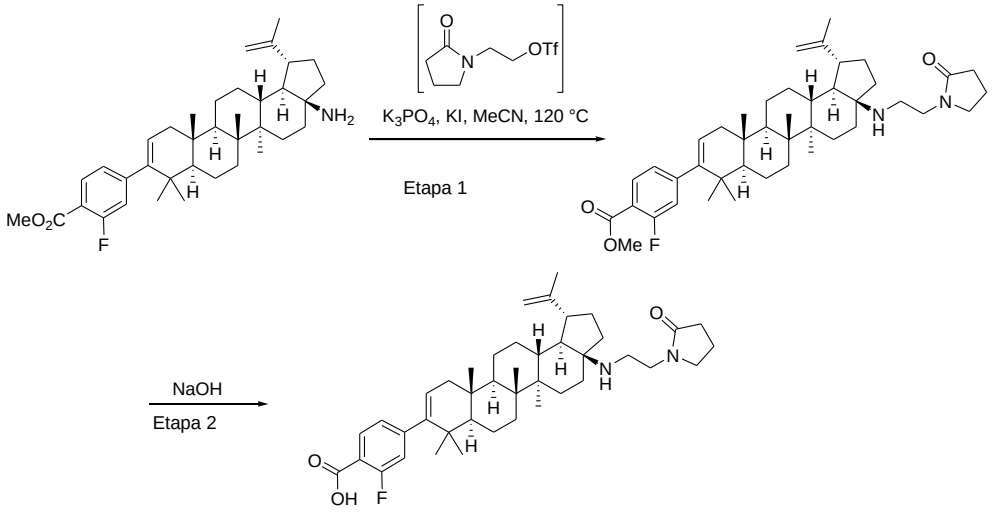
Etapa 2. Preparación de ácido 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-morfolinoetilamino)-1-(prop-1-en-2-il)-

2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

A una solución de 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-morfolinoetilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (0.075 g, 0.111 mmol) en 1,4-dioxano (1 mL), se agregó NaOH (1M) (0.5 mL, 0.500 mmol). La mezcla se calentó a 75 °C durante 15 horas, luego se enfrió a temperatura ambiente. La mezcla se purificó mediante HPLC preparativa. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida para obtener ácido 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-morfolinoetilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico (30 mg, 0.043 mmol, 38.8 % de rendimiento) como un sólido blanco. LCMS: m/e 661.5 $(M+H)^+$, 1.66 min (método 2). ^{1}H NMR (500 MHz, *Ácido acético* d_4) δ ppm 7.96 (1 H, t, *J*= 7.9 Hz), 7.09 (1 H, dd, *J*= 8.2, 1.2 Hz), 7.03 (1 H, d, *J*= 11.6 Hz), 5.42 (1 H, d, *J*= 4.6 Hz), 4.86 (1 H, s), 4.74 (1 H, s), 3.89-3.99 (4 H, m), 3.53-3.69 (4 H, m), 3.29 (4 H, br. s.), 2.81-2.90 (1 H, m), 1.77 (3 H, s), 1.23 (3 H, s), 1.13 (3 H, s), 1.08 (3 H, s), 1.04 (3 H, s), 1.01 (3 H, s), 0.85-2.26 (22 H, m).

Ejemplo A4

Preparación de ácido 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(2-oxopirrolidin-1-il)etilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



Etapa 1. Preparación de 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(2-oxopirrolidin-1-il)etilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

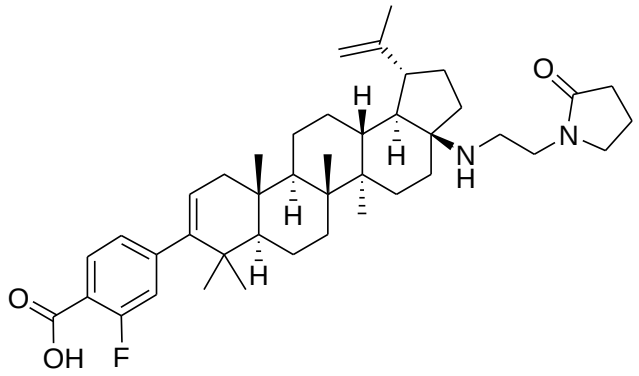
A un vial que contenía *N*-(2-hidroxietil)-2-pirrolidona (0.5 mL, 4.42 mmol), se agregaron DMAP (0.054 g, 0.442 mmol) y TEA (0.925 mL, 6.64 mmol). La mezcla se diluyó con d-cloroformo (10 mL) y se enfrió a 0 °C; luego se agregó lentamente anhídrido tríflico (0.822 mL, 4.87 mmol). La

mezcla se volvió de color rojo oscuro a medida que se agregaba el anhídrido. La mezcla se calentó a temperatura ambiente y se agitó durante 45 minutos. La solución 0.442 M se usó directamente como agente de alquilación para la siguiente reacción.

A un recipiente sellable que contenía 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)-2-fluorobenzoato de metilo (50 mg, 0.089 mmol) se agregó yoduro de potasio (39.9 mg, 0.240 mmol), ácido fosfórico y sal de potasio (83 mg, 0.392 mmol). La mezcla se diluyó con acetonitrilo (1 mL), y se agregó la solución de alquilación cruda descrita anteriormente (1.007 mL, 0.445 mmol). La mezcla se purgó con N_2, y el vial se selló y se calentó a 120 °C. Después de 15.5 h de calentamiento, la mezcla se enfrió a temperatura ambiente. Se agregaron 0.5 mL adicionales de la solución de alquilación cruda, y la mezcla se calentó nuevamente a 120 °C. Después de 70.25 h, la mezcla se enfrió a temperatura ambiente. La mezcla se adsorbió en gel de sílice y se purificó mediante cromatografía instantánea con un gradiente de 0-5% de MeOH en DCM y una columna de gel de sílice Thomson de 12 g. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida para obtener

2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(2-oxopirrolidin-1-il)etilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (25 mg, 0.037 mmol, 41.7 % de rendimiento) como una película amarilla. LCMS: m/e 673.5 $(M+H)^+$, 2.03 min (método 2).

Etapa 2. Preparación de ácido 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(2-oxopirrolidin-1-il)etilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



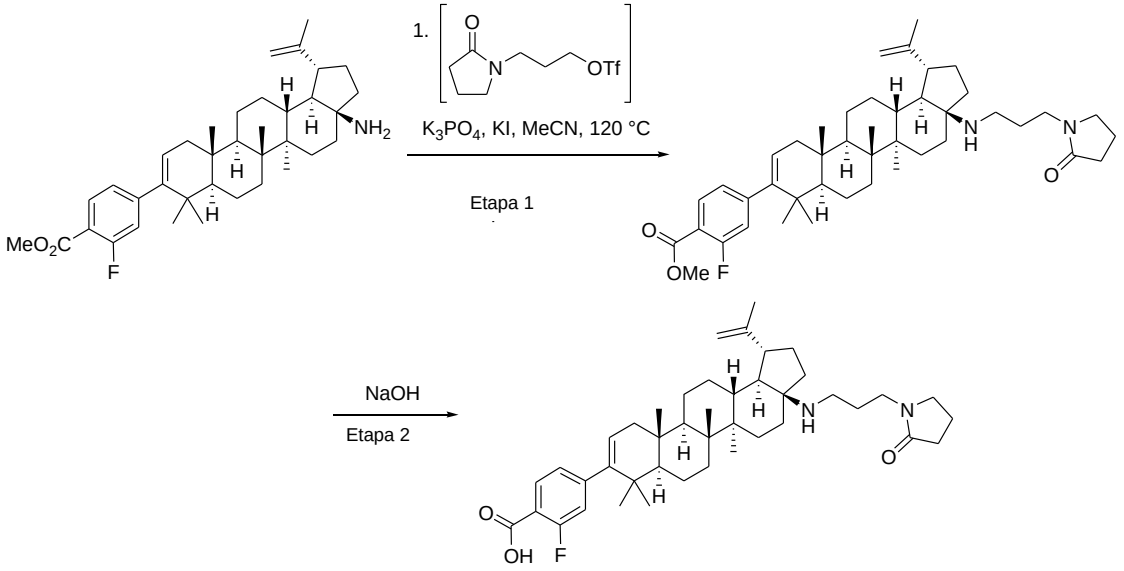
A una solución de 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(2-oxopirrolidin-1-il)etilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (0.025 g, 0.037 mmol) en 1,4-dioxano (1 mL) se

agregó NaOH (1 N) (0.5 mL, 0.500 mmol). La mezcla se calentó a 60 °C durante 15, 5 h, luego se enfrió a temperatura ambiente y se purificó mediante HPLC preparativa. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida para obtener ácido 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(2-oxopirrolidin-1-il)etilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico (11 mg, 0.016 mmol, 42,2 % de rendimiento) como un sólido blanco. LCMS: m/e 659.5 $(M+H)^+$, 1.77 min (método 2). ^{1}H NMR (500MHz, CLOROFORMO-d) δ 7.82 (t, *J*= 6.9 Hz, 1H), 6.91 (d, *J*= 6.1 Hz, 1H), 6.86 (d, *J*= 11.9 Hz, 1H), 5.27 (d, *J*= 4.6 Hz, 1H), 4.71 (s, 1H), 4.58 (s, 1H), 3.54-3.43 (m, 3H), 3.39-3.31 (m, 1H), 1.68 (s, 3H), 1.06 (s, 3H), 0.96 (s, 3H), 0.93 (s, 3H), 0.90 (s, 3H), 0.90 (s, 3H), 2.75-0.66 (m, 29H).

Ejemplo A5

Preparación de ácido 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(3-(2-oxopirrolidin-1-il)propilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



Etapa 1. Preparación de 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(3-(2-oxopirrolidin-1-il)propilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

A un vial que contenía 1-(3-hidroxipropil)-2-pirrolidona (0.5 mL, 3.84 mmol) se agregaron DMAP (0.047 g, 0.384 mmol) y TEA (0.803 mL, 5.76 mmol). La mezcla se diluyó con d-cloroformo (10 mL) y se enfrió a 0 °C. A la solución enfriada se agregó lentamente anhídrido trifluorometansulfónico (0.714 mL, 4.23 mmol). La mezcla se volvió rojo oscuro a medida que se agregaba el anhídrido. La mezcla se calentó lentamente a temperatura ambiente a

medida que se derretía el baño de hielo. Después de 1 h de agitación a temperatura ambiente, ^{1}HNMR mostró que no había restos de material de inicio. La mezcla de reacción cruda se usó directamente en la siguiente reacción sin purificación.

A un recipiente sellable que contenía 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)-2-fluorobenzoato de metilo (50 mg, 0.089 mmol) se agregaron yoduro de potasio (39.9 mg, 0.240 mmol), ácido fosfórico y sal de potasio (83 mg, 0.392 mmol). La mezcla se diluyó con acetonitrilo (1 mL), y se agregó trifluorometansulfonato de 3-(2-oxopirrolidin-1-il)propilo (la solución cruda preparada anteriormente) (1.0 mL, 0.384 mmol) La mezcla se purgó con N_2, y el vial se selló y se calentó a 120 °C. Después de 15.5 h de calentamiento, la mezcla se enfrió a temperatura ambiente. Se agregaron 0.5 mL adicionales de la solución cruda anterior que contenía el triflato, y la mezcla se calentó nuevamente a 120 °C. Después de calentar la mezcla durante 70.25 h más, la mezcla se enfrió a temperatura ambiente. La mezcla se adsorbió en gel de sílice y se purificó mediante cromatografía instantánea con un gradiente de 0-5% de MeOH en DCM y una columna de gel de

sílice Thomson de 12 g. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida para obtener 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(3-(2-oxopirrolidin-1-il)propilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (16 mg, 0.023 mmol, 26.2 % de rendimiento) como una película amarilla. LCMS: m/e 687.5 $(M+H)^+$, 2.04 min (método 2).

Etapa 2. Preparación de ácido 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-(3-oxopirrolidin-1-il)propilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

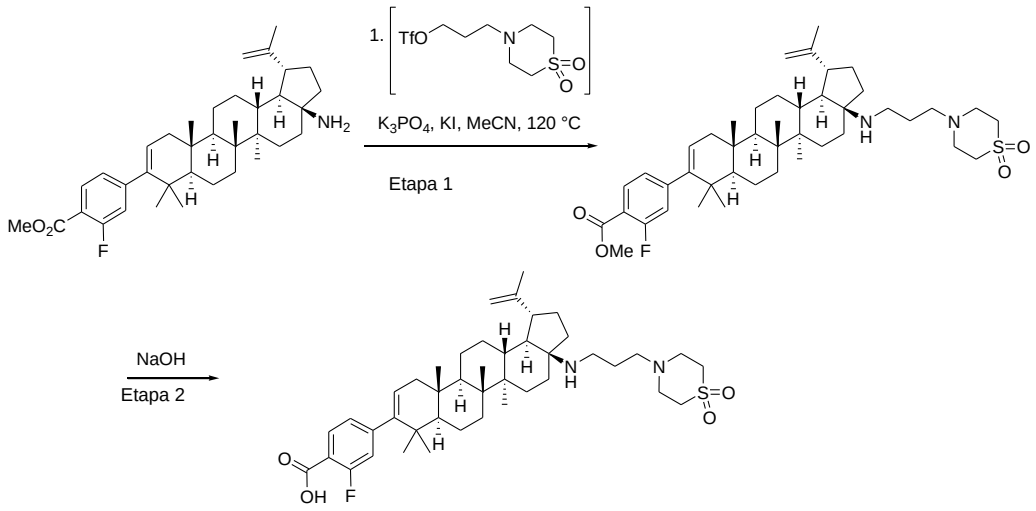
A una solución de 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(3-(2-oxopirrolidin-1-il)propilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (16 mg, 0.023 mmol) en 1,4-dioxano (1 mL), se agregó NaOH (1N) (0.25 mL, 0.250 mmol). La mezcla se calentó a 60

°C durante la noche a 15.25 h y luego se enfrió a temperatura ambiente. La mezcla se cargó directamente en la HPLC preparativa para la purificación. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida para obtener ácido 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(3-(2-oxopirrolidin-1-il)propilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico (6 mg, 8.02 µmol, 34.5 % de rendimiento) como una película transparente incolora. LCMS: m/e 673.5 $(M+H)^+$, 1.75 min (método 2). ^{1}H NMR (500MHz, *Ácido acético* d_4) δ 7.96 (t, *J*= 7.9 Hz, 1H), 7.09 (dd, *J*= 7.9, 1.2 Hz, 1H), 7.03 (d, *J*= 11.9 Hz, 1H), 5.42 (d, *J*= 4.6 Hz, 1H), 4.86 (s, 1H), 4.74 (s, 1H), 3.58-3.40 (m, 4H), 3.26-3.16 (m, 2H), 2.94-2.85 (m, 1H), 2.56-2.48 (m, 2H), 1.76 (s, 3H), 1.22 (s, 3H), 1.13 (s, 3H), 1.08 (s, 3H), 1.04 (s, 3H), 1.01 (s, 3H), 2.29-0.85 (m, 26H).

Ejemplo A6

Preparación de ácido benzoico, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-tiomorfolinil)propil]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-1H-

ciclopenta[a]crisen-9-il]-2-fluoro-



Etapa 1. Preparación de ácido benzoico, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-tiomorfolinil)propil]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-1H-ciclopenta[a]crisen-9-il]-2-fluoro-, metiléster.

A un vial que contenía *N*-(3-hidroxipropil)tiomorfolin-1,1-dióxido (0.15 g, 0.776 mmol) se agregaron DMAP (9.48 mg, 0.078 mmol) y TEA (0.162 mL, 1.164 mmol). La mezcla se diluyó con d-cloroformo (2 mL) y se enfrió a 0 °C. A la solución enfriada se agregó lentamente anhídrido trifluorometansulfónico (0.144 mL, 0.854 mmol). La mezcla se volvió naranja a medida que se agregaba el anhídrido y se convirtió en un gel espeso que no se agitaba

bien. Después de 2 h, la mezcla se diluyó con 1 mL adicional de d-cloroformo y se usó directamente en la siguiente reacción como mezcla de reacción cruda.

A un recipiente sellable que contenía 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)-2-fluorobenzoato de metilo (50 mg, 0.089 mmol) se agregaron yoduro de potasio (39.9 mg, 0.240 mmol), ácido fosfórico y sal de potasio (83 mg, 0.392 mmol). La mezcla se diluyó con acetonitrilo (1 mL), y se agregó una solución de la mezcla cruda de la reacción anterior (1.718 mL, 0.445 mmol). La mezcla se purgó con N_2, y el vial se selló y se calentó a 120 °C. Después de agitar la mezcla durante 66 h, se enfrió a temperatura ambiente. La mezcla se adsorbió en gel de sílice y se purificó mediante cromatografía instantánea usando una columna de gel de sílice Thomson de 12 g y un gradiente de 0-5% de MeOH en DCM. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida para obtener ácido benzoico, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-tiomorfolinil)propil]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-1H-ciclopenta[a]crisen-9-il]-2-fluoro-, metiléster (43 mg, 0.058

mmol, 65,6% de rendimiento) como una película amarilla. LCMS: m/e 737.5 $(M+H)^+$, 1.88 min (método 2).

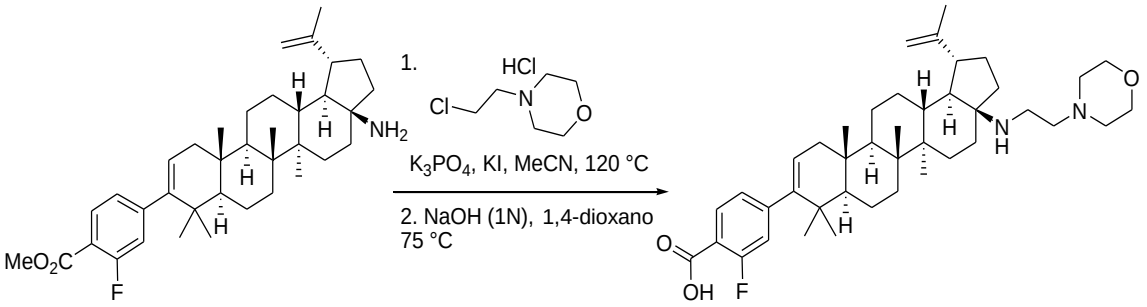
Etapa 2. Preparación de ácido benzoico, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-tiomorfolinil)propil]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-1H-ciclopenta[a]crisen-9-il]-2-fluoro-.

A una solución de ácido benzoico, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-tiomorfolinil)propil]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-1H-ciclopenta[a]crisen-9-il]-2-fluoro-, metiléster (0.043 g, 0.058 mmol) en 1,4-dioxano (1 mL) se agregó NaOH (1 M) (0.5 ml, 0.500 mmol). La mezcla se calentó a 60 °C durante 15.25 h y se enfrió a temperatura ambiente. La mezcla se cargó directamente en la HPLC preparativa para la purificación. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida para obtener ácido benzoico, 4-[(1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-[[3-(1,1-dioxido-4-tiomorfolinil)propil]amino]-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-5a,5b,8,8,11a-pentametil-1-(1-metiletenil)-1H-ciclopenta[a]crisen-9-il]-2-fluoro- (13.2 mg, 0.017 mmol,

29.4 % de rendimiento) como un sólido blanco. LCMS: m/e 723.5 $(M+H)^+$, 1.62 min (método 2). ^{1}H NMR (400MHz, *Ácido acético d4*) δ 7.92 (t, *J*= 7.9 Hz, 1H), 7.04 (d, *J*= 8.0 Hz, 1H), 6.98 (d, *J*= 11.8 Hz, 1H), 5.38 (d, *J*= 4.8 Hz, 1H), 4.82 (s, 1H), 4.70 (s, 1H), 3.71 (br. s., 4H), 3.48 (br. s., 4H), 3.25 (t, *J*= 7.5 Hz, 4H), 2.82 (br. s., 1H), 2.46-2.30 (m, 2H), 1.72 (s, 3H), 1.16 (s, 3H), 1.08 (s, 3H), 1.03 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 2.24-0.82 (m, 22H).

Ejemplo A7

Preparación de ácido 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-morfolinoetilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahydro-1H-ciclopenta[a]crisen-9-il)benzoico



Etapa 1. Preparación de 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-morfolinoetilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

A un recipiente sellable que contenía clorhidrato de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)-2-fluorobenzoato de metilo (0.1 g, 0.167 mmol) se agregaron clorhidrato de 4-(2-cloroetil)morfolino (0.093 g, 0.501 mmol), ácido fosfórico, sal de potasio (0.156 g, 0.735 mmol) y yoduro de potasio (0.075 g, 0.451 mmol). La mezcla se diluyó con acetonitrilo (3 mL), se purgó con nitrógeno, y luego se selló y calentó el vial a 120 °C. Después de calentar la mezcla durante 16 h, esta se enfrió a temperatura ambiente. El producto crudo se adsorbió en gel de sílice, luego se purificó mediante cromatografía instantánea usando una columna de gel de sílice Thomson de 12 g y un gradiente de 0-5% de metanol en diclorometano. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida para obtener 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-morfolinoetilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (77 mg, 0.114 mmol, 68.3 % de rendimiento) como una espuma blancuzca. LCMS: m/e 675.5 $(M+H)^+$, 1.91 min (método 2).

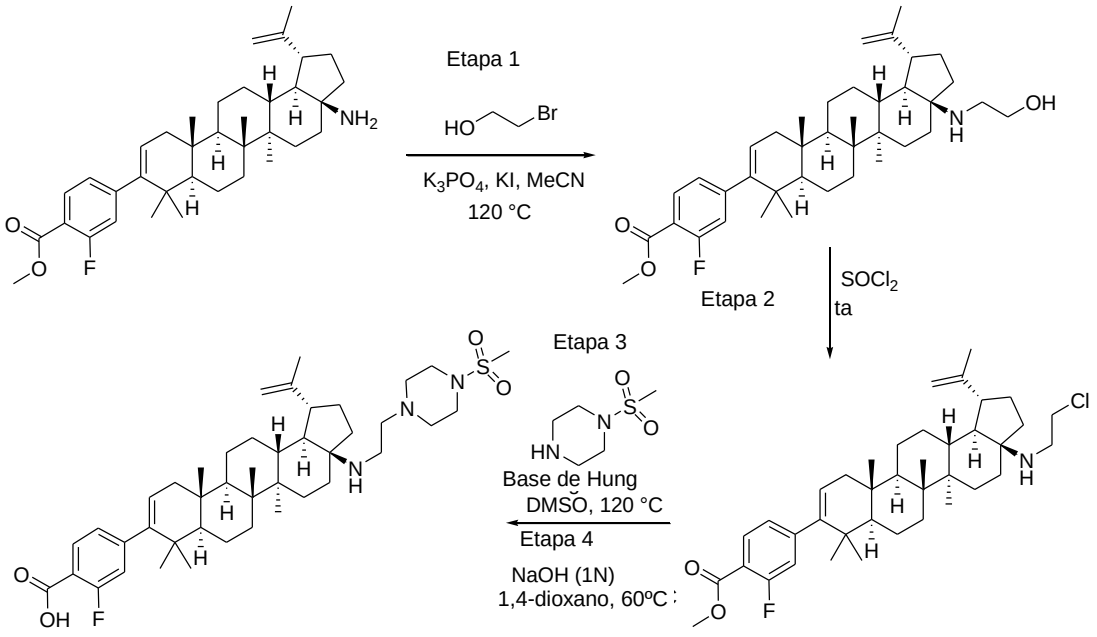
Etapa 2. A una solución de 2-fluoro-4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-morfolinoetilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (0.075 g, 0.111 mmol) en 1,4-dioxano (1 mL), se agregó NaOH (1M) (0.5 mL, 0.500 mmol). La mezcla se calentó a 75 °C durante 15 horas, luego se enfrió a temperatura ambiente. La mezcla se acidificó con HCl 1 N (3 mL) y se concentró a presión reducida. El residuo se diluyó con 15 mL de agua, y los sólidos restantes se recolectaron por filtración y se lavaron con agua y luego con éter. El compuesto se disolvió en DMF y metanol, y se purificó mediante HPLC preparativa. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida para obtener ácido 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-(2-morfolinoetilamino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico (30 mg, 0.043 mmol, 38.8 % de rendimiento) como un sólido blanco. LCMS: m/e 661.5 $(M+H)^+$, 1.67 min (método 2). ^{1}H NMR (500 MHz, *Ácido acético* d_4) δ ppm 7.96 (1 H, t, *J*= 7.9 Hz), 7.09 (1 H, dd, *J*= 8.2, 1.2 Hz), 7.03 (1 H, d, *J*= 11.6 Hz), 5.42 (1 H, d, *J*= 4.6 Hz), 4.86 (1 H, s), 4.74 (1 H, s), 3.89-3.99 (4 H, m), 3.53-3.69 (4 H, m), 3.29 (4 H, br. s.), 2.81-2.90 (1 H, m), 1.77 (3 H, s), 1.23 (3 H, s), 1.13 (3 H, s), 1.08 (3 H, s),

1.04 (3 H, s), 1.01 (3 H, s), 0.85-2.26 (22 H, m).

Ejemplo A8

Preparación de ácido 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(4-(metilsulfonil)piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



Etapa 1. Preparación de 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-hidroxietil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

A un recipiente sellable que contenía 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-

5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)-2-fluorobenzoato de metilo, HCl (1.0 g, 1.671 mmol) se agregaron yoduro de potasio (0.694 g, 4.18 mmol), ácido fosfórico, sal de potasio (1.774 g, 8.36 mmol) y 2-bromoetanol (0.475 mL, 6.69 mmol). La mezcla se diluyó con acetonitrilo (15 mL), y el vial se selló, se calentó a 120 °C durante 21 h, luego se enfrió a temperatura ambiente y se diluyó con agua (50 mL). Los sólidos se recolectaron mediante filtración y luego se lavaron con agua. Los sólidos se purificaron mediante cromatografía instantánea en gel de sílice con usando un gradiente de 0-5% de metanol en diclorometano con la adición de 0.1 % de hidróxido de amonio a la mezcla. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida. El producto se volvió a purificar por segunda vez usando un gradiente de 0-20% de EtOAc en hexanos con la adición de 0.1 % de TEA a la mezcla. Las fracciones que contenían el producto se combinaron y se concentraron a presión reducida para obtener 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-hidroxietil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (0.135 g, 0.223 mmol, 13 % de rendimiento) como un sólido blancuzco. LCMS: m/e 606,7 $(M+H)^+$, 2.02 min (método 2).

Etapa 2. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-cloroetil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)-2-fluorobenzoato de metilo, HCl.

A un recipiente que contenía 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-hidroxietil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (0.135 g, 0.223 mmol) se agregó cloruro de tionilo (2.5 ml, 34.3 mmol). La solución incolora transparente se agitó a temperatura ambiente durante 2.5 h; la reacción se inactivó cuidadosamente con agua (20 mL), y los sólidos que se formaron se recolectaron mediante filtración y se lavaron con agua. El producto previsto, 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-cloroetil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)-2-

fluorobenzoato de metilo, HCl (0.173 g, 0.262 mmol, 117 % de rendimiento), se aisló como un sólido blancuzco que se usó directamente en la siguiente etapa sin purificación adicional. LCMS: m/e 624,6 $(M+H)^+$, 2.42 min (método 11).

Etapa 3. Preparación de 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(4-(metilsulfonil)piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

A una suspensión de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-cloroetil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)-2-fluorobenzoato de metilo, HCl (0.147 g, 0.223 mmol) en DMSO (2 mL) se agregaron 1-metansulfonil-piperazina (0.073 g, 0.446 mmol) y base de Hunig (0.195 mL, 1.115 mmol). Luego de la adición de la base, se disolvieron los sólidos. La solución se calentó a 120 °C durante 2 h, luego se enfrió a temperatura ambiente, se diluyó con agua (20 mL) y se extrajo con acetato de etilo (3 x 20 mL). Las capas orgánicas combinadas se lavaron con agua (2 x 30 mL), luego con salmuera (20 mL), y a continuación se

secaron en sulfato de magnesio. El agente de secado se retiró mediante filtración, y el filtrado se concentró a presión reducida. El residuo se purificó mediante cromatografía instantánea en gel de sílice usando un gradiente de 0-50% de acetato de etilo en hexanos, con la adición de 0.1 % de trietilamina a la mezcla. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida para obtener 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(4-(metilsulfonil)piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (0.056 g, 0.074 mmol, 33.4 % de rendimiento) como un sólido blancuzco. LCMS: m/e 752.7 $(M+H)^+$, 1.95 min (método 2).

Etapa 4. A una solución de 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(4-(metilsulfonil)piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (0.056 g, 0.074 mmol) en 1,4-dioxano (2 mL), se agregó NaOH (1N) (0.372 mL, 0.372 mmol). La mezcla se

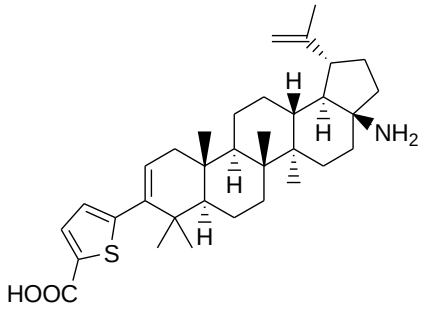
calentó a 60 °C durante 6.5 horas, luego se enfrió a temperatura ambiente. La mezcla se diluyó con metanol y 1,4-dioxano, se filtró a través de un tapón de lana de vidrio y se purificó mediante HPLC preparativa. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida para obtener ácido 2-fluoro-4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(4-(metilsulfonil)piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico (30.1 mg, 0.039 mmol, 52.0 % de rendimiento) como un sólido blanco. LCMS: m/e 738.6 $(M+H)^+$, 1.66 min (método 2). ^{1}H NMR (400MHz, *Ácido acético d*$_4$) δ7.92 (t, *J*= 7.9 Hz, 1H), 7.04 (dd, *J*= 8.0, 1.5 Hz, 1H), 7.01-6.96 (m, 1H), 5.38 (d, *J*= 5.0 Hz, 1H), 4.81 (s, 1H), 4.70 (s, 1H), 3.59-3.25 (m, 8H), 3.15 (br. s., 4H), 2.90 (s, 3H), 2.94-2.81 (m, 1H), 1.72 (s, 3H), 1.21 (s, 3H), 1.09 (s, 3H), 1.04 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 2.23-0.83 (m, 22H).

Sección B. Aminas (continuación)

Ejemplo B1

Preparación de ácido 5-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-

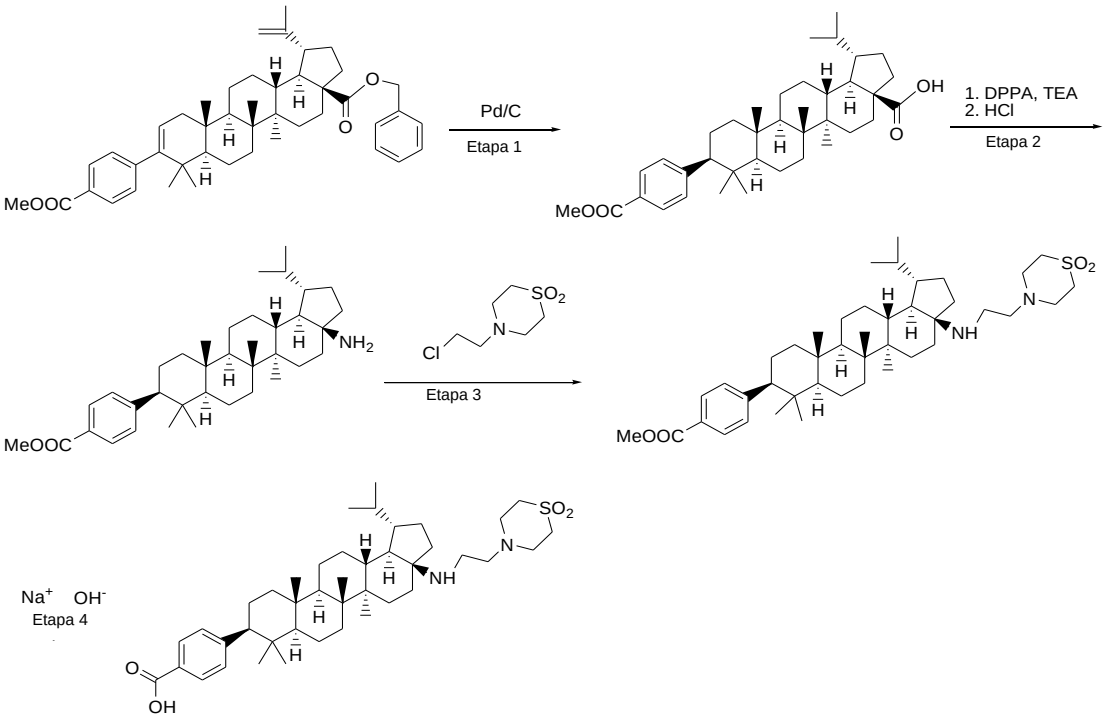
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)tiofen-2-carboxílico.



El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)-2-fluorobenzoico usando ácido 5-(metoxicarbonil)tiofen-2-ilborónico como reactivo de acoplamiento en la Etapa 1. El producto se aisló como un sólido blanco (2.7 mg, 44%). LCMS: m/e 536.30 $(M+H)^+$, 2.25 min (método 10). ^{1}H NMR (500MHz, Acético) δ 7.77 (d, *J*= 4.0 Hz, 1H), 6.98 (d, *J*= 3.7 Hz, 1H), 5.87 (d, *J*= 4.3 Hz, 1H), 4.88 (s, 1H), 4.75 (s, 1H), 2.79 (td, *J*= 10.5, 6.7 Hz, 1H), 2.35-2.13 (m, 4H), 1.98-1.85 (m, 4H), 1.83-1.07 (m, 14H), 1.77 (s, 3H), 1.19 (s, 3H), 1.14 (s, 3H), 1.14 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H).

Ejemplo B2

Preparación de ácido 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidotiomorfolino)etil)amino)-1-isopropil-5a,5b,8,8,11a-pentametilicosahidro-1H-ciclopenta[a]crisen-9-il)benzoico



Etapa 1. Preparación de ácido (1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-1-isopropil-9-(4-(metoxicarbonil)fenil)-5a,5b,8,8,11a-pentametilicosahidro-1H-ciclopenta[a]crisen-3a-carboxílico

Se agitó una mezcla de paladio en carbono (67.4 mg, 0.063 mmol) y 9-(4-(metoxicarbonil)fenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-3a-carboxilato de (1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-bencilo (140 mg, 0.211 mmol) en metanol (2mL) a 20 °C en hidrógeno con 1 atmósfera de presión durante 20 horas. La mezcla de reacción se filtró a través de una almohadilla de Celite para retirar Pd/C. Los filtrados se concentraron a presión reducida para obtener el compuesto del título como un sólido blanco (100 mg, 82 %). LCMS: m/e 577.33 $(M+H)^+$, 3.22 min (método 10).

Etapa 2. Preparación de 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-amino-1-isopropil-5a,5b,8,8,11a-pentametilicosahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo

Se sometió a reflujo una mezcla de ácido (1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-1-isopropil-9-(4-(metoxicarbonil)fenil)-5a,5b,8,8,11a-pentametilicosahidro-1H-ciclopenta[a]crisen-3a-carboxílico (100 mg, 0.173 mmol), fosforazidato de difenilo (0.056 mL, 0.260 mmol) y trietilamina (0.072 mL, 0.520 mmol) en tolueno (4 mL) durante 18 horas. La TLC indicó el consumo del material de inicio y la formación del producto deseado. La mezcla se enfrió a temperatura ambiente, se filtró a través de una almohadilla de gel de sílice, y los filtrados se concentraron a presión reducida para obtener el intermediario deseado como un

aceite incoloro. A este intermediario (70 mg, 0.122 mmol) en THF (4 mL) se agregó HCl (0.037 mL, 1.220 mmol). La mezcla de reacción se agitó durante 18 horas a temperatura ambiente. La mezcla de reacción se purificó mediante cromatografía en gel de sílice con 20-70 % de acetato de etilo/hexanos para obtener el compuesto del título como un sólido blanco (50 mg, 50 %). LCMS: m/e 548.49 $(M+H)^+$, 2.58 min (método 11).

Etapa 3. Preparación de 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidotiomorfolino)etil)amino)-1-isopropil-5a,5b,8,8,11a-pentametilicosahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo

Se calentó una mezcla de 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-amino-1-isopropil-5a,5b,8,8,11a-pentametilicosahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (50 mg, 0.091 mmol), 1,1-dióxido de 4-(2-cloroetil)tiomorfolino (54.1 mg, 0.274 mmol), fosfato de potasio (77 mg, 0.365 mmol) y yoduro de potasio (36.4 mg, 0.219 mmol) en acetonitrilo (2 mL) a 120 °C durante 20 horas. La mezcla de reacción se inactivó con agua destilada (5 mL) y se extrajo con diclorometano (3 x 5 mL); las fases orgánicas se combinaron, se secaron en sulfato de sodio, se filtraron y se concentraron a presión reducida para obtener el

producto crudo como un sólido amarillo (40 mg, 62 %). LCMS: m/e 709.53 $(M+H)^+$, 2.46 min (método 11).

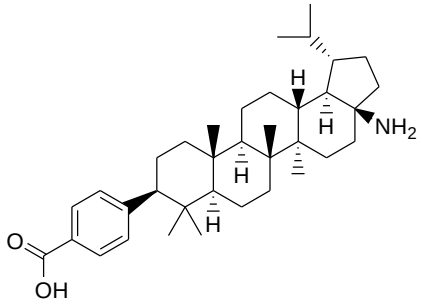
Etapa 4. Preparación de ácido 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidotiomorfolino)etil)amino)-1-isopropil-5a,5b,8,8,11a-pentametilicosahidro-1H-ciclopenta[a]crisen-9-il)benzoico

Se calentó una mezcla de 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidotiomorfolino)etil)amino)-1-isopropil-5a,5b,8,8,11a-pentametilicosahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (40 mg, 0.056 mmol) e hidróxido de sodio (0.564 mL, 0.564 mmol) en dioxano (1 mL) a 80 °C durante 3 horas. La mezcla de reacción se filtró y se purificó mediante HPLC para obtener el compuesto del título como un sólido blanco (30 mg, 73 %). LCMS: m/e 695.46 $(M+H)^+$, 2.55 min (método 10). ^{1}H NMR (500MHz, Acético) δ 8.02 (d, *J*= 8.5 Hz, 2H), 7.36 (d, *J*= 8.5 Hz, 2H), 3.44-3.36 (m, 1H), 3.35-3.21 (m, 6H), 3.19-2.99 (m, 5H), 2.50 (dd, *J*= 13.0, 2.9 Hz, 1H), 2.34-1.01 (m, 26H), 1.28 (s, 3H), 1.13 (s, 3H), 1.10 (s, 3H), 0.93 (d, *J*= 6.7 Hz, 3H), 0.85 (d, *J*= 6.7 Hz, 3H), 0.84 (s, 3H), 0.80 (s, 3H).

Ejemplo B3

Preparación de ácido 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-amino-1-isopropil-5a,5b,8,8,11a-pentametilicosahidro-1H-

ciclopenta[a]crisen-9-il)benzoico

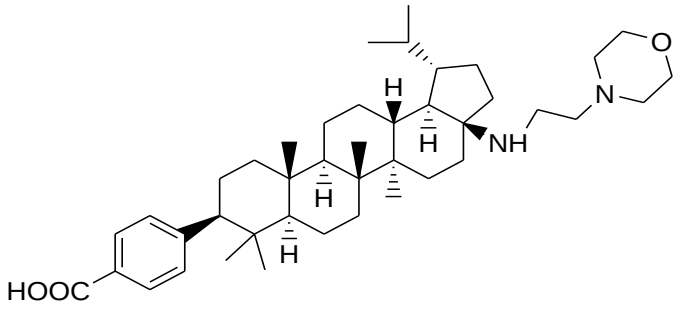


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)-2-fluorobenzoico usando 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-amino-1-isopropil-5a,5b,8,8,11a-pentametilicosahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo como material de inicio en la Etapa 5. El producto se aisló como un sólido blanco (12 mg, 47%). LCMS: m/e 532.43 $(M-H)^-$, 2.37 min (método 10). ^{1}H NMR (500MHz, METANOL-d_4) δ 7.84 (d, *J*= 8.2 Hz, 2H), 7.19 (d, *J*= 8.2 Hz, 2H), 2.42 (dd, *J*= 13.0, 2.9 Hz, 1H), 2.18 (qd, *J*= 13.3, 3.1 Hz, 1H), 2.07-1.24 (m, 25H), 1.16 (s, 3H), 1.07 (s, 3H), 1.03 (s, 3H), 0.93 (d, *J*= 6.7 Hz, 3H), 0.83 (d, *J*= 6.7 Hz, 3H), 0.79 (s, 3H), 0.74 (s, 3H).

Ejemplo B4

Preparación de ácido 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-1-isopropil-

5a,5b,8,8,11a-pentametil-3a-((2-morfolinoetil)amino)icosahidro-1H-ciclopenta[a]crisen-9-il)benzoico

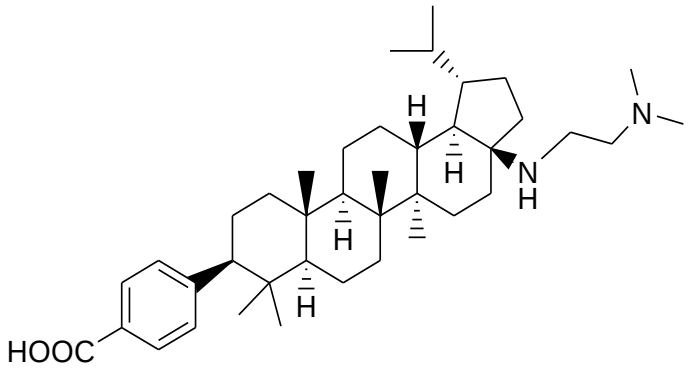


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis del ácido 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidotiomorfolino)etil)amino)-1-isopropil-5a,5b,8,8,11a-pentametilicosahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando 4-(2-cloroetil)morfolino como reactivo de alquilación en la Etapa 3. El producto se aisló como un aceite incoloro (4 mg, 39%). LCMS: m/e 647.58 $(M+H)^+$, 2.35 min (método 11). ^{1}H NMR (500MHz, Acético) δ 8.02 (d, *J*= 8.2 Hz, 2H), 7.36 (d, *J*= 8.2 Hz, 2H), 3.94 (d, *J*= 3.7 Hz, 4H), 3.73-3.44 (m, 4H), 3.27 (br. s., 4H), 2.50 (d, *J*= 10.4 Hz, 1H), 2.32-1.01 (m, 26H), 1.21 (s, 3H), 1.12 (s, 3H), 1.08 (s, 3H), 0.93 (d, *J*= 6.7 Hz, 3H), 0.86 (d, *J*= 6.7 Hz, 3H), 0.83 (s, 3H), 0.79 (s, 3H).

Ejemplo B5

Preparación de ácido 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-(2-(dimetilamino)etil)amino)-1-isopropil-5a,5b,8,8,11a-

pentametilicosahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

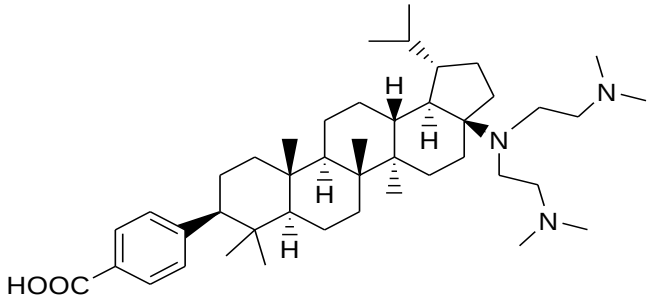


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis del ácido 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidotiomorfolino)etil)amino)-1-isopropil-5a,5b,8,8,11a-pentametilicosahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando 2-cloro-N,N-dimetiletanamina como reactivo de alquilación en la Etapa 3. El producto se aisló como un aceite incoloro (0.9 mg, 37%). LCMS: m/e 605.56 $(M+H)^+$, 2.35 min (método 11). ^{1}H NMR (500MHz, Acético) δ 8.02 (d, *J*= 8.2 Hz, 2H), 7.36 (d, *J*= 8.2 Hz, 2H), 3.89-3.72 (m, 2H), 3.70-3.55 (m, 1H), 3.07-2.91 (m, 1H), 3.00 (s, 6H), 2.60-2.40 (m, 1H), 2.34-1.04 (m, 26H), 1.18 (s, 3H), 1.12 (s, 3H), 1.07 (s, 3H), 0.93 (d, *J*= 6.7 Hz, 3H), 0.86 (d, *J*= 6.7 Hz, 3H), 0.83 (s, 3H), 0.79 (s, 3H).

Ejemplo B6

Preparación de ácido 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-(bis(2-(dimetilamino)etil)amino)-1-isopropil-5a,5b,8,8,11a-

pentametilicosahidro-1H-ciclopenta[a]crisen-9-il)benzoico

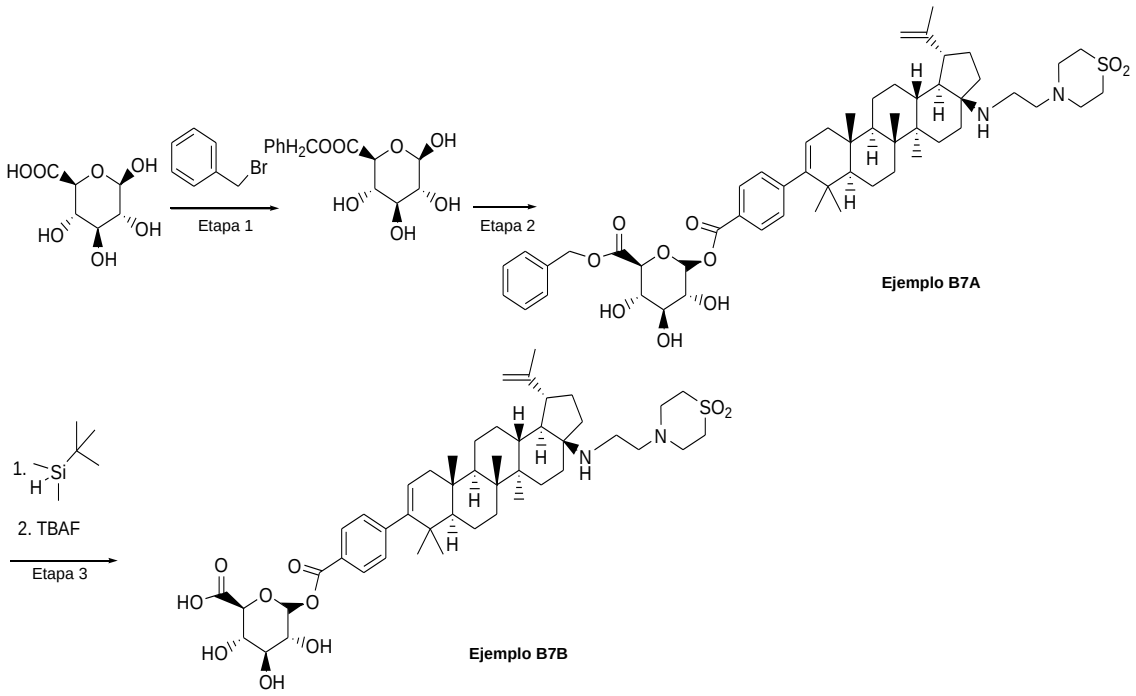


El compuesto del título se obtuvo como subproducto en la preparación de ácido 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-(dimetilamino)etil)amino)-1-isopropil-5a,5b,8,8,11a-pentametilicosahidro-1H-ciclopenta[a]crisen-9-il)benzoico. El producto se aisló como un aceite incoloro (0.7 mg, 26 %). LCMS: m/e 676.63 $(M+H)^+$, 2.33 min (método 11). ^{1}H NMR (500MHz, Acético) δ 8.02 (d, *J*= 8.2 Hz, 2H), 7.35 (d, *J*= 8.2 Hz, 2H), 4.33-4.09 (m, 4H), 3.85 (br. s., 3H), 3.73 (br. s., 1H), 3.40 (s, 6H), 3.01 (s, 6H), 2.50 (d, *J*= 14.0 Hz, 1H), 2.37-1.04 (m, 26H), 1.17 (s, 3H), 1.12 (s, 3H), 1.07 (s, 3H), 0.93 (d, *J*= 6.7 Hz, 3H), 0.87 (d, *J*= 6.7 Hz, 3H), 0.8s (s, 3H), 0.79 (s, 3H).

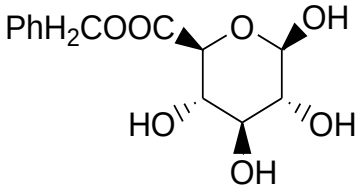
Ejemplos B7A y B7B

Preparación de ácido (2S,3S,4S,5R,6R)-6-((4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidotiomorfolino)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoil)oxi)-3.4.5-trihidroxitetrahidro-2H-piran-2-carboxílico



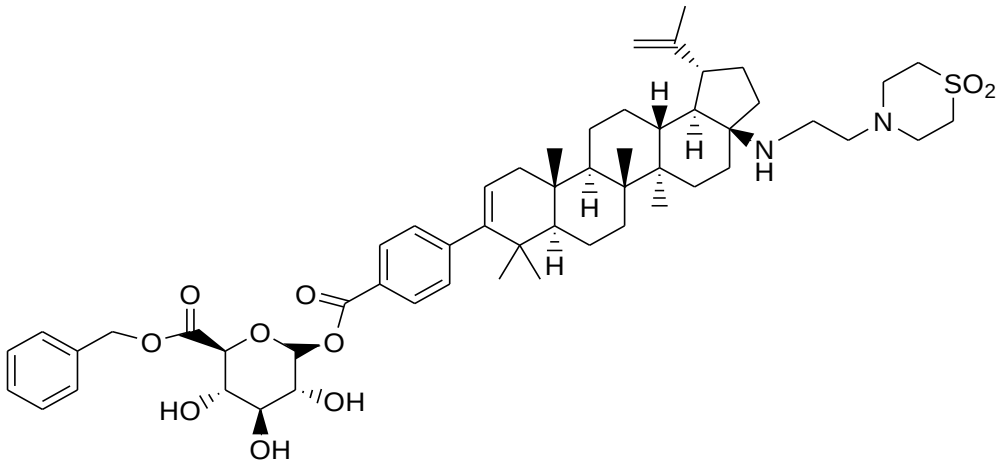
Etapa 1. Preparación de 3,4,5,6-tetrahidroxitetrahidro-2H-piran-2-carboxilato de (2S,3S,4S,5R,6R)-bencilo



A una solución de ácido (2S,3S,4S,5R,6R)-3,4,5,6-tetrahidroxitetrahidro-2H-piran-2-carboxílico (1 g, 5.15 mmol) y TBAF en THF (6.18 mL, 6.18 mmol) en DMF (7 mL) se agregó lentamente (bromometil)benceno (0.925 g, 5.41 mmol) a 0 °C. La solución transparente se calentó a temperatura

ambiente lentamente y se agitó durante 17 horas. La TLC indicó que se completó la reacción (20% iPrOH/CH_2Cl_2). El solvente se retiró, y el residuo de reacción se purificó mediante cromatografía en gel de sílice con 10-20% iPrOH/CH_2Cl_2 para obtener el producto deseado como un aceite incoloro (950 mg, 65 %). LCMS: m/e 283.31 $(M-H)^-$, 2.55 min (método 10).

Etapa 2. Preparación de 6-((4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidotiomorfolino)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoil)oxi)-3.4.5-trihidroxitetrahidro-2H-piran-2-carboxilato de (2S,3S,4S,5R,6R)-bencilo

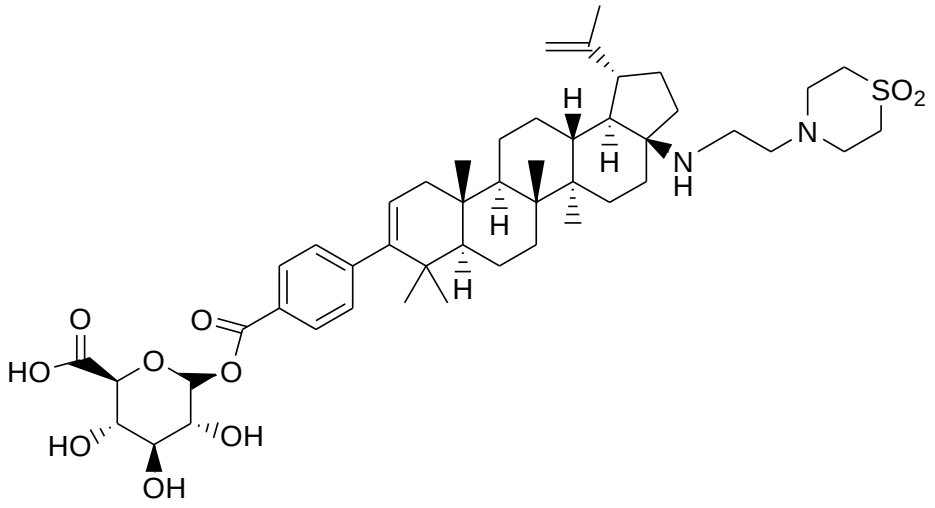


Una mezcla de 3,4,5,6-tetrahidroxitetrahidro-2H-piran-2-carboxilato de (2S,3S,4S,5R)-bencilo (61.7 mg, 0.217

mmol), ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidotiomorfolino)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico (100 mg, 0.145 mmol), HATU (88 mg, 0.232 mmol) y N-metilmorfolina (0.048 mL, 0.434 mmol) en dioxano (3 mL) se agitó durante la noche a temperatura ambiente. La mezcla de reacción se filtró, y la solución transparente se purificó mediante HPLC preparativa con acetonitrilo/agua/acetato de amonio para obtener el producto deseado como un sólido blanco (20 mg, 14 %). LCMS: m/e 957.7 $(M+H)^+$, 2.36 min (método 6). ^{1}H NMR (500MHz, Acético) δ 8.05 (d, *J*= 8.2 Hz, 2H), 7.58-7.14 (m, 7H), 5.95 (d, *J*= 7.6 Hz, 1H), 5.38 (d, *J*= 4.6 Hz, 1H), 5.26 (s, 2H), 4.84 (s, 1H), 4.74 (s, 1H), 4.30 (d, *J*= 9.5 Hz, 1H), 4.05-3.78 (m, 3H), 3.46 (d, *J*= 11.9 Hz, 1H), 3.38-3.22 (m, 6H), 3.20-3.11 (m, 3H), 3.07 (br. s., 2H), 2.95 (dt, *J*= 10.8, 5.5 Hz, 1H), 2.42-1.01 (m, 22H), 1.77 (s, 3H), 1.30 (s, 3H), 1.15 (s, 3H), 1.12 (s, 3H), 1.03 (s, 3H), 1.00 (s, 3H).

Etapa 3. Preparación de ácido (2S,3S,4S,5R,6R)-6-((4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidotiomorfolino)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoil)oxi)-3.4.5-

trihidroxitetrahidro-2H-piran-2-carboxílico

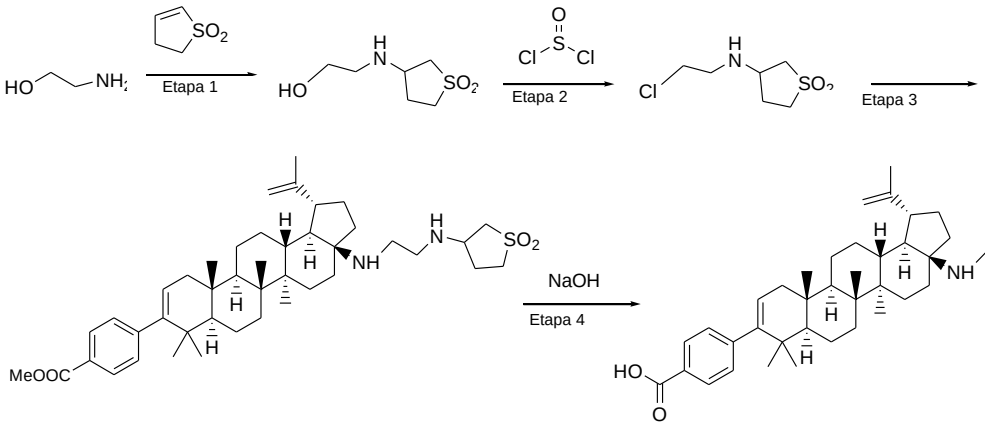


Una mezcla de 6-((4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidotiomorfolino)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoil)oxi)-3.4.5-trihidroxitetrahidro-2H-piran-2-carboxilato de (2S,3S,4S,5R,6R)-bencilo (8 mg, 8.36 µmol), terc-butildimetilsilano (1.943 mg, 0.017 mmol), acetato de paladio (3.75 mg, 0.017 mmol) y trietilamina (5.82 µl, 0.042 mmol) en dicloroetano (1 mL) se calentó a 60 °C durante 2 horas. La mezcla de reacción se enfrió a temperatura ambiente, se filtró, y los filtrados se concentraron para obtener el residuo. A este residuo en THF (1.0 mL), se agregó TBAF (10.93 mg, 0.042 mmol), y la mezcla de reacción se agitó durante 1 hora. Luego, la mezcla de reacción se purificó

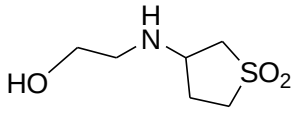
mediante HPLC preparativa para obtener el producto deseado como un aceite incoloro (4 mg, 52 %). LCMS: m/e 867.69 $(M+H)^+$, 2.42 min (método 10). ^{1}H NMR (500MHz, Acético) δ 8.06 (d, *J*= 8.2 Hz, 2H), 7.31 (d, *J*= 8.2 Hz, 2H), 5.96 (d, *J*= 7.9 Hz, 1H), 5.37 (d, *J*= 4.4 Hz, 1H), 4.84 (s, 1H), 4.74 (s, 1H), 4.40-4.16 (m, 1H), 4.02-3.76 (m, 3H), 3.46 (d, *J*= 12.3 Hz, 1H), 3.37-3.22 (m, 6H), 3.20-3.11 (m, 3H), 3.07 (br. s., 2H), 3.00-2.82 (m, 1H), 2.37-1.03 (m, 22H), 1.76 (s, 3H), 1.29 (s, 3H), 1.14 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 0.99 (s, 3H).

Ejemplo B8

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-((1,1-dioxidotetrahidrotiofen-3-il)amino)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

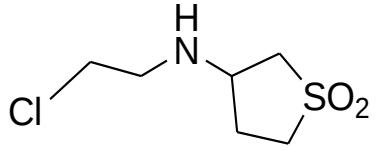


Etapa 1. Preparación de 1,1-dióxido de 3-((2-hidroxietil)amino)tetrahidrotiofeno



Una mezcla de 2-aminoetanol (310 mg, 5.08 mmol), trietilamina (514 mg, 5.08 mmol) y 1,1-dióxido de 2,3-dihidrotiofeno (200 mg, 1.693 mmol) en etanol (3 mL) se calentó a 78 °C durante16 horas. TLC indicó que se consumió el material de inicio y que se formó el producto deseado (30 % metanol/acetato de etilo). La mezcla de reacción se concentró a presión reducida, el residuo se purificó mediante cromatografía en gel de sílice con 0-35 % de metanol/acetato de etilo para obtener el compuesto del título como un aceite incoloro (260 mg, 86 %). ^{1}H NMR (400MHz, CLOROFORMO-d) δ 3.78-3.56 (m, 3H), 3.38-3.21 (m, 2H), 3.14-3.00 (m, 1H), 2.94 (dd, *J*= 13.3, 6.0 Hz, 1H), 2.85-2.68 (m, 2H), 2.53-2.34 (m, 1H), 2.22-2.03 (m, 1H).

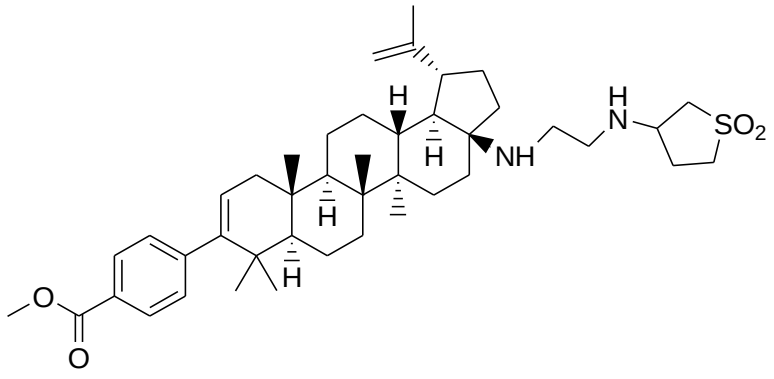
Etapa 2. Preparación de 1,1-dióxido de 3-((2-cloroetil)amino)tetrahidrotiofeno



Una mezcla de 1,1-dióxido de 3-((2-hidroxietil)amino)tetrahidrotiofeno (260 mg, 1.451 mmol) y dicloruro sulfuroso (863 mg, 7.25 mmol) en dicloroetano (3 mL) se calentó a 78 °C durante 3 horas. La mezcla se enfrió a temperatura ambiente y se concentró a presión reducida para

obtener el aceite negro. A este aceite negro se agregaron THF (5 mL) y diclorometano (5 mL), y se observó un sólido blanco grisáceo. El sólido se filtró y se recolectó para obtener el producto deseado como un sólido gris (230 mg, 80 %). LCMS: m/e 198.1 $(M+H)^+$, 0.60 min (método 6).

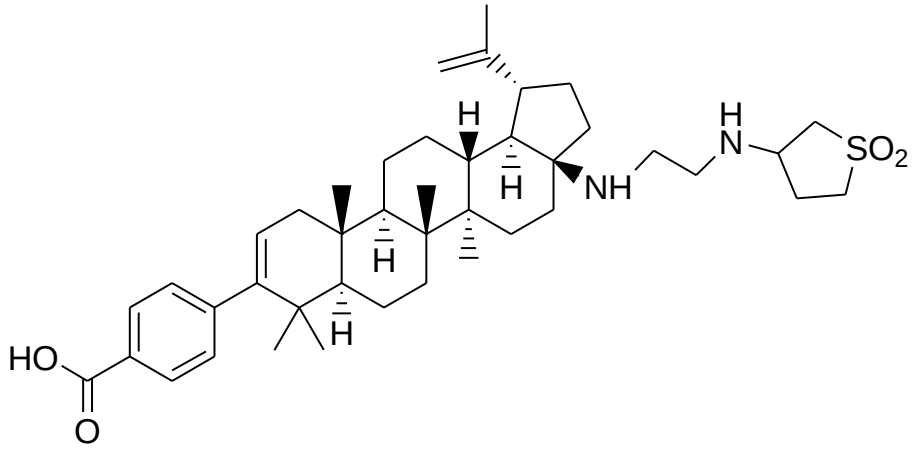
Etapa 3. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-((1,1-dioxidotetrahidrotiofen-3-il)amino)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



Una mezcla de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (50 mg, 0.092 mmol), 1,1-dióxido de 3-((2-cloroetil)amino)tetrahidrotiofeno (45.4 mg, 0.230 mmol), fosfato de potasio (58.5 mg, 0.276 mmol) y

yoduro de potasio (30.5 mg, 0.184 mmol) en acetonitrilo (1 mL) se calentó a 120 °C durante 18 horas. La mezcla de reacción se inactivó con agua destilada (3 mL), se extrajo con diclorometano (3 x 3 mL), las fases orgánicas se combinaron, se secaron en sulfato de sodio, se filtraron y se concentraron a presión reducida para obtener el producto crudo como un sólido blanco (40 mg, 62 %). LCMS: m/e 705.48 $(M+H)^+$, 2.44 min (método 11).

Etapa 4. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-((1,1-dioxidotetrahidrotiofen-3-il)amino)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

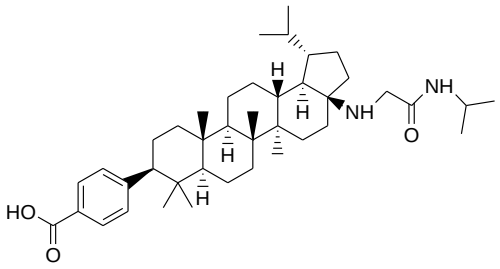


Una mezcla de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-((1,1-dioxidotetrahidrotiofen-3-il)amino)etil)amino)-

5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (40 mg, 0.057 mmol) e hidróxido de sodio (0.567 mL, 0.567 mmol) en dioxano (1 mL) se calentó a 78 °C durante 3 horas. La mezcla de reacción se enfrió a temperatura ambiente, se filtró, y la solución transparente se purificó mediante HPLC para obtener el compuesto del título como un sólido blanco (26 mg, 63 %). LCMS: m/e 691.46 $(M+H)^+$, 2.24 min (método 11). ^{1}H NMR (500MHz, Acético) δ 8.04 (d, *J*= 8.2 Hz, 2H), 7.30 (d, *J*= 8.2 Hz, 2H), 5.37 (d, *J*= 4.9 Hz, 1H), 4.87 (s, 1H), 4.75 (s, 1H), 4.06 (quin, *J*= 7.7 Hz, 1H), 3.67-3.45 (m, 4H), 3.44-3.34 (m, 1H), 3.33-3.11 (m, 2H), 2.92-2.80 (m, 1H), 2.77-2.59 (m, 1H), 2.42-2.29 (m, 1H), 2.26-1.02 (m, 23H), 1.77 (s, 3H), 1.22 (s, 3H), 1.13 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H).

Ejemplo B9

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-((1,1-dioxidotetrahidrotiofen-3-il)amino)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

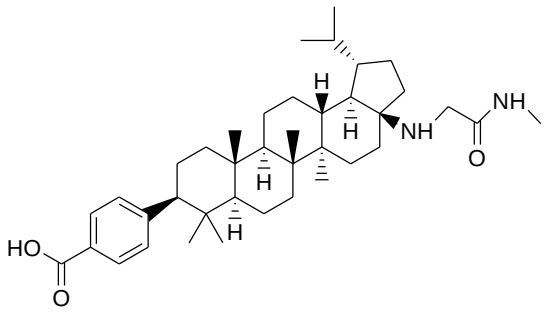


Una mezcla de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(isopropilamino)-2-oxoetil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico (15 mg, 0.024 mmol) y Pd/C (7.61 mg, 7.16 µmol) en metanol (1 mL) y acetato de etilo (1.000 mL) se agitó durante 12 horas a temperatura ambiente en hidrógeno con 1 atmósfera de presión. La mezcla de reacción se filtró, y la solución se purificó mediante HPLC para obtener el compuesto del título como un sólido blanco (6 mg, 38 %). LCMS: m/e 633.48 $(M+H)^+$, 2.62 min (método 10). ^{1}H NMR (500MHz, Acético) δ 8.02 (d, *J*= 8.2 Hz, 2H), 7.36 (d, *J*= 8.5 Hz, 2H), 4.17 (d, *J*= 15.6 Hz, 1H), 4.09 (quin, *J*= 6.6 Hz, 1H), 3.82 (d, *J*= 15.3 Hz, 1H), 2.50 (dd, *J*= 13.1, 2.7 Hz, 1H), 2.34-1.05 (m, 26H), 1.27 (s, 3H), 1.19 (s, 3H), 1.18 (s, 3H), 1.13 (s, 3H), 1.08 (s, 3H), 0.94 (d, *J*= 6.7 Hz, 3H), 0.86 (d, *J*= 6.7 Hz, 3H), 0.84 (s, 3H), 0.80 (s, 3H).

Ejemplo B10

Preparación de ácido 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-1-isopropil-

5a,5b,8,8,11a-pentametil-3a-((2-(metilamino)-2-oxoetil)amino)icosahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

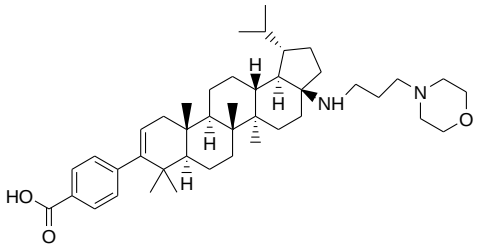


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-((1,1-dioxidotetrahidrotiofen-3-il)amino)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(metilamino)-2-oxoetil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico como material de inicio. El producto se aisló como un sólido blanco (3 mg, 28 %). LCMS: m/e 605.45 $(M+H)^+$, 2.58 min (método 10). ^{1}H NMR (500MHz, Acético) δ 8.02 (d, *J*= 8.2 Hz, 2H), 7.36 (d, *J*= 8.2 Hz, 2H), 4.22 (d, *J*= 15.6 Hz, 1H), 3.85 (d, *J*= 15.6 Hz, 1H), 2.87 (s, 3H), 2.50 (dd, *J*= 13.1, 2.4 Hz,

1H), 2.35-1.02 (m, 26H), 1.28 (s, 3H), 1.13 (s, 3H), 1.08 (s, 3H), 0.95 (d, *J*= 6.7 Hz, 3H), 0.87 (d, *J*= 6.7 Hz, 3H), 0.84 (s, 3H), 0.80 (s, 3H).

Ejemplo B11

Preparación de ácido 4-((1S,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-1-isopropil-5a,5b,8,8,11a-pentametil-3a-((3-morfolinopropil)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

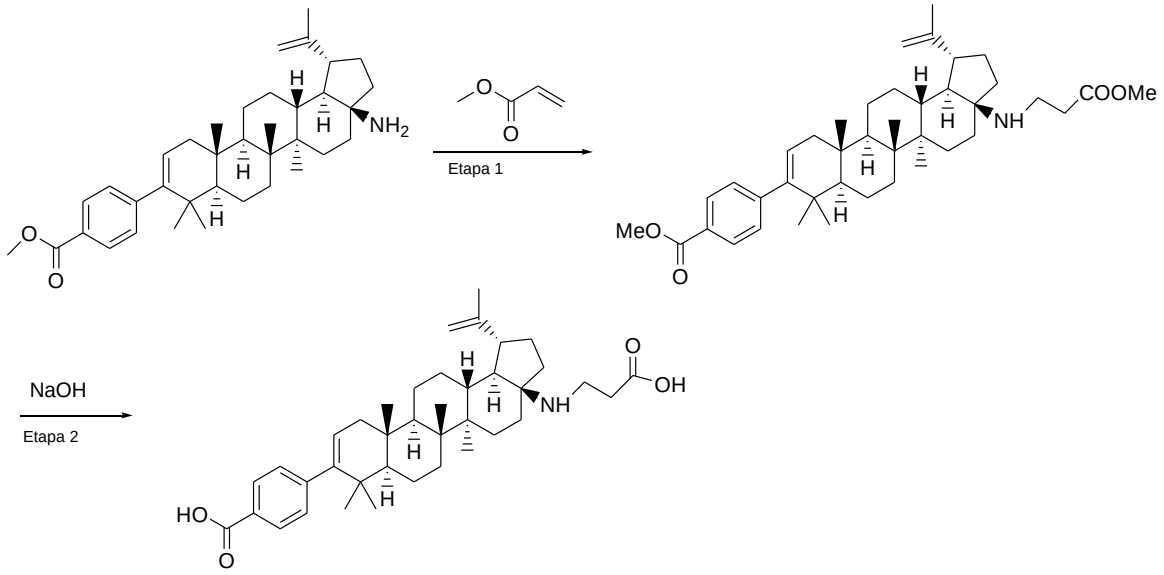


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-((1,1-dioxidotetrahidrotiofen-3-il)amino)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((3-morfolinopropil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico como material de inicio. El producto se aisló como un sólido blanco (5 mg, 40 %). LCMS: m/e 659.55 $(M+H)^+$,

2.86 min (método 10). ^{1}H NMR (500MHz, Acético) δ 8.04 (d, *J*= 8.5 Hz, 2H), 7.30 (d, *J*= 8.2 Hz, 2H), 5.38 (d, *J*= 4.6 Hz, 1H), 3.98 (br. s., 4H), 3.47-3.14 (m, 6H), 2.58-2.34 (m, 1H), 2.30-1.04 (m, 27H), 1.21 (s, 3H), 1.11 (s, 3H), 1.11 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H), 0.93 (d, *J*= 6.7 Hz, 4H), 0.86 (d, *J*= 6.7 Hz, 3H).

Ejemplo B12

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-carboxietil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((3-metoxi-3-oxopropil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo

Se sometió a reflujo una mezcla de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (20 mg, 0.037 mmol), acrilato de metilo (0.013 mL, 0.147 mmol) y trietilamina (0.026 mL, 0.184 mmol) en etanol (1 mL) durante 5 horas. La mezcla de reacción se enfrió a temperatura ambiente y luego se concentró a presión reducida para obtener el producto deseado como un aceite amarillo (15 mg, 65 %). LCMS: m/e 630.43 $(M+H)^+$, 3.81 min (método 10).

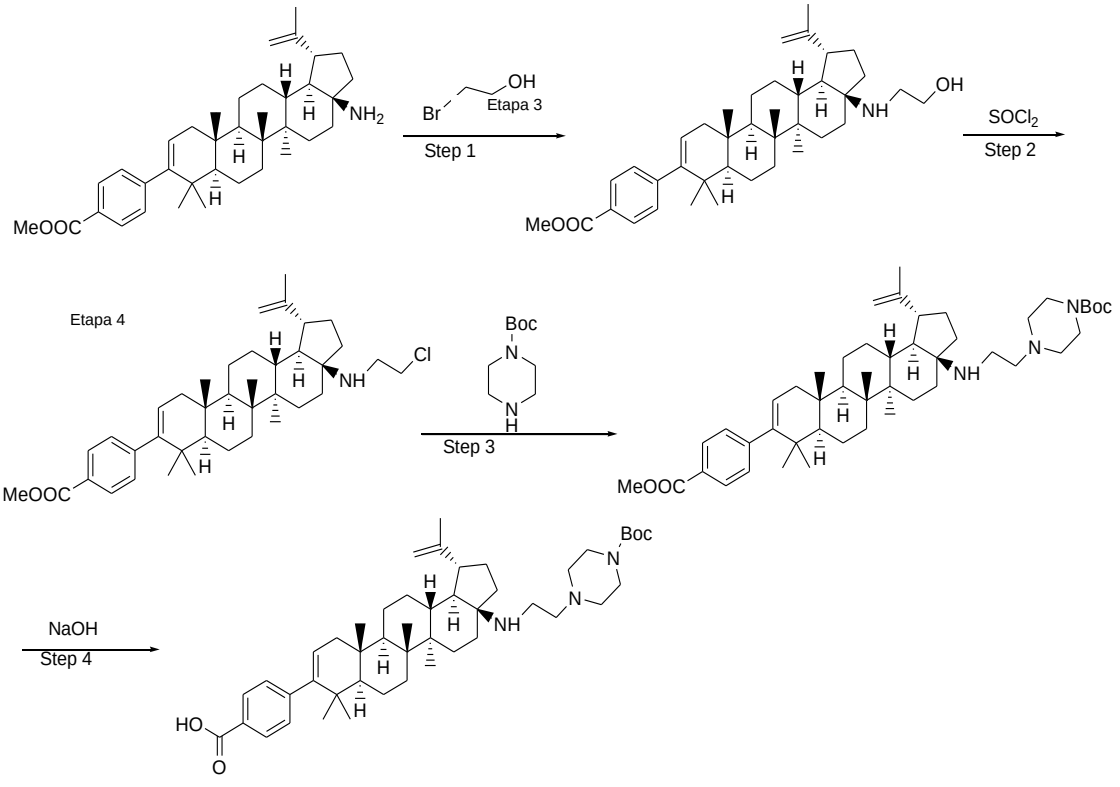
Etapa 2. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-carboxietil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

Una mezcla de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((3-metoxi-3-oxopropil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (15 mg, 0.024 mmol) e hidróxido de sodio (0.238 mL, 0.238 mmol) en dioxano (1 mL) se calentó a 80 °C durante 3 horas. La mezcla de reacción se enfrió a temperatura ambiente y luego se filtró; la solución transparente se purificó mediante HPLC para obtener el compuesto del título como un sólido blanco (5 mg, 33 %). LCMS: m/e 602.43 $(M+H)^+$, 2.25 min

(método 10). ^{1}H NMR (500MHz, Acético) δ 8.04 (d, *J*= 8.2 Hz, 2H), 7.30 (d, *J*= 8.2 Hz, 2H), 5.37 (d, *J*= 4.9 Hz, 1H), 4.86 (s, 1H), 4.74 (s, 1H), 3.39 (t, *J*= 4.4 Hz, 2H), 3.17-3.02 (m, 1H), 2.98-2.80 (m, 2H), 2.31-1.02 (m, 22H), 1.77 (s, 3H), 1.24 (s, 3H), 1.14 (s, 3H), 1.09 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H).

Ejemplo B13

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(terc-butoxicarbonil)piperazin-[Etapa 1]-il)amino)-5a,5b,8,8,11a-pe[Etapa 2]-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-

hidroxietil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

Se calentó una mezcla de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (1500 mg, 2.76 mmol), 2-bromoetanol (1034 mg, 8.27 mmol), fosfato de potasio (1756 mg, 8.27 mmol) y yoduro de potasio (916 mg, 5.52 mmol) en acetonitrilo (10 mL) a 120 °C durante 15 horas. La mezcla de reacción se vertió en agua destilada (40 mL). El precipitado blanco se filtró y se lavó con agua destilada (100 mL). El sólido blanco se secó al vacío para obtener el producto deseado (1.4 g, 86 %). LCMS: m/e 588.5 $(M+H)^+$, 2.40 min (método 11).

Etapa 2. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-cloroetil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

Se calentó una mezcla de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-hidroxietil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (1400 mg, 2.381 mmol) y cloruro de tionilo (1.738 mL, 23.81 mmol) en dicloroetano (15 mL) a 60 °C durante 2 horas. La mezcla de reacción se concentró a presión reducida para obtener el producto deseado como un sólido marrón (1.3 g, 90 %). LCMS: m/e 606.48 $(M+H)^+$, 2.46 min (método 11).

Etapa 3. Preparación de 4-(2-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(metoxicarbonil)fenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-il)amino)etil)piperazin-1-carboxilato de terc-butilo

Se calentó una mezcla de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-cloroetil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (230 mg, 0.379 mmol), base de Hunig (0.331 mL, 1.895 mmol) y piperazin-1-carboxilato de terc-butilo (141 mg, 0.759 mmol) en DMSO (3 mL) a 120 °C durante 1 hora. La mezcla de reacción se inactivó con agua (10 mL) y se extrajo con acetato de etilo (3 x 8 mL); los extractos se combinaron, se secaron en sulfato de sodio, se filtraron y se concentraron a presión reducida para obtener el crudo, que se purificó mediante cromatografía en gel de sílice con 0-30 % acetato de

etilo/hexanos para obtener el producto deseado como un sólido blanco (150 mg, 52 %). LCMS: m/e 756,66 $(M+H)^+$, 2.50 min (método 11).

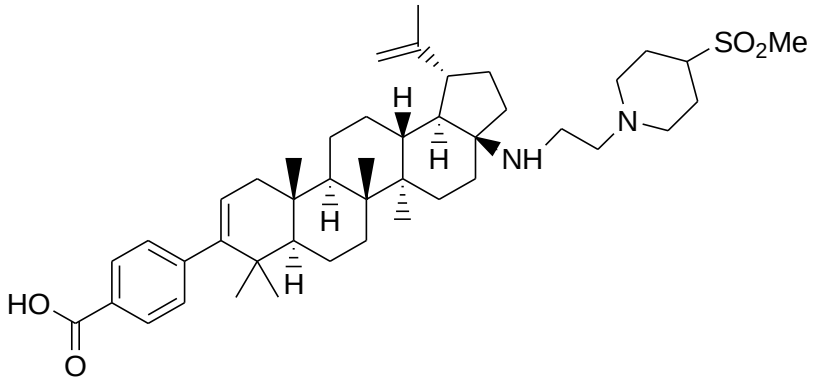
Etapa 4. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(terc-butoxicarbonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

Se calentó una mezcla de 4-(2-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(metoxicarbonil)fenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-il)amino)etil)piperazin-1-carboxilato de terc-butilo (4 mg, 5.29 µmol) e hidróxido de sodio (0.053 mL, 0.053 mmol) en dioxano (1 mL) a 80 °C durante 3 horas. La mezcla de reacción se filtró, y la solución transparente se purificó mediante HPLC para obtener el producto deseado como un sólido blanco (1.6 mg, 39 %). LCMS: m/e 742.65 $(M-H)^-$, 2.68 min (método 10). ^{1}H NMR (500MHz, Acético) δ 8.03 (d, *J*= 8.2 Hz, 2H), 7.30 (d, *J*= 8.2 Hz, 2H), 5.37 (d, *J*= 4.6 Hz, 1H), 4.86 (s, 1H), 4.75 (s, 1H), 3.73 (br. s., 4H), 3.66-3.45 (m, 4H), 3.21 (br. s., 4H), 2.98-2.75 (m, 1H), 2.31-1.00 (m, 22H), 1.77 (s, 3H), 1.50 (s, 9H), 1.23 (s, 3H), 1.13 (s, 3H), 1.09 (s, 3H), 1.02

(s, 3H), 1.00 (s, 3H).

Ejemplo B14

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(4-(metilsulfonil)piperidin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

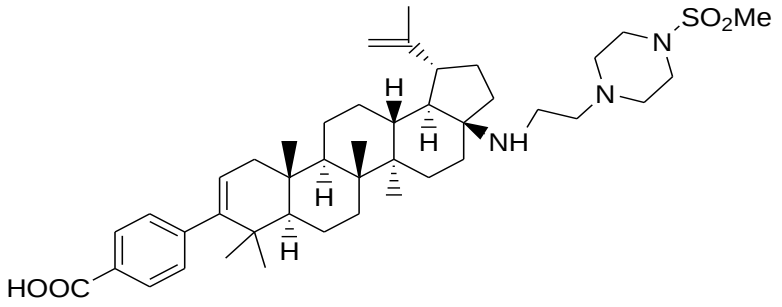


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(terc-butoxicarbonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando 4-(metilsulfonil)piperidina como agente de alquilación en la Etapa 3. El producto se aisló como un sólido blanco (200 mg, 84 %). LCMS: m/e 719.58 $(M+H)^+$, 2.31 min (método 11). ^{1}H NMR (500MHz, Acético) δ 8.04 (d, *J*= 8.5 Hz, 2H), 7.30 (d, *J*= 8.2

Hz, 2H), 5.37 (d, *J*= 4.6 Hz, 1H), 4.87 (s, 1H), 4.75 (s, 1H), 3.76-3.70 (m, 2H), 3.68-3.54 (m, 4H), 3.48-3.29 (m, 1H), 3.18-3.03 (m, 2H), 3.02 (s, 3H), 2.84 (td, *J*= 11.8, 4.7 Hz, 1H), 2.46-1.03 (m, 26H), 1.77 (s, 3H), 1.22 (s, 3H), 1.14 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H).

Ejemplo B15

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(4-(metilsulfonil)piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

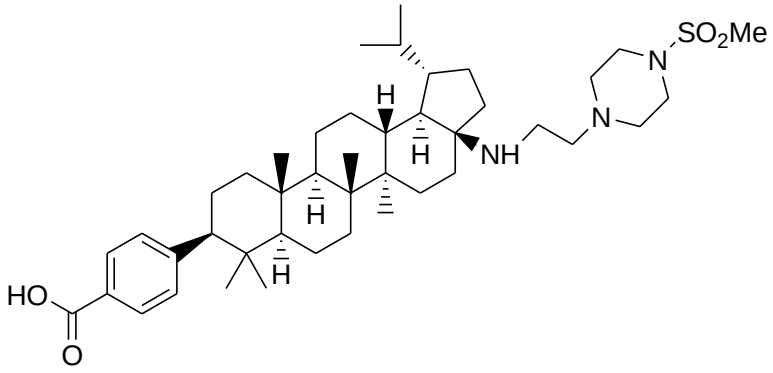


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(terc-butoxicarbonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando 1-

(metilsulfonil)piperazina como agente de alquilación en la Etapa 3. El producto se aisló como un sólido blanco (220 mg, 89 %). LCMS: m/e 720.58 $(M+H)^+$, 2.25 min (método 11). ^{1}H NMR (500MHz, Acético) δ 8.04 (d, *J*= 8.2 Hz, 2H), 7.30 (d, *J*= 8.2 Hz, 2H), 5.37 (d, *J*= 4.6 Hz, 1H), 4.86 (s, 1H), 4.74 (s, 1H), 3.74-3.38 (m, 7H), 3.37-3.25 (m, 1H), 3.17 (br. s., 4H), 2.94 (s, 3H), 2.91-2.80 (m, 1H), 2.35-1.01 (m, 22H), 1.77 (s, 3H), 1.26 (s, 3H), 1.14 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H).

Ejemplo B16

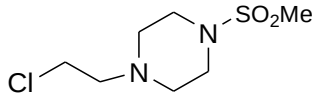
Preparación de ácido 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-1-isopropil-5a,5b,8,8,11a-pentametil-3a-((2-(4-(metilsulfonil)piperazin-1-il)etil)amino)icosahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



El compuesto del título se preparó de acuerdo con el método descrito en el Ejemplo B2 para la síntesis de ácido 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidotiomorfolino)etil)amino)-1-isopropil-5a,5b,8,8,11a-

pentametilicosahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando 1-(2-cloroetil)-4-(metilsulfonil)piperazina (preparada como se describió anteriormente) como reactivo de alquilación en la Etapa 3. El producto se aisló como un sólido blanco (11 mg, 56 %). LCMS: m/e 724.6 $(M+H)^+$, 2.44 min (método 10). ^1H NMR (500MHz, Acético) δ 8.02 (d, *J*= 8.2 Hz, 2H), 7.36 (d, *J*= 8.2 Hz, 2H), 3.63-3.29 (m, 7H), 3.25-3.14 (m, 1H), 3.13-2.99 (m, 4H), 2.93 (s, 3H), 2.50 (dd, *J*= 13.0, 2.6 Hz, 1H), 2.32-0.98 (m, 26H),1.25 (s, 3H), 1.12 (s, 3H), 1.08 (s, 3H), 0.93 (d, *J*= 6.7 Hz, 3H), 0.86 (d, *J*= 6.7 Hz, 3H), 0.83 (s, 3H), 0.79 (s, 3H).

Preparación de 1-(2-cloroetil)-4-(metilsulfonil)piperazina

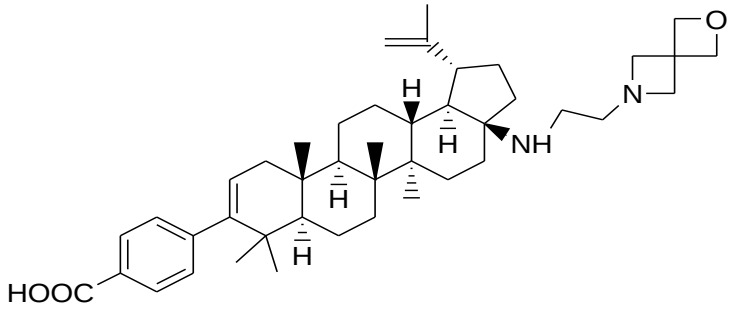


Se agitó una mezcla de 1-(metilsulfonil)piperazina (250 mg, 1.522 mmol), carbonato de potasio (1262 mg, 9.13 mmol) y 1-bromo-2-cloroetano (1092 mg, 7.61 mmol) en acetonitrilo (5 mL) durante 6 horas a temperatura ambiente. LCMS indicó la formación del producto deseado. La mezcla de reacción se filtró para retirar el precipitado blanco, luego se inactivó con agua destilada (10 mL) y se extrajo con acetato de etilo (3 x 8 mL); los extractos se combinaron, se secaron en sulfato de sodio, se filtraron y se concentraron a presión reducida para obtener el producto deseado puro como

un sólido blanco (100 mg, 29 %). LCMS: m/e 227.15 $(M+H)^+$, 1.21 min (método 10).

Ejemplo B17

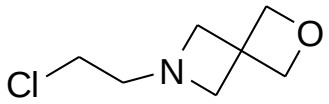
Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(2-oxa-6-azaspiro[3.3]heptan-6-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-((1,1-dioxidotetrahidrotiofen-3-il)amino)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando 6-(2-cloroetil)-2-oxa-6-azaspiro[3.3]heptano (preparado como se describió anteriormente) como reactivo de alquilación en la Etapa 3. El producto se aisló como un sólido blanco (1.1 mg, 18 %). LCMS: m/e 655.53 $(M+H)^+$,

2.29 min (método 11). ^{1}H NMR (500MHz, Acético) δ 8.04 (d, *J*= 8.2 Hz, 2H), 7.30 (d, *J*= 8.5 Hz, 2H), 5.37 (d, *J*= 4.9 Hz, 1H), 4.93 (s., 4H), 4.86 (s, 1H), 4.75 (br. s., 1H), 4.71-4.32 (m, 4H), 4.05-3.86 (m, 2H), 3.70-3.40 (m, 2H), 3.00-2.66 (m, 1H), 2.25-1.05 (m, 22H), 1.76 (s, 3H), 1.18 (s, 3H), 1.13 (s, 3H), 1.08 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H).

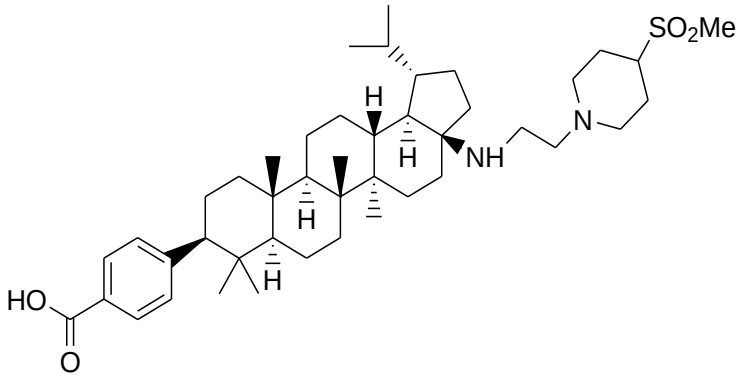
Preparación de 6-(2-cloroetil)-2-oxa-6-azaspiro[3.3]heptano



El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de 1-(2-cloroetil)-4-(metilsulfonil)piperazina usando 2-oxa-6-azaspiro[3.3]heptano como reactivo de inicio. El producto se aisló como un aceite incoloro (10 mg, 12 %). LCMS: m/e 162.15 $(M+H)^+$, 0.87 min (método 10).

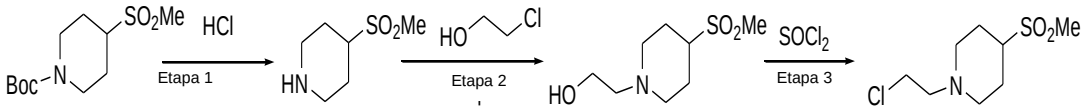
Ejemplo B18

Preparación de ácido 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-1-isopropil-5a,5b,8,8,11a-pentametil-3a-((2-(4-(metilsulfonil)piperidin-1-il)etil)amino)icosahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

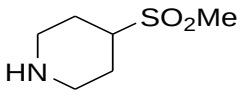


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1S,3aS,5aR,5bR,7aS,9S,11aS,11bR,13aR,13bR)-3a-((2-(1,1-dioxidotiomorfolino)etil)amino)-1-isopropil-5a,5b,8,8,11a-pentametilicosahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando 1-(2-cloroetil)-4-(metilsulfonil)piperidina (preparada como se describió anteriormente) como reactivo de alquilación en la Etapa 3. El producto se aisló como un sólido blanco (24 mg, 36 %). LCMS: m/e 723.56 $(M+H)^+$, 2.28 min (método 11). ^1H NMR (500MHz, Acético) δ 8.02 (d, *J*= 8.2 Hz, 2H), 7.36 (d, *J*= 8.2 Hz, 2H), 3.77-3.63 (m, 2H), 3.62-3.54 (m, 3H), 3.50 (d, *J*= 5.5 Hz, 1H), 3.35 (td, *J*= 11.4, 3.7 Hz, 1H), 3.08-2.89 (m, 2H), 3.02 (s, 3H), 2.50 (d, *J*= 13.1 Hz, 1H), 2.42-2.29 (m, 2H), 2.28-1.03 (m, 28H), 1.21 (s, 3H), 1.12 (s, 3H), 1.08 (s, 3H), 1.01 (d, *J*= 11.3 Hz, 1H), 0.93 (d, *J*= 6.7 Hz, 4H), 0.86 (d, *J*= 6.7 Hz, 4H), 0.83 (s, 3H), 0.79 (s, 3H).

Preparación de 1-(2-cloroetil)-4-(metilsulfonil)piperidina

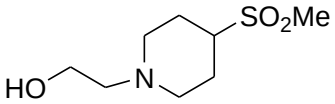


Etapa 1. Preparación de 4-(metilsulfonil)piperidina



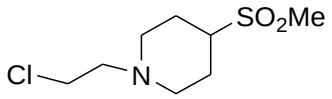
Se agitó una mezcla de 4-(metilsulfonil)piperidin-1-carboxilato de terc-butilo (1.5 g, 5.70 mmol) y cloruro de hidrógeno (7.12 mL, 28.5 mmol) en THF (20 mL) a 20 °C durante 15 horas. La TLC indicó la formación del producto deseado; la mezcla de reacción se filtró, y el sólido amarillo pálido se recolectó para obtener el producto deseado (1 g, 88 %). LCMS: m/e 163.96 $(M+H)^+$, 0.25 min (método 10).

Etapa 2. Preparación de 2-(4-(metilsulfonil)piperidin-1-il)etanol



Se calentó una mezcla de clorhidrato de 4-(metilsulfonil)piperidina (900 mg, 4.51 mmol), 2-bromoetanol (1126 mg, 9.01 mmol) y carbonato de potasio (1869 mg, 13.52 mmol) en acetonitrilo (4 mL) a 60 °C durante 13 horas. La mezcla de reacción se enfrió a temperatura ambiente y se concentró a presión reducida para obtener el crudo, que se purificó mediante 0-35 % acetato de etilo/metanol para obtener el producto deseado como un aceite incoloro (620 mg, 66 %). LCMS: m/e 208.1 $(M+H)^+$, 0.27 min (método 6).

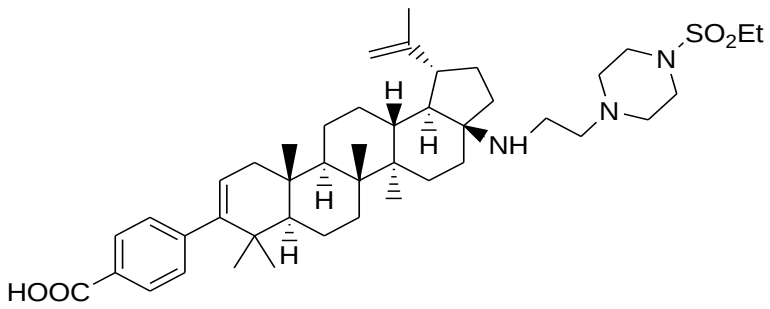
Etapa 3. Preparación de 1-(2-cloroetil)-4-(metilsulfonil)piperidina



Se calentó una mezcla de 2-(4-(metilsulfonil)piperidin-1-il)etanol (620 mg, 2.99 mmol) y cloruro de tionilo (1.092 mL, 14.95 mmol) en dicloroetano (5 mL) a 74 °C durante 4 horas. La mezcla de reacción se concentró a presión reducida para obtener el crudo, al cual se agregó THF (10 mL); se observó y recolectó el precipitado gris. El sólido se secó al vacío durante 20 horas para obtener el producto deseado como un sólido gris (400 mg, 59 %). LCMS: m/e 226.1 $(M+H)^+$, 1.00 min (método 6).

Ejemplo B19

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(etilsulfonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

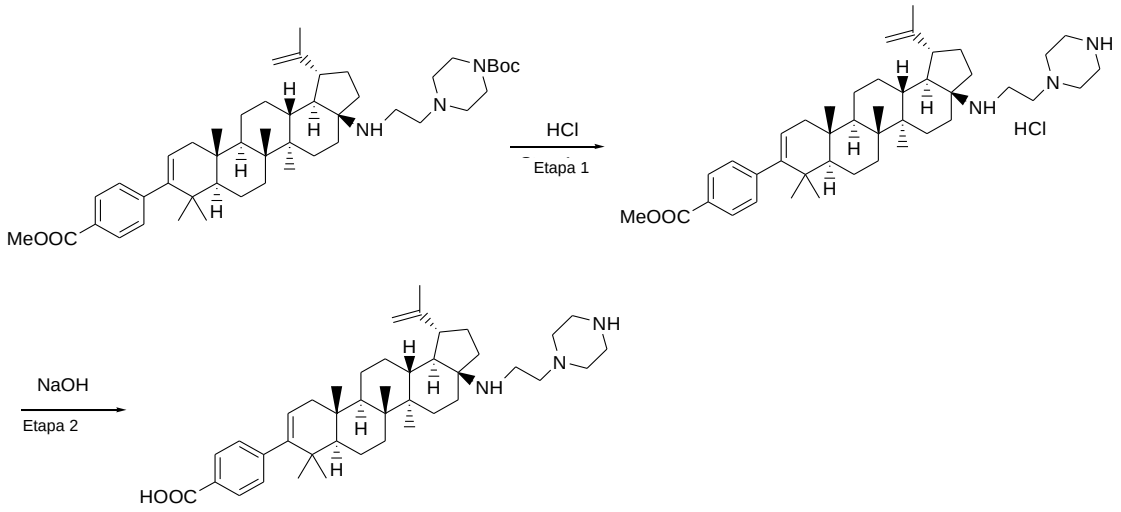


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(terc-butoxicarbonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando 1-(etilsulfonil)piperazina como reactivo de alquilación en la Etapa 3. El producto se aisló como un sólido blanco (11 mg, 53 %). LCMS: m/e 734.56 $(M+H)^+$, 2.28 min (método 11). ^{1}H NMR (400MHz, Acético) δ 7.99 (d, *J*= 8.5 Hz, 2H), 7.26 (d, *J*= 8.3 Hz, 2H), 5.34 (d, *J*= 4.5 Hz, 1H), 4.81 (s, 1H), 4.70 (s, 1H), 3.63-3.28 (m, 7H), 3.26-3.16 (m, 1H), 3.14-2.98 (m, 6H), 2.95-2.75 (m, 1H), 2.33-1.06 (m, 22H), 1.73 (s, 3H), 1.32 (t, *J*= 7.4 Hz, 3H), 1.23 (s, 3H), 1.10 (s, 3H), 1.06 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H).

Ejemplo B20

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



Etapa 1. Preparación de clorhidrato de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo

Una mezcla de 4-(2-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-(metoxicarbonil)fenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-il)amino)etil)piperazin-1-carboxilato de terc-butilo (150 mg, 0.198 mmol) y HCl (0.248 mL, 0.992 mmol) en THF (4 mL) se agitó a 20 °C durante 18 horas. La mezcla de reacción se concentró a presión reducida para obtener el producto deseado como un sólido marrón (120 mg, 87 %). LCMS: m/e 656,7 $(M+H)^+$,

1.62 min (método 11).

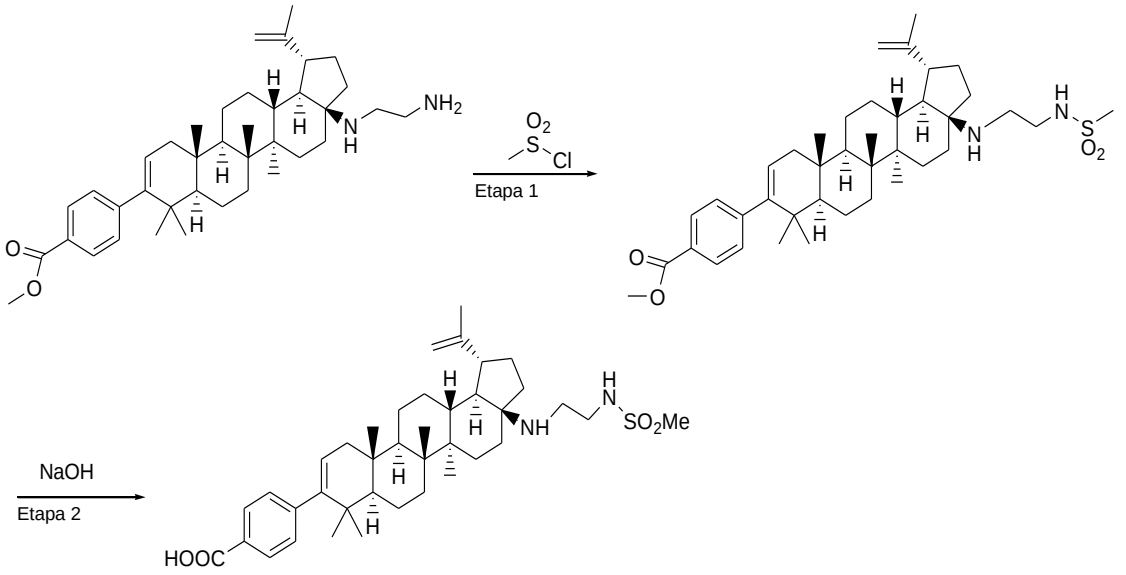
Etapa 2. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

Una mezcla de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (7.5 mg, 0.011 mmol) e hidróxido de sodio (0.057 mL, 0.057 mmol) en dioxano (1 mL) se calentó a 80 °C durante 3 horas. La mezcla de reacción se filtró, y la solución transparente se purificó mediante HPLC para obtener el producto deseado como un sólido blanco (2.3 mg, 31 %). LCMS: m/e 642,62 $(M+H)^+$, 2.29 min (método 11). ^{1}H NMR (400MHz, Acético) δ 8.00 (d, *J*= 8.5 Hz, 2H), 7.26 (d, *J*= 8.5 Hz, 2H), 5.34 (d, *J*= 4.8 Hz, 1H), 4.80 (s, 1H), 4.70 (s, 1H), 3.59-3.28 (m, 6H), 3.25-3.11 (m, 1H), 3.09-2.73 (m, 6H), 2.31-1.15 (m, 22H), 1.73 (s, 3H), 1.26 (s, 3H), 1.11 (s, 3H), 1.08 (s, 3H), 0.99 (s, 3H), 0.97 (s, 3H).

Ejemplo B21

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-

pentametil-3a-((2-(metilsulfonamido)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(metilsulfonamido)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-aminoetil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (15 mg, 0.026 mmol) y base de Hunig (0.013 mL, 0.077 mmol) en diclorometano (1 mL) se agregó cloruro de metansulfonilo

(3.81 mg, 0.033 mmol) en diclorometano (1 mL). La mezcla de reacción se agitó a 20 °C durante 2 horas. La mezcla de reacción se diluyó con agua destilada (3 mL) y se extrajo con diclorometano (3 x 3 mL); los extractos se combinaron, se secaron en sulfato de sodio, se filtraron y se concentraron a presión reducida para obtener el producto deseado como un sólido amarillo (15 mg, 88 %). LCMS: m/e 665.55 $(M+H)^+$, 2.44 min (método 11).

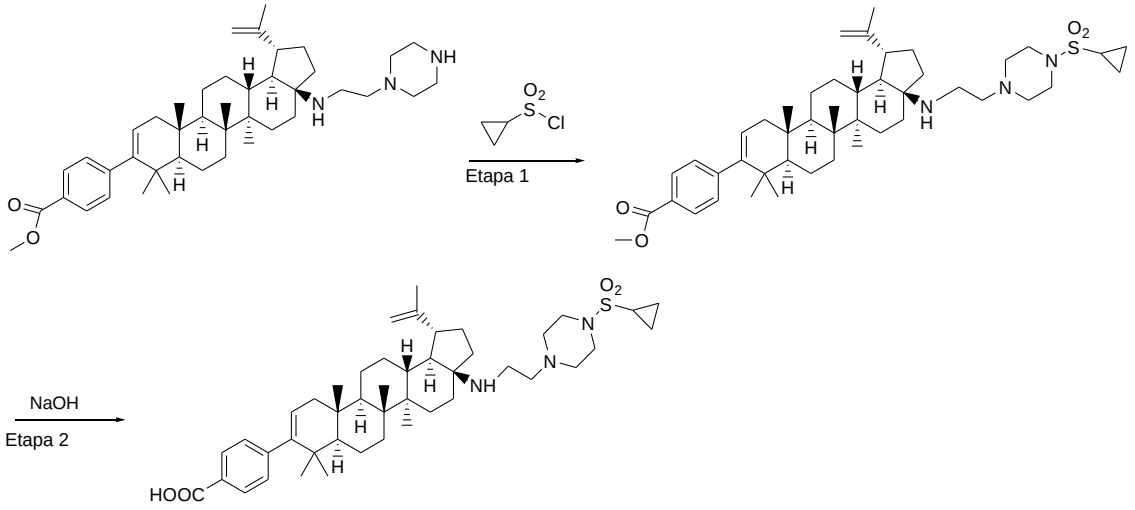
Etapa 2. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(metilsulfonamido)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

Una mezcla de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(metilsulfonamido)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (15 mg, 0.023 mmol) e hidróxido de sodio (0.113 mL, 0.113 mmol) en dioxano (1 mL) se calentó a 80 °C durante 3 horas. La mezcla de reacción se filtró, y la solución transparente se purificó mediante HPLC para obtener el compuesto del título como un sólido blanco (7 mg, 45 %). LCMS: m/e 651.52 $(M+H)^+$, 2.28 min (método 11). ^{1}H NMR (400MHz, Acético) δ 7.99 (d, *J*= 8.3 Hz, 2H), 7.26 (d, *J*= 8.3 Hz, 2H), 5.33 (d, *J*= 4.5

Hz, 1H), 4.81 (s, 1H), 4.71 (s, 1H), 3.53 (br. s., 2H), 3.36-3.26 (m, 2H), 3.07 (s, 3H), 2.96-2.75 (m, 1H), 2.30-2.11 (m, 3H), 1.84-1.06 (m, 19H), 1.74 (s, 3H), 1.22 (s, 3H), 1.10 (s, 3H), 1.06 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H).

Ejemplo B22

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(ciclopropilsulfonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(ciclopropilsulfonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo.

A una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (26 mg, 0.040 mmol) y base de Hunig (0.035 mL, 0.198 mmol) en diclorometano (1 mL) se agregó una solución de cloruro de ciclopropansulfonilo (11.14 mg, 0.079 mmol) en diclorometano (1 mL) a temperatura ambiente. La mezcla de reacción se agitó durante 2 horas a 20 °C, o LCMS indicó la formación del producto deseado y el consumo del material de inicio. La mezcla de reacción se diluyó con agua destilada (4 mL) y se extrajo con diclorometano (3 x 4 mL); los extractos se combinaron, se secaron en sulfato de sodio, se filtraron y se concentraron a presión reducida para obtener el producto deseado como un sólido amarillo (30 mg, 100 %). LCMS: m/e 760.61 $(M+H)^+$, 2.40 min (método 11).

Etapa 2. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(ciclopropilsulfonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

Una mezcla de 4-

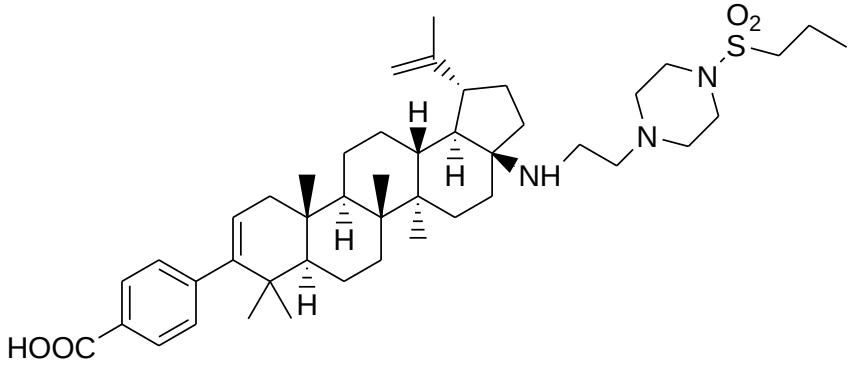
((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(ciclopropilsulfonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (30 mg, 0.039 mmol) e hidróxido de sodio (0.395 mL, 0.395 mmol) en dioxano (0.5 mL) se calentó a 80 °C durante 3 horas. La mezcla de reacción se filtró, y la solución transparente se purificó mediante HPLC para obtener el compuesto del título como un sólido blanco (13 mg, 42%). LCMS: m/e 746.58 $(M+H)^+$, 2.27 min (método 11). ^{1}H NMR (400MHz, Acético) δ 7.99 (d, *J*= 8.3 Hz, 2H), 7.26 (d, *J*= 8.3 Hz, 2H), 5.34 (d, *J*= 4.8 Hz, 1H), 4.81 (s, 1H), 4.70 (s, 1H), 3.63-3.44 (m, 5H), 3.43-3.26 (m, 2H), 3.24-3.13 (m, 1H), 3.05 (d, *J*= 4.3 Hz, 4H), 2.86 (br. s., 1H), 2.58-2.40 (m, 1H), 2.27-1.02 (m, 22H), 1.73 (s, 3H)

1.24 (s, 3H), 1.13 (d, *J*= 4.5 Hz, 2H), 1.10 (s, 3H), 1.06 (s, 3H), 1.02 (d, *J*= 4.5 Hz, 2H), 0.97 (s, 3H), 0.96 (s, 3H).

Ejemplo B23

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-((2-(4-(propilsulfonil)piperazin-1-il)etil)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

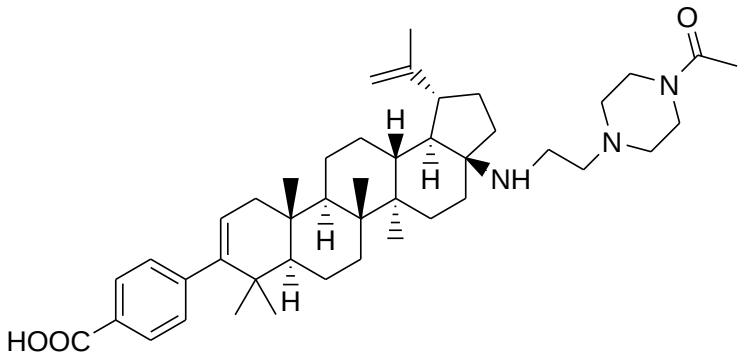


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(ciclopropilsulfonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando cloruro de propan-1-sulfonilo como reactivo en la Etapa 1. El producto se aisló como un sólido blanco (8 mg, 48 %). LCMS: m/e 748.6 $(M+H)^+$, 2.30 min (método 11). ^{1}H NMR (400MHz, Acético) δ 7.99 (d, *J*= 8.3 Hz, 2H), 7.26 (d, *J*= 8.5 Hz, 2H), 5.34 (d, *J*= 4.5 Hz, 1H), 4.81 (s, 1H), 4.70 (s, 1H), 3.59-3.26 (m, 7H), 3.23-3.11 (m, 1H), 3.09-2.95 (m, 6H), 2.93-2.80 (m, 1H), 2.27-1.02 (m, 24H), 1.73 (s, 3H), 1.24 (s, 3H), 1.10 (s, 3H), 1.07 (s, 3H), 1.05 (t, *J*= 8.3 Hz, 3H), 0.98 (s, 3H), 0.97 (s, 3H).

Ejemplo B24

Preparación de ácido 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-acetilpiperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

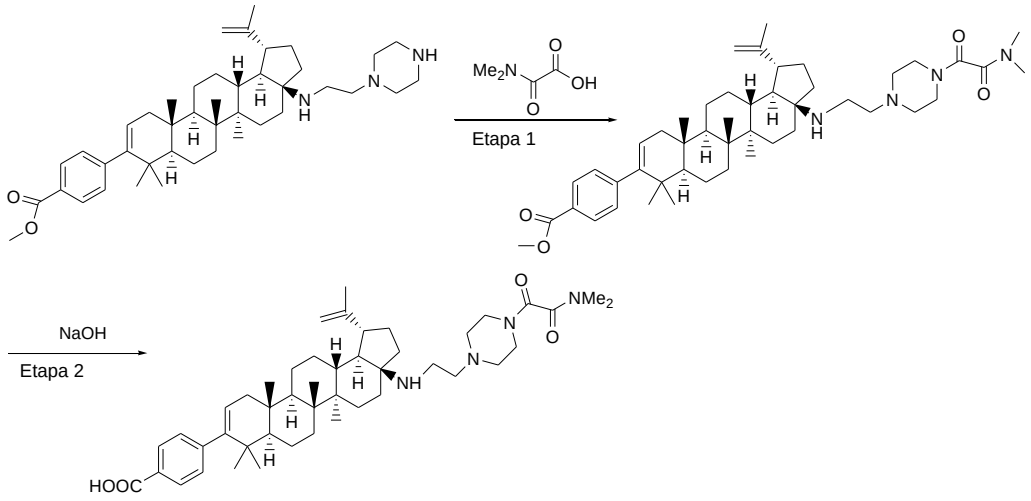


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(ciclopropilsulfonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando cloruro de acetilo como reactivo en la Etapa 1. El producto se aisló como un sólido blanco (5.4 mg, 35 %). LCMS: m/e 684.67 $(M+H)^+$, 2.27 min (método 11). ^{1}H NMR (400MHz, Acético) δ 7.99 (d, *J*= 8.3 Hz, 2H), 7.26 (d, *J*= 8.5 Hz, 2H), 5.33 (d, *J*= 4.8 Hz, 1H), 4.82 (s, 1H), 4.72 (s, 1H), 4.09-3.89 (m, 1H), 3.85 (br. s., 3H), 3.68 (br. s., 4H), 3.53-3.14 (m, 4H), 2.92-2.66 (m, 1H), 2.28-1.01 (m, 22H), 2.17 (s, 3H), 1.73 (s,

3H), 1.18 (s, 3H), 1.10 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H).

Ejemplo B25

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(2-(dimetilamino)-2-oxoacetil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



Etapa 1. Preparación de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(2-(dimetilamino)-2-oxoacetil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo

Una mezcla de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (50 mg, 0.076 mmol), tetrafluoroborato de 2-(1H-benzo[d][1,2,3]triazol-1-il)-1,1,3,3-tetrametilisouronio (29.4 mg, 0.091 mmol), N-etil-N-isopropilpropan-2-amina (11.82 mg, 0.091 mmol) y ácido 2-(dimetilamino)-2-oxoacético (26.8 mg, 0.229 mmol) en diclorometano (2 mL) se agitó a 20 °C durante 2 horas. La mezcla de reacción se diluyó con agua destilada (5 mL) y se extrajo con acetato de etilo (3 x 4 mL); los extractos se combinaron, se secaron en sulfato de sodio, se filtraron y se concentraron a presión reducida para obtener el producto deseado como un aceite amarillo (40 mg, 70 %). LCMS: m/e 755.68 $(M+H)^+$, 2.42 min (método 11).

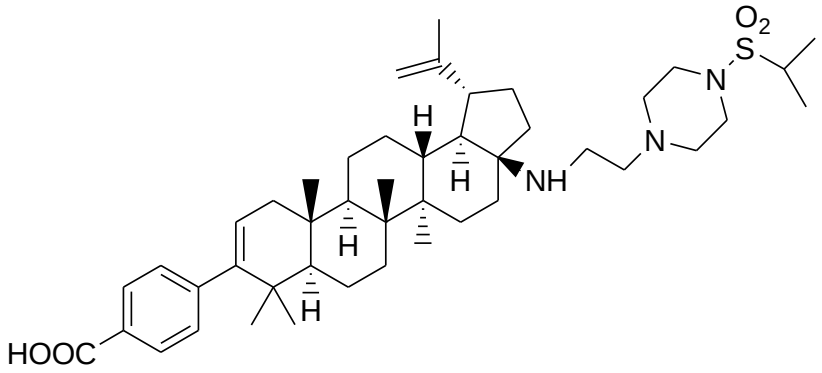
Etapa 2. Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(2-(dimetilamino)-2-oxoacetil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

Una mezcla de 4-

((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(2-(dimetilamino)-2-oxoacetil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (40 mg, 0.053 mmol) e hidróxido de sodio (0.530 mL, 0.530 mmol) en dioxano (1 mL) se calentó a 82 °C durante 3 horas. La mezcla de reacción se enfrió a temperatura ambiente, se filtró, y la solución transparente se purificó mediante HPLC para obtener el compuesto del título como un sólido blanco (17 mg, 41 %). LCMS: m/e 741.65 $(M+H)^+$, 2.29 min (método 11). ^{1}H NMR (400MHz, Acético) δ 7.99 (d, *J*= 8.3 Hz, 2H), 7.26 (d, *J*= 8.3 Hz, 2H), 5.33 (d, *J*= 4.5 Hz, 1H), 4.82 (s, 1H), 4.71 (s, 1H), 4.14-3.78 (m, 2H), 3.75-3.36 (m, 6H), 3.22 (br. s., 4H), 3.03 (s, 3H), 3.00 (s, 3H), 2.92-2.75 (m, 1H), 2.29-1.05 (m, 22H), 1.73 (s, 3H), 1.20 (s, 3H), 1.10 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H).

Ejemplo B26

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(isopropilsulfonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

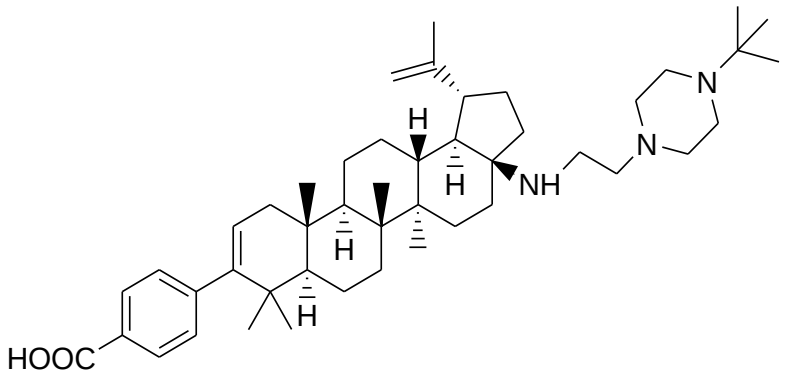


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(ciclopropilsulfonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando cloruro de propan-2-sulfonilo como reactivo en la Etapa 1. El producto se aisló como un aceite incoloro (6 mg, 36 %). LCMS: m/e 748.63 $(M+H)^+$, 2.31 min (método 11). ^{1}H NMR (400MHz, Acético) δ 7.99 (d, *J*= 8.0 Hz, 2H), 7.26 (d, *J*= 8.0 Hz, 2H), 5.33 (d, *J*= 5.3 Hz, 1H), 4.82 (s, 1H), 4.71 (s, 1H), 3.80-3.55 (m, 8H), 3.49-3.25 (m, 5H), 2.92-2.68 (m, 1H), 2.32-1.04 (m, 22H), 1.73 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H), 1.17 (s, 3H), 1.10 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H).

Ejemplo B27

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(terc-butil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-

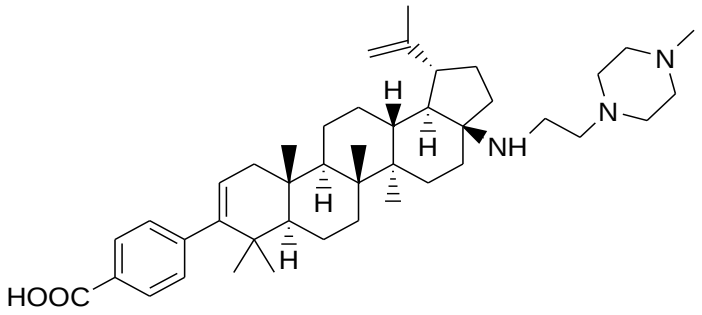
(prop-1-en-2-il)-
2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-
octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(terc-butoxicarbonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando 1-(terc-butil)piperazina como reactivo de alquilación en la Etapa 3. El producto se aisló como un sólido blanco (9 mg, 40 %). LCMS: m/e 698.67 $(M+H)^+$, 2.27 min (método 11). ^{1}H NMR (500MHz, Acético) δ 8.04 (d, *J*= 8.0 Hz, 2H), 7.30 (d, *J*= 8.0 Hz, 2H), 5.38 (d, *J*= 5.2 Hz, 1H), 4.84 (s, 1H), 4.74 (s, 1H), 3.77 (br. s., 2H), 3.51-2.82 (m, 11H), 2.41-1.16 (m, 22H), 1.77 (s, 3H), 1.49 (s, 9H), 1.30 (s, 3H), 1.15 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 1.01 (s, 3H).

Ejemplo B28

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(4-metilpiperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

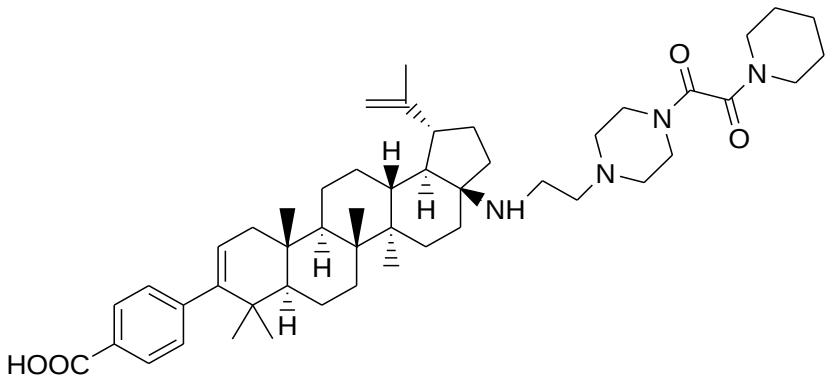


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(terc-butoxicarbonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando 1-metilpiperazina como reactivo de alquilación en la Etapa 3. El producto se aisló como un sólido blanco (3 mg, 19 %). LCMS: m/e 656.62 $(M+H)^+$, 2.19 min (método 11). ^{1}H NMR (500MHz, Acético) δ 8.04 (d, *J*= 8.0 Hz, 2H), 7.30 (d, *J*= 8.0 Hz, 2H), 5.38 (d, *J*= 5.7 Hz, 1H), 4.84 (s, 1H), 4.74 (s, 1H), 3.73 (br. s., 1H), 3.62-2.85 (m, 12H), 2.94 (s, 3H), 2.34-1.15 (m,

22H), 1.77 (s, 3H), 1.29 (s, 3H), 1.15 (s, 3H), 1.11 (s, 3H), 1.03 (s, 3H), 1.01 (s, 3H).

Ejemplo B29

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(4-(2-oxo-2-(piperidin-1-il)acetil)piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

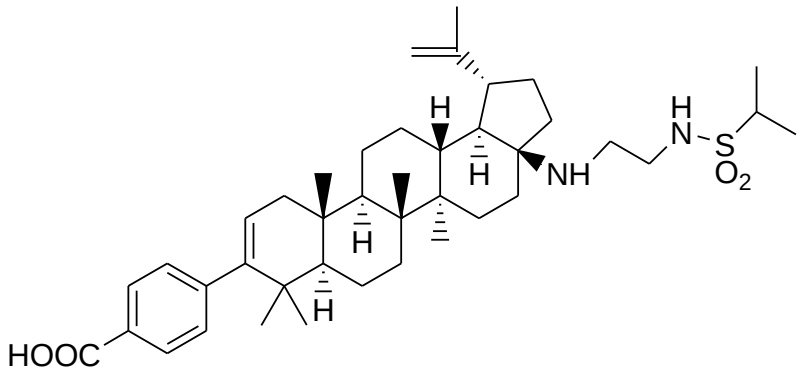


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(2-(dimetilamino)-2-oxoacetil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando ácido 2-oxo-2-(piperidin-1-il)acético como ácido en la Etapa 1. El producto se aisló como un sólido blanco (1.1 mg, 18 %). LCMS: m/e 781.7 $(M+H)^+$, 1.72 min (método 11). ^{1}H NMR (500MHz,

CLOROFORMO-d) δ 7.99 (d, *J*= 8.4 Hz, 2H), 7.24 (d, *J*= 8.4 Hz, 2H), 5.31 (d, *J*= 4.6 Hz, 1H), 4.77 (s, 1H), 4.65 (s, 1H), 3.84 (dd, *J*= 7.6, 2.7 Hz, 1H), 3.68-3.56 (m, 3H), 3.49 (t, *J*= 4.9 Hz, 2H), 3.43-3.30 (m, 2H), 2.93-2.63 (m, 9H), 2.60-1.05 (m, 28H), 1.72 (s, 3H), 1.17 (s, 3H), 1.04 (s, 3H), 1.00 (s, 3H), 0.97 (s, 3H), 0.97 (s, 3H).

Ejemplo B30

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(1-metiletilsulfonamido)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

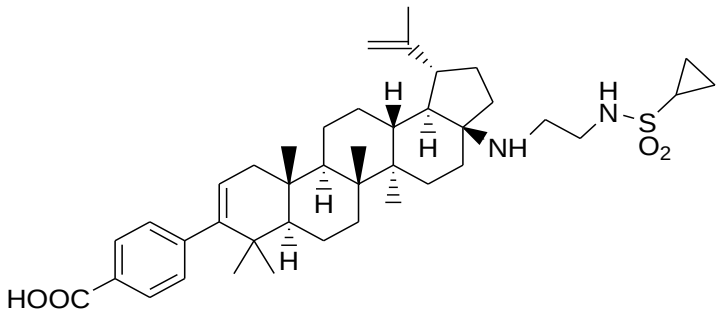


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(metilsulfonamido)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando cloruro de propan-2-sulfonilo como reactivo en la Etapa 1. El producto se aisló como un aceite incoloro (3.5 mg, 34 %). LCMS: m/e 679.55 $(M+H)^+$, 2.36 min (método 11). ^1H NMR (400MHz, CLOROFORMO-d) δ 9.56 (br. s., 1H), 7.98 (d, *J*= 8.5 Hz, 2H), 7.23 (d, *J*= 8.3 Hz, 2H), 6.91 (t, *J*= 6.3 Hz, 1H), 5.94 (br. s., 1H), 5.18 (d, *J*= 4.5 Hz, 1H), 4.87 (s, 1H), 4.71 (s, 1H), 3.88-3.69 (m, 1H), 3.63-3.49 (m, 1H), 3.37-3.16 (m, 3H), 2.90-2.68 (m, 1H), 2.26-1.07 (m, 22H), 1.70 (s, 3H), 1.44 (dd, *J*= 8.8, 6.8 Hz, 6H), 1.20 (s, 3H), 1.02 (s, 3H), 0.96 (s, 3H), 0.96 (s, 3H), 0.92 (s, 3H).

Ejemplo B31

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(ciclopropansulfonamido)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



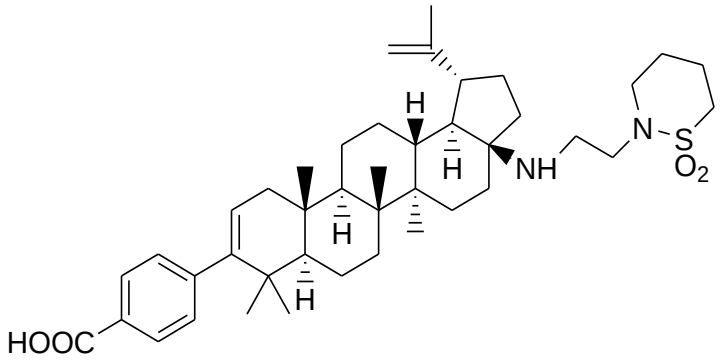
El compuesto del título se preparó de acuerdo

con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(metilsulfonamido)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando cloruro de ciclopropansulfonilo como reactivo de la Etapa 1. El producto se aisló como un aceite incoloro (3.5 mg, 34 %). LCMS: m/e 677.52 $(M+H)^+$, 2.32 min (método 11). ^{1}H NMR (400MHz, CLOROFORMO-d) δ 9.55 (br. s., 1H), 7.98 (d, *J*= 8.3 Hz, 2H), 7.23 (d, *J*= 8.3 Hz, 2H), 6.76 (br. s., 1H), 5.99 (br. s., 1H), 5.21 (d, *J*= 5.0 Hz, 1H), 4.85 (s, 1H), 4.71 (s, 1H), 3.92-3.71 (m, 1H), 3.69-3.55 (m, 1H), 3.23 (br. s., 2H), 2.91-2.70 (m, 1H), 2.63-2.44 (m, 1H), 2.25-1.02 (m, 26H), 1.70 (s, 3H), 1.18 (s, 3H), 1.02 (s, 3H), 0.97 (s, 3H), 0.92 (s, 3H), 0.92 (s, 3H).

Ejemplo B32

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a((2-(1,1-dioxido-1,2-tiazinan-2-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-

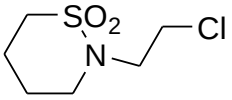
il)benzoico.



El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-((1,1-dioxidotetrahidrotiofen-3-il)amino)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando 1-(2-cloroetil)-4-(metilsulfonil)piperazina (preparada como se describió anteriormente) como reactivo de alquilación en la Etapa 3. El producto se aisló como un sólido blanco (5.2 mg, 36 %). LCMS: m/e 691.55 $(M+H)^+$, 2.35 min (método 11). ^{1}H NMR (400MHz, CLOROFORMO-d) δ 7.99 (d, *J*= 8.3 Hz, 2H), 7.23 (d, *J*= 8.5 Hz, 2H), 5.27 (d, *J*= 4.5 Hz, 1H), 4.82 (s, 1H), 4.70 (s, 1H), 3.87-3.74 (m, 1H), 3.72-3.48 (m, 3H), 3.39 (br. s., 2H), 3.18-3.08 (m, 2H), 2.96-2.78 (m, 1H), 2.34-1.10 (m, 26H), 1.71 (s, 3H), 1.23 (s, 3H), 1.05 (s, 3H), 0.99 (s, 3H), 0.96 (s, 3H), 0.96 (s, 3H).

Preparación de 1-(2-cloroetil)-4-

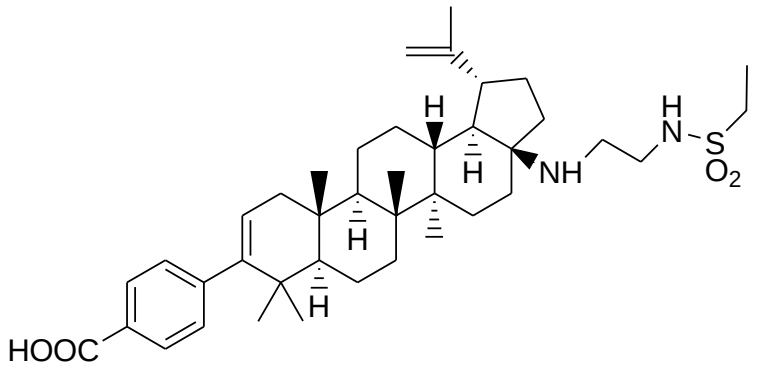
(metilsulfonil)piperazina



El compuesto del título se preparó de acuerdo con el método descrito previamente para la síntesis de 1-(2-cloroetil)-4-(metilsulfonil)piperazina usando 1,1-dióxido de 1,2-tiazinan como reactivo de inicio e hidruro de sodio como base. El producto se aisló como un aceite incoloro (120 mg, 41 %). LCMS: m/e 198.08 $(M+H)^+$, 1.24 min (método 11).

Ejemplo B33

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(etilsulfonamido)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

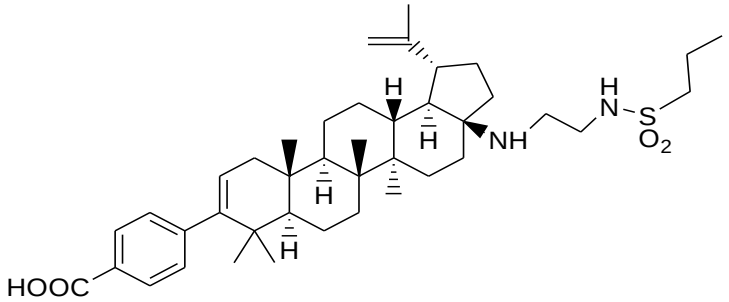


El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-

pentametil-3a-((2-(metilsulfonamido)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando cloruro de etansulfonilo como reactivo en la Etapa 1. El producto se aisló como un sólido blanco (8.7 mg, 56 %). LCMS: m/e 665.46 $(M+H)^+$, 2.29 min (método 11). ^{1}H NMR (500MHz, CLOROFORMO-d) δ 9.27 (br. s., 1H), 8.00 (d, *J*= 7.1 Hz, 2H), 7.25 (d, *J*= 7.1 Hz, 2H), 6.84 (br. s., 1H), 6.07 (br. s., 1H), 5.24 (d, *J*= 6.3 Hz, 1H), 4.85 (s, 1H), 4.73 (s, 1H), 3.84-3.68 (m, 1H), 3.54 (d, *J*= 14.8 Hz, 1H), 3.37-3.21 (m, 2H), 3.17 (q, *J*= 7.4 Hz, 2H), 2.83-2.76 (m, 1H), 2.36 – 0.95 (m, 22H), 1.72 (s, 3H), 1.46 (t, *J*= 7.4 Hz, 3H), 1.20 (s, 3H), 1.05 (s, 3H), 0.97 (s, 3H), 0.95 (s, 3H), 0.95 (s, 3H).

Ejemplo B34

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-((2-(propilsulfonamido)etil)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



El compuesto del título se preparó de acuerdo con el método descrito anteriormente para la síntesis de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(metilsulfonamido)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico usando cloruro de propan-1-sulfonilo como reactivo en la Etapa 1. El producto se aisló como un sólido blanco (9 mg, 49 %). LCMS: m/e 679.48 $(M+H)^+$, 2.34 min (método 11). ^{1}H NMR (500MHz, CLOROFORMO-d) δ 9.36 (br. s., 1H), 8.00 (d, *J*= 8.4 Hz, 2H), 7.25 (d, *J*= 8.2 Hz, 2H), 6.81 (br. s., 1H), 6.04 (br. s., 1H), 5.31-5.19 (m, 1H), 4.86 (s, 1H), 4.73 (s, 1H), 3.85-3.67 (m, 1H), 3.54 (d, *J*= 14.7 Hz, 1H), 3.38-3.18 (m, 2H), 3.15-3.07 (m, 2H), 2.80 (td, *J*= 11.2, 5.9 Hz, 1H), 2.26 – 0.95 (m, 24H), 1.71 (s, 3H), 1.20 (s, 3H), 1.12 (t, *J*= 7.4 Hz, 3H), 1.05 (s, 3H), 0.97 (s, 3H), 0.96 (s, 3H), 0.94 (s, 3H).

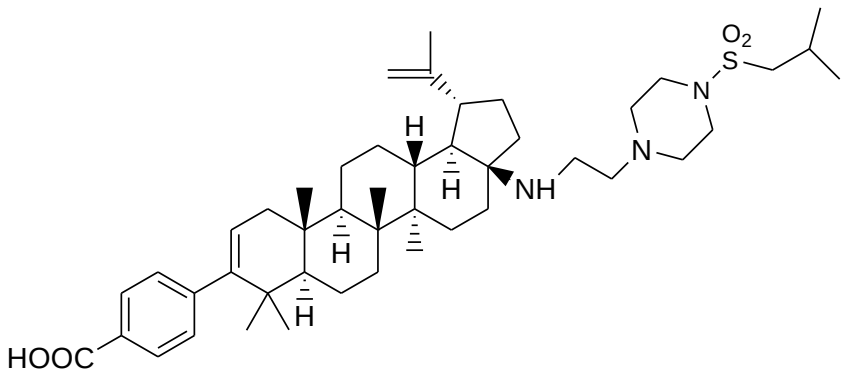
Procedimiento general para la preparación de los ejemplos B35-B52

Al reactivo de cloruro de sulfonilo sustituido correspondiente (agente de sulfonilación) (0.075 mmol) se agregó una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo

(29 mg, 0.044 mmol) y DIPEA (0.039 mL, 0.221 mmol) en DCE (1 mL) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante la noche. El solvente se evaporó para obtener el residuo seco. Al residuo en dioxano (0.8 mL) se agregó una solución de hidróxido de litio monohidrato (14.7 mg, 0.35 mmol) en agua (0.2 mL). La mezcla de reacción se agitó a 350 rpm en un agitador de plataforma Innova a 70 °C durante la noche. Se retiró el solvente, y se agregó DMF (1.5 mL). La mezcla se filtró, y la solución transparente se purificó mediante HPLC para obtener los productos deseados con un rendimiento que varió de 6-50% en dos etapas.

Ejemplo B35

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(isobutilsulfonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



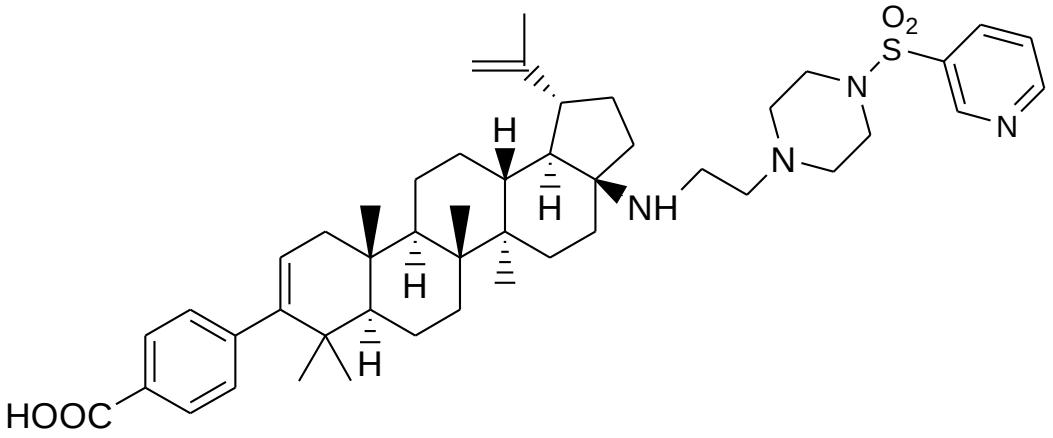
El compuesto del título se preparó para

obtener 11.9 mg de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito anteriormente usando cloruro de isobutansulfonilo como agente de sulfonilación. LCMS: m/e 762.8 $(M+H)^+$, 3.65 min (método 14). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.87 (d, *J*= 8.2 Hz, 2H), 7.22 (d, *J*= 8.2 Hz, 2H), 5.25 (d, *J*= 4.9 Hz, 1H), 4.70 (s, 1H), 4.57 (s, 1H), 3.17 (br. s., 4H), 3.00-2.82 (m, 2H), 2.70-2.53 (m, 5H), 2.48-2.30 (m, 4H), 2.24-2.03 (m, 2H), 2.00-1.83 (m, 2H), 1.80-1.01 (m, 19H), 1.67 (s, 3H), 1.11 (s, 3H), 1.06 (s, 3H), 1.05 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H).

Ejemplo B36

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-((2-(4-(piridin-3-ilsulfonil)piperazin-1-il)etil)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

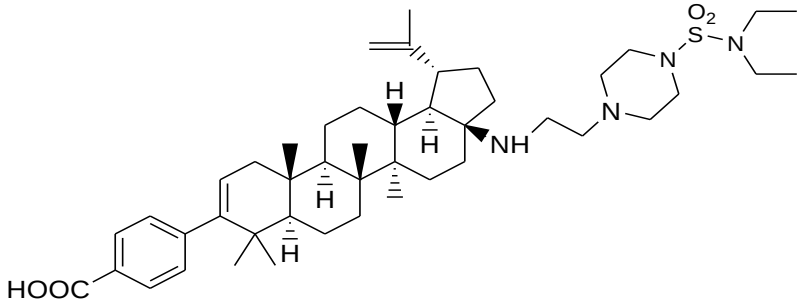
octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



El compuesto del título se preparó para obtener 12.7 mg de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito anteriormente usando cloruro de piridin-3-sulfonilo como agente de sulfonilación. LCMS: m/e 783.8 $(M+H)^+$, 3.42 min (método 14). ^{1}H NMR (500MHz, DMSO-d_6) δ 8.95 (d, *J*= 2.1 Hz, 1H), 8.89 (dd, *J*= 4.7, 1.4 Hz, 1H), 8.32-8.16 (m, 1H), 7.88 (d, *J*= 8.2 Hz, 2H), 7.73 (dd, *J*= 7.9, 4.9 Hz, 1H), 7.25 (d, *J*= 7.9 Hz, 2H), 5.25 (d, *J*= 4.9 Hz, 1H), 4.64 (d, *J*= 1.8 Hz, 1H), 4.53 (s, 1H), 3.11-2.92 (m, 4H), 2.65-2.46 (m, 5H), 2.45-2.20 (m, 4H), 2.05 (dd, *J*= 17.4, 6.4 Hz, 1H), 1.91-1.76 (m, 2H), 1.73 – 0.99 (m, 19H), 1.63 (s, 3H), 1.03 (s, 3H), 0.94 (s, 3H), 0.91 (s, 3H), 0.87 (s, 3H), 0.61 (s, 3H).

Ejemplo B37

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(N,N-dietilsulfamoil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

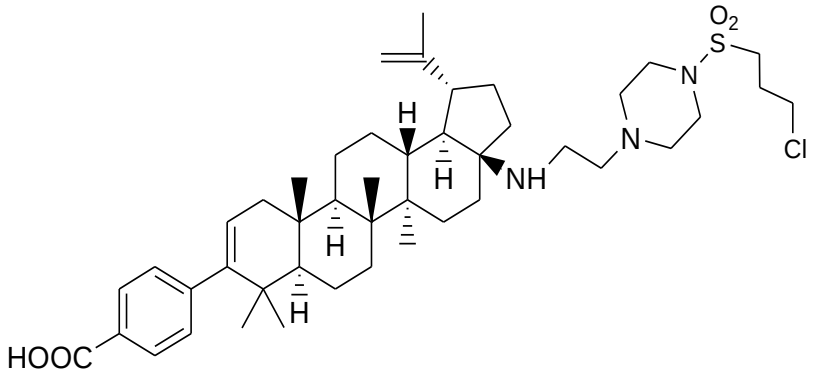


El compuesto del título se preparó para obtener 10.6 mg de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito anteriormente usando cloruro de dimetilsulfamoil como agente de sulfonilación. LCMS: m/e 777.8 $(M+H)^+$, 3.82 min (método 14). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.87 (d, *J*= 7.9 Hz, 2H), 7.22 (d, *J*= 8.2 Hz, 2H), 5.25 (d, *J*= 4.6 Hz, 1H), 4.70 (d, *J*= 2.1 Hz, 1H), 4.56 (s, 1H), 3.22 (q, *J*= 7.1 Hz, 4H), 3.08 (br. s., 4H), 2.69-2.57 (m, 1H), 2.56-2.47 (m, 4H), 2.44-2.31 (m, 4H),

2.08 (dd, *J*= 17.5, 6.3 Hz, 1H), 1.95-1.00 (m, 21H), 1.67 (s, 3H), 1.12 (t, *J*= 7.0 Hz, 6H), 1.09 (s, 3H), 0.97 (s, 3H), 0.96 (s, 3H), 0.91 (s, 3H), 0.90 (s, 3H).

Ejemplo B38

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-((3-cloropropil)sulfonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

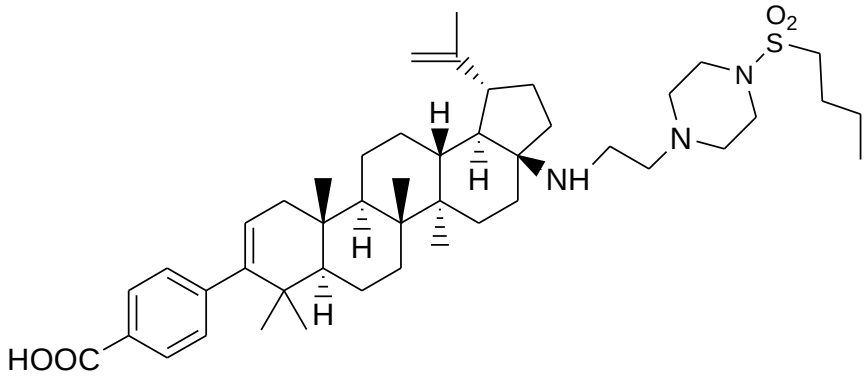


El compuesto del título se preparó para obtener 10.9 mg de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito anteriormente usando cloruro de 3-cloropropansulfonilo como agente de sulfonilación. LCMS: m/e 782.7 $(M+H)^+$, 3.59 min

(método 14). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.87 (d, *J*= 7.9 Hz, 2H), 7.22 (d, *J*= 8.2 Hz, 2H), 5.25 (d, *J*= 4.9 Hz, 1H), 4.70 (d, *J*= 2.1 Hz, 1H), 4.57 (s, 1H), 3.76 (t, *J*= 6.4 Hz, 2H), 3.26-3.13 (m, 6H), 2.63 (td, *J*= 10.5, 4.9 Hz, 1H), 2.56 (d, *J*= 7.6 Hz, 4H), 2.48-2.33 (m, 4H), 2.21-2.04 (m, 3H), 1.98-1.83 (m, 2H), 1.83-1.02 (m, 19H), 1.67 (s, 3H), 1.10 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H), 0.90 (s, 3H), 0.90 (s, 3H).

Ejemplo B39

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(butilsulfonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

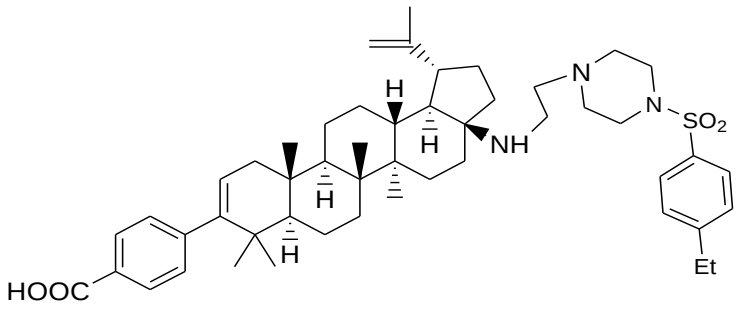


El compuesto del título se preparó para obtener 13.6 mg de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito anteriormente usando cloruro de butan-1-sulfonilo como agente de sulfonilación. LCMS: m/e 762.8 $(M+H)^+$, 3.66 min (método 14). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.87 (d, *J*= 8.2 Hz, 2H), 7.22 (d, *J*= 8.2 Hz, 2H), 5.25 (d, *J*= 4.6 Hz, 1H), 4.70 (d, *J*= 2.1 Hz, 1H), 4.56 (s, 1H), 3.19 (br. s., 4H), 3.12-2.96 (m, 2H), 2.63 (td, *J*= 10.8, 5.3 Hz, 1H), 2.55 (br. s., 4H), 2.47-2.30 (m, 4H), 2.08 (dd, *J*= 17.2, 6.3 Hz, 1H), 1.98-1.83 (m, 2H), 1.82-1.02 (m, 23H), 1.67 (s, 3H), 1.10 (s, 3H), 0.98 (s, 3H), 0.96 (s, 3H), 0.91 (t, *J*= 4.7 Hz, 3H), 0.90 (s, 3H), 0.89 (s, 3H).

Ejemplo B40

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-((4-etilfenil)sulfonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



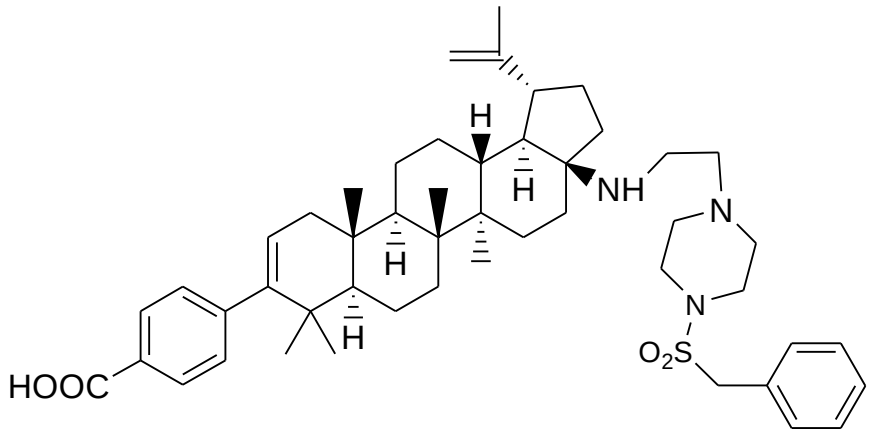
El compuesto del título se preparó para

obtener 3.7 mg de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito anteriormente usando cloruro de 4-etil-bencen-1-sulfonilo como agente de sulfonilación. LCMS: m/e 810.9 $(M+H)^+$, 4.12 min (método 14). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.89 (d, *J*= 8.2 Hz, 2H), 7.68 (d, *J*= 8.2 Hz, 2H), 7.49 (d, *J*= 8.2 Hz, 2H), 7.24 (d, *J*= 8.2 Hz, 2H), 5.26 (d, *J*= 4.9 Hz, 1H), 4.63 (br. s., 1H), 4.55 (br. s., 1H), 3.03-2.90 (m, 4H), 2.71 (q, *J*= 7.7 Hz, 2H), 2.52 (d, *J*= 1.5 Hz, 5H), 2.49-2.34 (m, 4H), 2.06 (dd, *J*= 17.7, 6.4 Hz, 1H), 1.80 (d, *J*= 9.8 Hz, 2H), 1.75-1.01 (m, 19H), 1.63 (s, 3H), 1.21 (t, *J*= 7.5 Hz, 3H), 0.96 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H), 0.92 (s, 3H), 0.85 (s, 3H).

Ejemplo B41

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(bencilsulfonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

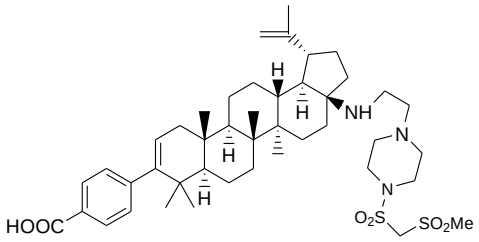
octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



El compuesto del título se preparó para obtener 16.4 mg de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito anteriormente usando cloruro de fenil-metansulfonilo como agente de sulfonilación. LCMS: m/e 796.8 $(M+H)^+$, 3.73 min (método 14). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.87 (d, *J*= 8.2 Hz, 2H), 7.46-7.41 (m, 2H), 7.41-7.31 (m, 3H), 7.22 (d, *J*= 8.2 Hz, 2H), 5.25 (d, *J*= 4.6 Hz, 1H), 4.72 (d, *J*= 1.5 Hz, 1H), 4.58 (s, 1H), 4.53-4.39 (m, 2H), 3.11 (br. s., 4H), 2.64-2.54 (m, 1H), 2.53-2.45 (m, 2H), 2.46-2.29 (m, 6H), 2.09 (dd, *J*= 17.2, 6.3 Hz, 1H), 1.96-1.80 (m, 3H), 1.78-1.02 (m, 18H), 1.68 (s, 3H), 1.10 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H), 0.89 (s, 3H), 0.87 (s, 3H).

Ejemplo B42

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(4-(((metilsulfonil)metil)sulfonil)piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

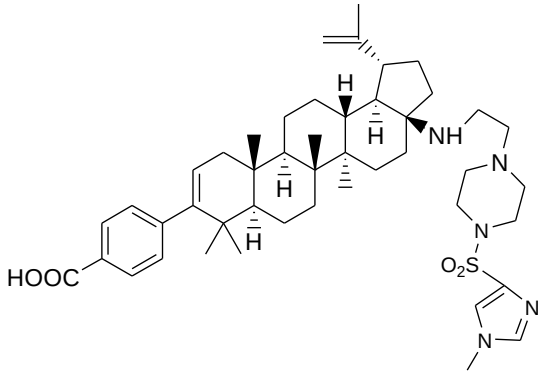


El compuesto del título se preparó para obtener 5.5 mg de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito anteriormente usando cloruro de metansulfonilo-metansulfonilo como agente de sulfonilación. LCMS: m/e 798.8 $(M+H)^+$, 3.28 min (método 14). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.87 (d, *J*= 7.9 Hz, 2H), 7.22 (d, *J*= 7.9 Hz, 2H), 5.29 (s, 2H), 5.25 (d, *J*= 4.6 Hz, 1H), 4.70 (s, 1H), 4.57 (s, 1H), 3.29 (br. s., 8H), 3.19 (s, 3H), 2.64-2.55 (m, 1H), 2.48-2.34 (m, 4H), 2.08 (dd,

J= 17.2, 6.3 Hz, 1H), 1.97-1.80 (m, 3H), 1.79 – 0.99 (m, 18H), 1.67 (s, 3H), 1.09 (s, 3H), 0.97 (s, 3H), 0.97 (s, 3H), 0.90 (s, 3H), 0.90 (s, 3H).

Ejemplo B43

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(4-((1-metil-1H-imidazol-4-il)sulfonil)piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

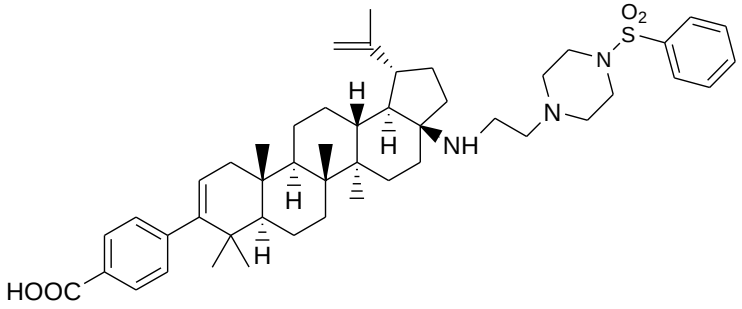


El compuesto del título se preparó para obtener 17 mg de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito anteriormente usando cloruro de 1-metil-1H-imidazol-4-sulfonilo como agente de sulfonilación. LCMS: m/e 786.8

$(M+H)^+$, 3.08 min (método 14). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.92-7.84 (m, 3H), 7.77 (s, 1H), 7.23 (d, *J*= 7.9 Hz, 2H), 5.26 (d, *J*= 4.9 Hz, 1H), 4.66 (d, *J*= 1.8 Hz, 1H), 4.55 (s, 1H), 3.73 (s, 3H), 3.04 (br. s., 4H), 2.63-2.47 (m, 5H), 2.45-2.26 (m, 4H), 2.08 (dd, *J*= 17.4, 6.4 Hz, 1H), 1.91-1.77 (m, 2H), 1.77-1.00 (m, 19H), 1.65 (s, 3H), 0.96 (s, 3H), 0.94 (s, 3H), 0.94 (s, 3H), 0.93 (s, 3H), 0.89 (s, 3H).

Ejemplo B44

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(4-(fenilsulfonil)piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

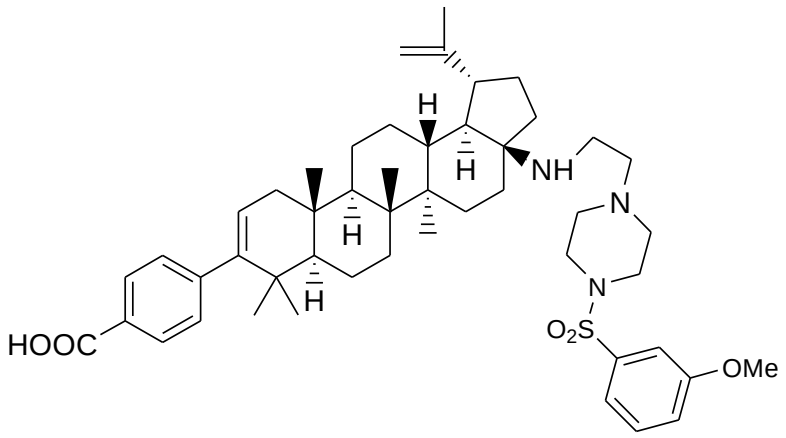


El compuesto del título se preparó para obtener 3.9 mg de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo

de acuerdo con el procedimiento general descrito anteriormente usando cloruro de bencensulfonilo como agente de sulfonilación. LCMS: m/e 782.8 $(M+H)^+$, 4.98 min (método 15). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.89 (d, *J*= 8.2 Hz, 2H), 7.78 (d, *J*= 7.0 Hz, 2H), 7.75-7.62 (m, 3H), 7.26 (d, *J*= 7.9 Hz, 2H), 5.25 (d, *J*= 4.9 Hz, 1H), 4.64 (br. s., 1H), 4.54 (br. s., 1H), 2.92 (br. s., 4H), 2.57 (br. s., 5H), 2.47-2.27 (m, 4H), 2.05 (dd, *J*= 17.4, 6.4 Hz, 1H), 1.93-1.77 (m, 2H), 1.76 – 0.98 (m, 19H), 1.63 (s, 3H), 1.03 (s, 3H), 0.95 (s, 3H), 0.91 (s, 3H), 0.86 (s, 3H), 0.58 (s, 3H).

Ejemplo B45

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-((3-metoxifenil)sulfonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



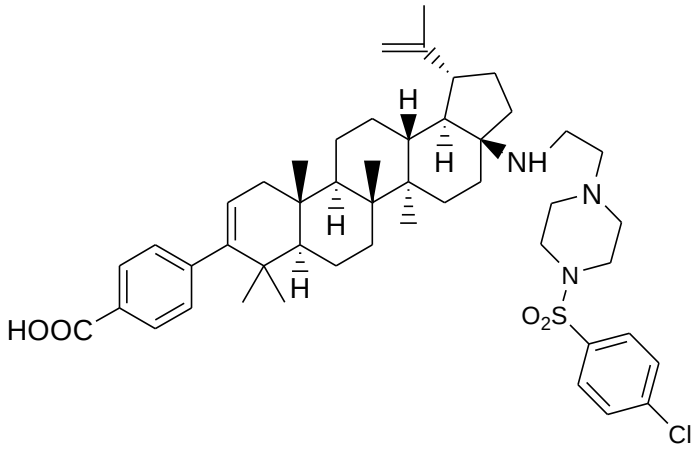
El compuesto del título se preparó para

obtener 3.2 mg de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito anteriormente usando cloruro de 3-metoxibencensulfonilo como agente de sulfonilación. LCMS: m/e 812.8 $(M+H)^+$, 4.98 min (método 15). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.89 (d, *J*= 8.2 Hz, 2H), 7.64-7.51 (m, 1H), 7.34 (d, *J*= 7.9 Hz, 1H), 7.28-7.13 (m, 4H), 5.25 (d, *J*= 4.6 Hz, 1H), 4.64 (s, 1H), 4.53 (s, 1H), 3.85 (s, 3H), 3.03-2.87 (m, 4H), 2.64-2.51 (m, 5H), 2.46-2.22 (m, 4H), 2.05 (dd, *J*= 17.2, 6.3 Hz, 1H), 1.93-1.76 (m, 2H), 1.75 – 0.98 (m, 19H), 1.63 (s, 3H), 1.02 (s, 3H), 0.94 (s, 3H), 0.91 (s, 3H), 0.87 (s, 3H), 0.63 (s, 3H).

Ejemplo B46

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-((4-clorofenil)sulfonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b

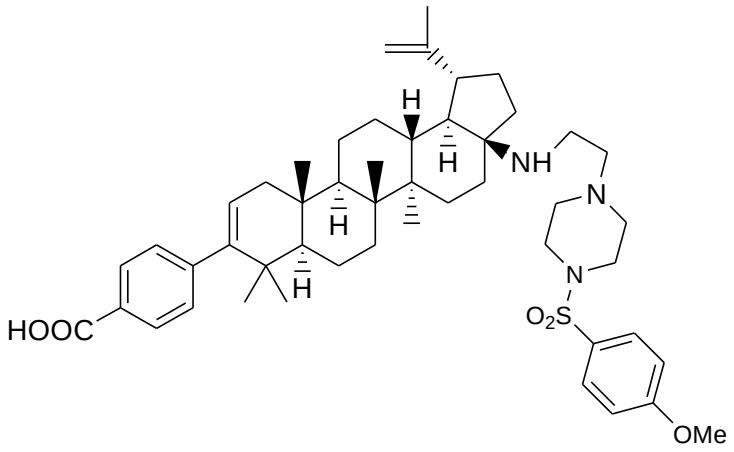
-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



El compuesto del título se preparó para obtener 2.1 mg de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito anteriormente usando cloruro de 4-clorobencen-1-sulfonilo como agente de sulfonilación. LCMS: m/e 816.8 $(M+H)^+$, 3.94 min (método 14). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.89 (d, *J*= 8.2 Hz, 2H), 7.81 (d, *J*= 8.5 Hz, 2H), 7.73 (d, *J*= 8.9 Hz, 2H), 7.24 (d, *J*= 7.9 Hz, 2H), 5.25 (d, *J*= 4.6 Hz, 1H), 4.66 (br. s., 1H), 4.57 (br. s., 1H), 2.96 (br. s., 4H), 2.71-2.55 (m, 4H), 2.51-2.30 (m, 5H), 2.06 (dd, *J*= 17.4, 6.4 Hz, 1H), 1.98-1.79 (m, 2H), 1.78 – 0.89 (m, 19H), 1.65 (s, 3H), 1.00 (s, 3H), 0.93 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H), 0.80 (s, 3H).

Ejemplo B47

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-((4-metoxifenil)sulfonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

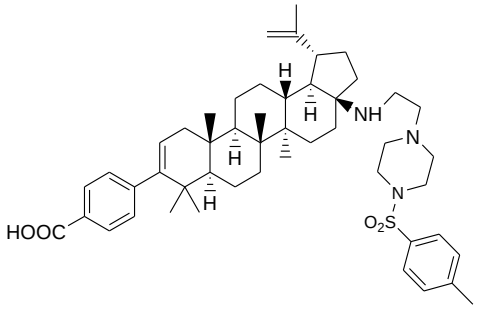


El compuesto del título se preparó para obtener 9.5 mg de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito anteriormente usando cloruro de 4-metoxibencen-1-sulfonilo como agente de sulfonilación. LCMS: m/e 812.8 $(M+H)^+$, 3.69 min (método 14). ^1H NMR (500MHz, DMSO-d_6) δ 7.89 (d, *J*= 8.2 Hz, 2H), 7.70 (d, *J*= 8.9 Hz, 2H), 7.24 (d, *J*= 8.2 Hz, 2H),

7.16 (d, *J*= 8.9 Hz, 2H), 5.25 (d, *J*= 4.6 Hz, 1H), 4.63 (d, *J*= 2.1 Hz, 1H), 4.53 (s, 1H), 3.83 (s, 3H), 2.91 (s, 4H), 2.61-2.46 (m, 5H), 2.41 (br. s., 2H), 2.36-2.22 (m, 2H), 2.05 (dd, *J*= 17.5, 6.3 Hz, 1H), 1.90-1.75 (m, 2H), 1.74-1.03 (m, 19H), 1.63 (s, 3H), 0.98 (s, 3H), 0.92 (s, 3H), 0.92 (s, 3H), 0.88 (s, 3H), 0.75 (s, 3H).

Ejemplo B48

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-((2-(4-tosilpiperazin-1-il)etil)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

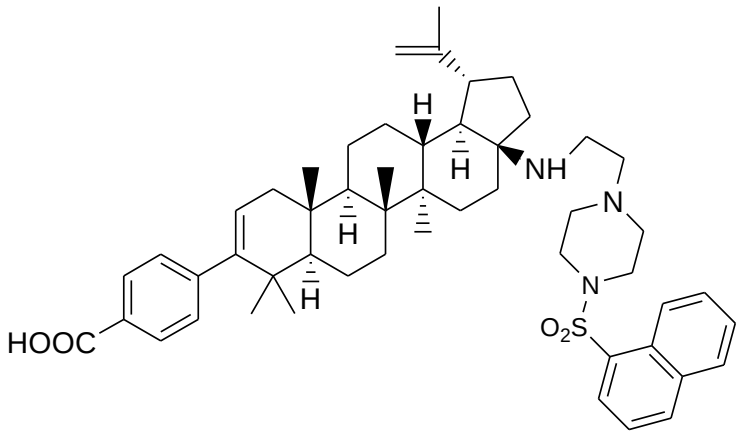


El compuesto del título se preparó para obtener 4.6 mg de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito

anteriormente usando cloruro de 4-metilbencen-1-sulfonilo como agente de sulfonilación. LCMS: m/e 796.8 $(M+H)^+$, 3.91 min (método 14). ^1H NMR (500MHz, DMSO-d_6) δ 7.88 (d, *J*= 8.2 Hz, 2H), 7.65 (d, *J*= 8.2 Hz, 2H), 7.46 (d, *J*= 8.2 Hz, 2H), 7.24 (d, *J*= 7.9 Hz, 2H), 5.25 (d, *J*= 4.6 Hz, 1H), 4.62 (d, *J*= 2.1 Hz, 1H), 4.53 (s, 1H), 2.91 (s, 4H), 2.59-2.45 (m, 5H), 2.41 (s, 5H), 2.36-2.25 (m, 2H), 2.06 (dd, *J*= 17.4, 6.4 Hz, 1H), 1.88-1.74 (m, 2H), 1.73 – 0.99 (m, 19H), 1.63 (s, 3H), 0.97 (s, 3H), 0.92 (s, 3H), 0.92 (s, 3H), 0.91 (s, 3H), 0.81 (s, 3H).

Ejemplo B49

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(4-(naftalen-1-ilsulfonil)piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.



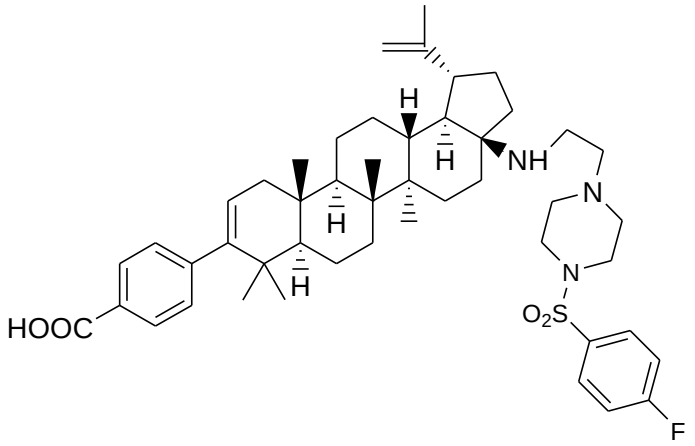
El compuesto del título se preparó para

obtener 3.0 mg de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito anteriormente usando cloruro de naftalen-1-sulfonilo como agente de sulfonilación. LCMS: m/e 832.8 $(M+H)^+$, 4.00 min (método 14). ^{1}H NMR (500MHz, DMSO-d_6) δ 8.75 (d, *J*= 8.5 Hz, 1H), 8.29 (d, *J*= 7.9 Hz, 1H), 8.17 (d, *J*= 7.3 Hz, 1H), 8.10 (d, *J*= 8.2 Hz, 1H), 7.90 (d, *J*= 7.9 Hz, 2H), 7.81-7.62 (m, 3H), 7.28 (d, *J*= 7.9 Hz, 2H), 5.24 (d, *J*= 5.5 Hz, 1H), 4.62 (br. s., 1H), 4.52 (br. s., 1H), 3.08 (br. s., 4H), 2.52 (br. s., 5H), 2.45-2.22 (m, 4H), 2.02 (dd, *J*= 17.7, 6.1 Hz, 1H), 1.91-1.74 (m, 2H), 1.73 – 1.02 (m, 19H), 1.61 (s, 3H), 1.06 (s, 3H), 0.94 (s, 3H), 0.87 (s, 3H), 0.79 (s, 3H), 0.48 (s, 3H).

Ejemplo B50

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-((4-fluorofenil)sulfonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

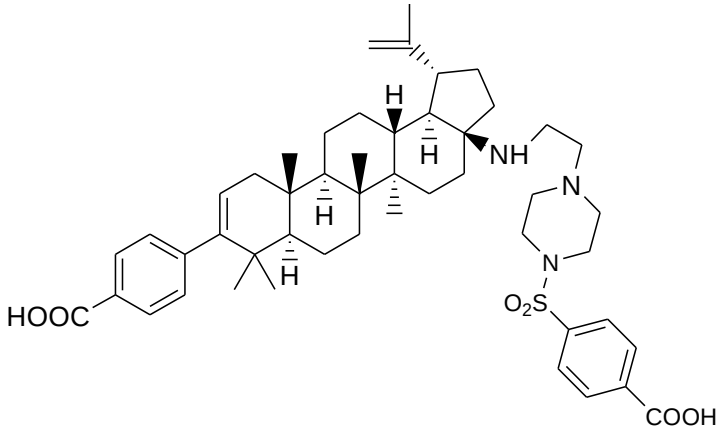
octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



El compuesto del título se preparó para obtener 5.7 mg de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito anteriormente usando cloruro de 4-fluorobencen-1-sulfonilo como agente de sulfonilación. LCMS: m/e 800.8 $(M+H)^+$, 4.95 min (método 15). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.93-7.80 (m, 4H), 7.50 (t, *J*= 8.7 Hz, 2H), 7.24 (d, *J*= 7.9 Hz, 2H), 5.25 (d, *J*= 4.9 Hz, 1H), 4.64 (d, *J*= 2.1 Hz, 1H), 4.53 (s, 1H), 3.05-2.84 (m, 4H), 2.64-2.47 (m, 5H), 2.40 (br. s., 2H), 2.35-2.22 (m, 2H), 2.05 (dd, *J*= 17.2, 6.3 Hz, 1H), 1.90 – 0.97 (m, 21H), 1.63 (s, 3H), 0.99 (s, 3H), 0.93 (s, 3H), 0.91 (s, 3H), 0.87 (s, 3H), 0.67 (s, 3H).

Ejemplo B51

Preparación de ácido 4-((4-(2-(((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-9-(4-carboxifenil)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-3a-il)amino)etil)piperazin-1-il)sulfonil)benzoico

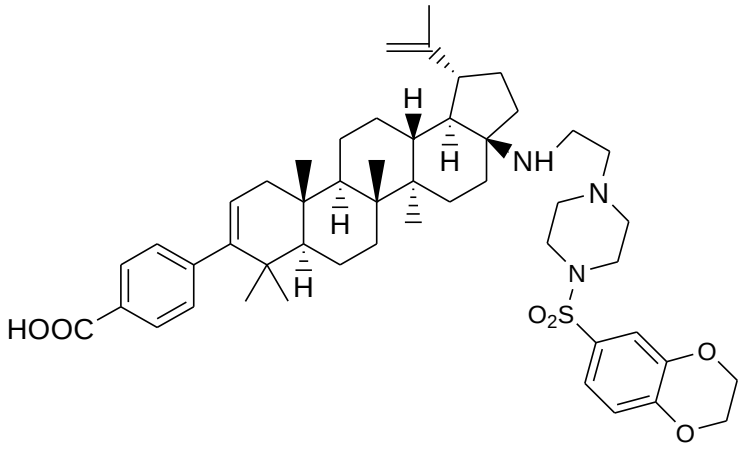


El compuesto del título se preparó para obtener 10.1 mg de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito anteriormente usando ácido 4-(clorosulfonil)benzoico como agente de sulfonilación. LCMS: m/e 826.8 $(M+H)^+$, 2.75 min (método 14). ^1H NMR (500MHz, DMSO-d_6) δ 8.18 (d, *J*= 8.2 Hz, 2H), 7.89 (dd, *J*= 8.4, 3.8 Hz, 4H), 7.25 (d, *J*= 8.2 Hz, 2H),

5.23 (d, *J*= 4.9 Hz, 1H), 4.63 (s, 1H), 4.54 (s, 1H), 3.10-2.93 (m, 4H), 2.68-2.53 (m, 5H), 2.49-2.32 (m, 4H), 2.03 (dd, *J*= 17.2, 6.0 Hz, 1H), 1.90-1.76 (m, 2H), 1.75 – 0.99 (m, 19H), 1.63 (s, 3H), 0.95 (s, 3H), 0.91 (s, 3H), 0.90 (s, 3H), 0.85 (s, 3H), 0.77 (s, 3H).

Ejemplo B52

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-((2,3-dihidrobenzo[b][1.4]dioxin-6-il)sulfonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



El compuesto del título se preparó para obtener 13.2 mg de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo

de acuerdo con el procedimiento general descrito anteriormente usando cloruro de 2,3-dihidro-1,4-benzodioxin-6-sulfonilo como agente de sulfonilación. LCMS: m/e 840.8 $(M+H)^+$, 3.66 min (método 14). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.88 (d, *J*= 8.2 Hz, 2H), 7.31-7.18 (m, 4H), 7.08 (d, *J*= 8.2 Hz, 1H), 5.25 (d, *J*= 4.6 Hz, 1H), 4.64 (d, *J*= 2.1 Hz, 1H), 4.54 (s, 1H), 4.42-4.21 (m, 4H), 2.91 (s, 4H), 2.62-2.51 (m, 5H), 2.41 (br. s., 2H), 2.36-2.26 (m, 2H), 2.06 (dd, *J*= 17.4, 6.4 Hz, 1H), 1.90-1.76 (m, 2H), 1.75 – 0.88 (m, 19H), 1.64 (s, 3H), 0.98 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H), 0.91 (s, 3H), 0.78 (s, 3H).

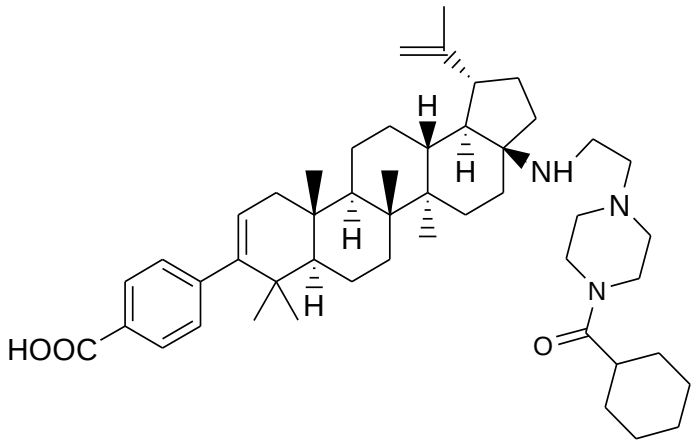
Procedimiento general para la preparación de los ejemplos B53-B64

Una solución del ácido carboxílico sustituido correspondiente (agente de acilación) (0.039 mmol) y HATU (14.78 mg, 0.039 mmol) en DMF (0.5 mL) se agitó durante 10 minutos; luego se introdujo una solución de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo (17 mg, 0.026 mmol) y DIPEA (0.018 mL, 0.104 mmol) en DMF (0.500 mL). La mezcla de reacción se agitó a 350 rpm en un agitador de plataforma Innova a temperatura ambiente durante la noche. El solvente se evaporó para obtener el residuo

seco. Al residuo en dioxano (0.8 mL) se agregó hidróxido de litio monohidrato (8.70 mg, 0.207 mmol) y se disolvió en agua (0.2 mL). La mezcla de reacción se agitó a 80 °C durante la noche. Se retiró el solvente, y se agregó DMF (1.0 mL). La mezcla se filtró, y la solución transparente se purificó mediante HPLC para obtener los productos deseados con un rendimiento que varió de 2-31 % en dos etapas.

Ejemplo B53

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(ciclohexancarbonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

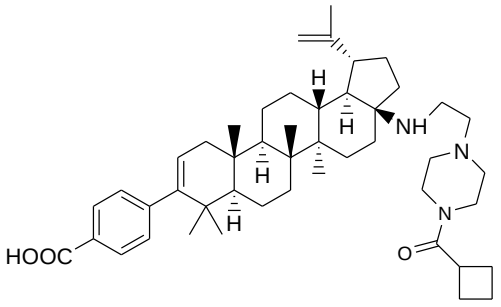


El compuesto del título (4.9 mg) se preparó de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito anteriormente usando ácido ciclohexancarboxílico como agente de acilación. LCMS: m/e 752.8 $(M+H)^+$, 3.90 min (método 14). ^1H NMR (500MHz, DMSO-d_6) δ 7.85 (d, *J*= 8.2 Hz, 2H), 7.19 (d, *J*= 8.2 Hz, 2H), 5.24 (d, *J*= 4.9 Hz, 1H), 4.70 (s, 1H), 4.56 (s, 1H), 3.49 (br. s., 4H), 2.70-2.53 (m, 4H), 2.48-2.31 (m, 5H), 2.31-2.18 (m, 1H), 2.08 (dd, *J*= 17.4, 6.1 Hz, 1H), 1.99-1.79 (m, 3H), 1.78-1.00 (m, 28H), 1.67 (s, 3H), 1.08 (s., 3H), 0.97 (s, 3H), 0.96 (s, 3H), 0.90 (s, 3H), 0.90 (s, 3H).

Ejemplo B54

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(ciclobutancarbonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

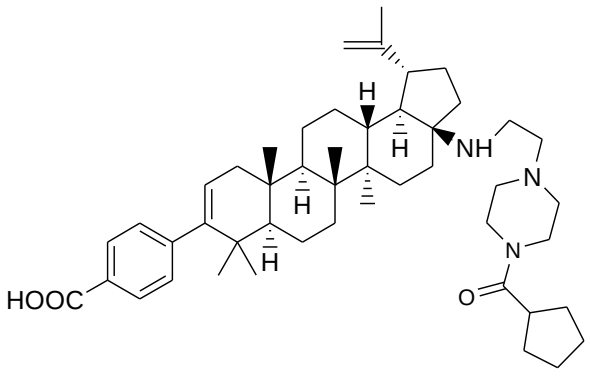


El compuesto del título (3.1 mg) se preparó de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-

il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito anteriormente usando ácido ciclobutancarboxílico como agente de acilación. LCMS: m/e 724,8 $(M+H)^+$, 3.66 min (método 14). ^{1}H NMR (500MHz, METANOL-d_4) δ 7.89 (d, *J*= 8.2 Hz, 2H), 7.17 (d, *J*= 8.2 Hz, 2H), 5.30 (d, *J*= 4.6 Hz, 1H), 4.79 (s, 1H), 4.68 (s, 1H), 3.83-3.54 (m, 2H), 3.53-3.38 (m, 3H), 2.91 (d, *J*= 2.1 Hz, 1H), 2.85-2.71 (m, 2H), 2.62 (d, *J*= 10.1 Hz, 3H), 2.55-2.39 (m, 2H), 2.36-1.18 (m, 29H), 1.75 (s, 3H), 1.22 (s., 3H), 1.11 (s, 3H), 1.05 (s, 3H), 0.97 (s, 3H), 0.96 (s, 3H).

Ejemplo B55

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(ciclopentancarbonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

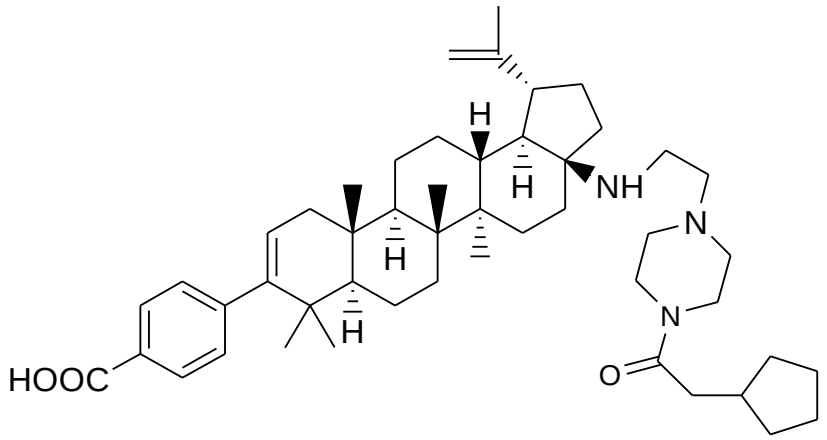


El compuesto del título (3.1 mg) se preparó de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito anteriormente usando ácido ciclopentancarboxílico como agente de acilación. LCMS: m/e 738.8 $(M+H)^+$, 3.84 min (método 14). ^{1}H NMR (500MHz, METANOL-d_4) δ 7.89 (d, *J*= 8.2 Hz, 2H), 7.17 (d, *J*= 8.2 Hz, 2H), 5.30 (d, *J*= 4.6 Hz, 1H), 4.79 (s, 1H), 4.69 (s, 1H), 3.78-3.52 (m, 4H), 3.13-3.01 (m, 2H), 2.97-2.89 (m, 1H), 2.86-2.73 (m, 2H), 2.72-2.61 (m, 3H), 2.60-2.41 (m, 2H), 2.20-1.80 (m, 8H), 1.75 (s, 3H), 1.74-1.18 (m, 22H), 1.23 (s., 3H), 1.11 (s, 3H), 1.06 (s, 3H), 0.97 (s, 3H), 0.97 (s, 3H).

Ejemplo B56

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(2-ciclopentilacetil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b

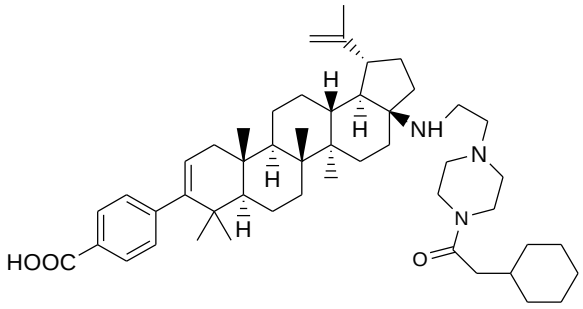
-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



El compuesto del título (3.1 mg) se preparó de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito anteriormente usando ácido ciclopentilacético como agente de acilación. LCMS: m/e 752.9 $(M+H)^+$, 3.93 min (método 14). ^1H NMR (500MHz, METANOL-d_4) δ 7.89 (d, *J*= 8.2 Hz, 2H), 7.17 (d, *J*= 8.2 Hz, 2H), 5.30 (d, *J*= 4.6 Hz, 1H), 4.80 (s, 1H), 4.69 (s, 1H), 3.70 (br. s., 1H), 3.66-3.53 (m, 3H), 3.12-3.01 (m, 1H), 2.95-2.89 (m, 1H), 2.86-2.72 (m, 2H), 2.71-2.61 (m, 3H), 2.60-2.54 (m, 1H), 2.51-2.47 (m, 1H), 2.45 (d, *J*= 7.3 Hz, 2H), 2.27-1.90 (m, 6H), 1.89-1.79 (m, 3H), 1.76 (s, 3H), 1.73-1.18 (m, 22H), 1.23 (s, 3H), 1.11 (s, 3H), 1.06 (s, 3H), 0.97 (s, 3H), 0.97 (s, 3H).

Ejemplo B57

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(2-ciclohexilacetil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

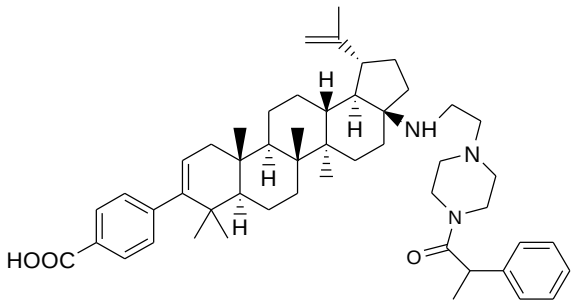


El compuesto del título (3.4 mg) se preparó de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito anteriormente usando ácido ciclopentilacético como agente de acilación. LCMS: m/e 766.9 $(M+H)^+$, 4.09 min (método 14). ^1H NMR (500MHz, METANOL-d_4) δ 7.89 (d, *J*= 8.2 Hz, 2H), 7.17 (d, *J*= 8.2 Hz, 2H), 5.30 (d, *J*= 4.9 Hz, 1H), 4.79 (s, 1H), 4.69 (s, 1H), 3.72 (dd, *J*= 10.5, 6.0 Hz, 1H), 3.67-3.53 (m, 3H), 3.11-3.01 (m, 1H), 2.92 (d, *J*= 10.7 Hz, 1H), 2.87-2.72 (m, 2H), 2.71-2.60 (m, 3H), 2.60-2.53 (m, 1H), 2.51-2.41 (m, 1H),

2.31 (d, *J*= 6.4 Hz, 2H), 2.20-1.90 (m, 5H), 1.84 (td, *J*= 12.1, 3.4 Hz, 1H), 1.75 (s, 3H), 1.75-1.02 (m, 27H), 1.23 (s, 3H), 1.11 (s, 3H), 1.06 (s, 3H), 0.97 (s, 3H), 0.97 (s, 3H).

Ejemplo B58

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(4-(2-fenilpropanoil)piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

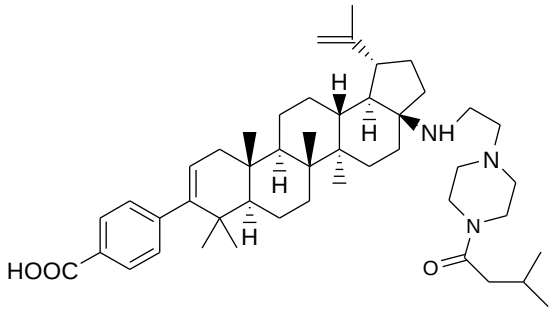


El compuesto del título (4.1 mg) se preparó de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito anteriormente usando ácido 2-fenilpropiónico como agente de acilación. LCMS: m/e 774.9 $(M+H)^+$, 3.87 min (método 14). ^1H NMR (500MHz, METANOL-d_4) δ 7.89 (d, *J*= 7.0 Hz, 2H), 7.41-7.31 (m, 2H), 7.29-7.22 (m, 3H), 7.18 (dd, *J*= 8.2, 3.1 Hz, 2H),

5.30 (d, *J*= 4.9 Hz, 1H), 4.77 (s, 1H), 4.67 (s, 1H), 4.11 (quin, *J*= 6.4 Hz, 1H), 3.89-3.44 (m, 4H), 2.99-2.92 (m, 1H), 2.86-2.67 (m, 3H), 2.67-2.57 (m, 1H), 2.51 (d, *J*= 13.7 Hz, 2H), 2.46-2.27 (m, 2H), 2.21-2.09 (m, 2H), 2.07-1.85 (m, 4H), 1.80-1.15 (m, 16H), 1.74 (s, 3H), 1.40 (d, *J*= 6.7 Hz, 3H), 1.09 (d, *J*= 8.5 Hz, 3H), 1.07 (d, *J*= 13 Hz, 3H), 1.04 (s, 3H), 1.01 (s, 3H), 0.98 (s, 3H).

Ejemplo B59

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(4-(3-metilbutanoil)piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

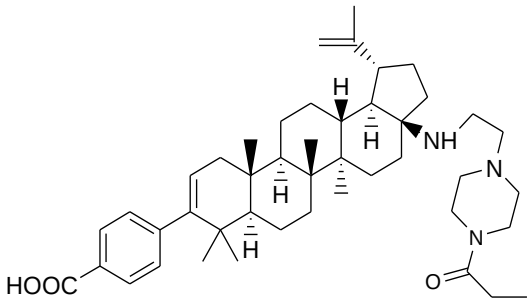


El compuesto del título (3,3 mg) se preparó de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito

anteriormente usando ácido isovalérico como agente de acilación. LCMS: m/e 726.8 $(M+H)^+$, 3.71 min (método 14). ^1H NMR (500MHz, METANOL-d_4) δ 7.89 (d, *J*= 8.2 Hz, 2H), 7.17 (d, *J*= 8.2 Hz, 2H), 5.30 (d, *J*= 4.9 Hz, 1H), 4.79 (s, 1H), 4.69 (s, 1H), 3.77-3.55 (m, 4H), 3.09-3.02 (m, 1H), 2.91 (br. s., 1H), 2.86-2.72 (m, 2H), 2.71-2.60 (m, 3H), 2.59-2.52 (m, 1H), 2.52-2.43 (m, 1H), 2.31 (d, *J*= 7.3 Hz, 2H), 2.21-1.80 (m, 7H), 1.76 (s, 3H), 1.73-1.08 (m, 16H), 1.22 (s, 3H), 1.11 (s, 3H), 1.05 (s, 3H), 0.99 (d, *J*= 6.4 Hz, 6H), 0.97 (s, 3H), 0.97 (s, 3H).

Ejemplo B60

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-3a-((2-(4-propionilpiperazin-1-il)etil)amino)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

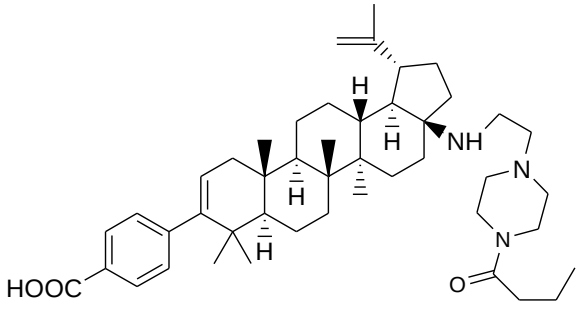


El compuesto del título (5.5 mg) se preparó de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-

il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito anteriormente usando ácido propiónico como agente de acilación. LCMS: m/e 698.8 $(M+H)^+$, 3.39 min (método 14). ^{1}H NMR (500MHz, DMSO-d_6) δ 7.87 (d, *J*= 8.2 Hz, 2H), 7.22 (d, *J*= 7.9 Hz, 2H), 5.25 (d, *J*= 4.9 Hz, 1H), 4.70 (s, 1H), 4.56 (s, 1H), 3.52-3.43 (m, 4H), 3.11 (br. s., 2H), 2.71-2.53 (m, 2H), 2.47-2.20 (m, 7H), 2.08 (dd, *J*= 17.2, 6.3 Hz, 1H), 1.97-1.80 (m, 3H), 1.79-1.03 (m, 18H), 1.67 (s, 3H), 1.08 (s, 3H), 0.99 (t, *J*= 8.0 Hz, 3H), 0.97 (s, 3H), 0.96 (s, 3H), 0.90 (s, 3H), 0.90 (s, 3H).

Ejemplo B61

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-butirilpiperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico.

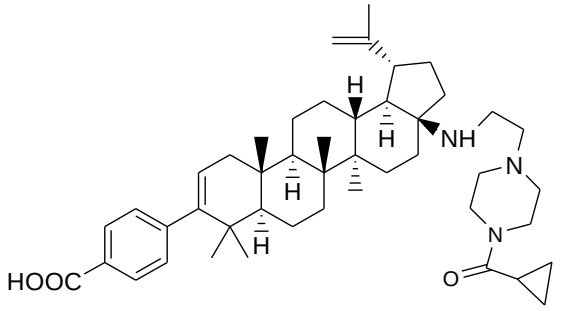


El compuesto del título (1.2 mg) se preparó de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-

pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito anteriormente usando ácido butírico como agente de acilación. LCMS: m/e 712.8 $(M+H)^+$, 4.97 min (método 15). ^{1}H NMR (500MHz, METANOL-d_4) δ 7.89 (d, *J*= 8.2 Hz, 2H), 7.16 (d, *J*= 8.2 Hz, 2H), 5.30 (d, *J*= 4.6 Hz, 1H), 4.78 (s, 1H), 4.68 (s, 1H), 3.79-3.55 (m, 4H), 3.12-2.98 (m, 1H), 2.97-2.82 (m, 2H), 2.78 (td, *J*= 10.9, 5.0 Hz, 1H), 2.71-2.61 (m, 3H), 2.60-2.54 (m, 1H), 2.52-2.44 (m, 1H), 2.40 (t, *J*= 7.5 Hz, 2H), 2.19-1.80 (m, 6H), 1.75 (s, 3H), 1.73-1.04 (m, 18H), 1.23 (s, 3H), 1.11 (s, 3H), 1.05 (s, 3H), 0.99 (t, *J*= 7.5 Hz, 3H), 0.97 (s, 3H), 0.97 (s, 3H).

Ejemplo B62

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-(ciclopropancarbonil)piperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

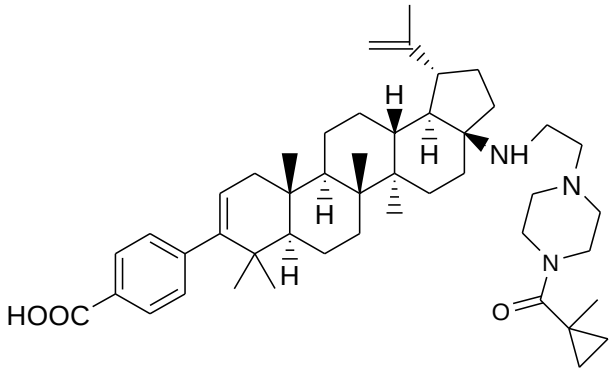


El compuesto del título (0.9 mg) se preparó de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito anteriormente usando ácido ciclopropancarboxílico como agente de acilación. LCMS: m/e 710.8 $(M+H)^+$, 4.41 min (método 15). ^{1}H NMR (500MHz, METANOL-d_4) δ 7.88 (d, *J*= 7.9 Hz, 2H), 7.16 (d, *J*= 7.9 Hz, 2H), 5.30 (d, *J*= 4.9 Hz, 1H), 4.78 (s, 1H), 4.67 (s, 1H), 3.84 (br. s., 2H), 3.77-3.50 (m, 2H), 3.09-2.97 (m, 1H), 2.94-2.81 (m, 2H), 2.77 (td, *J*= 10.5, 5.3 Hz, 1H), 2.73-2.57 (m, 4H), 2.48 (br. s., 1H), 2.21-1.82 (m, 8H), 1.75 (s, 3H), 1.73-1.07 (m, 15H), 1.24 (s, 3H), 1.10 (s, 3H), 1.06 (s, 3H), 0.97 (s, 3H), 0.97 (s, 3H), 0.93-0.87 (m, 2H), 0.87-0.79 (m, 2H).

Ejemplo B63

Preparación de ácido 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(4-(1-metilciclopropancarbonil)piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-

octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico

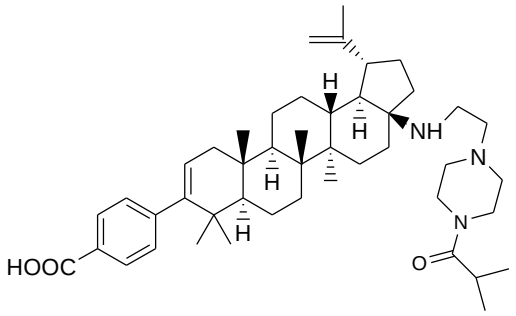


El compuesto del título (0.9 mg) se preparó de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito anteriormente usando ácido 1-metilciclopropan-1-carboxílico como agente de acilación. LCMS: m/e 724,8 $(M+H)^+$, 4.49 min (método 15). ^{1}H NMR (500MHz, METANOL-d_4) δ 7.89 (d, *J*= 8.2 Hz, 2H), 7.16 (d, *J*= 8.2 Hz, 2H), 5.30 (d, *J*= 4.6 Hz, 1H), 4.78 (s, 1H), 4.67 (s, 1H), 3.90-3.63 (m, 4H), 3.09-2.98 (m, 1H), 2.96-2.82 (m, 2H), 2.81-2.73 (m, 1H), 2.71-2.61 (m, 3H), 2.54 (br. s., 2H), 2.24-2.12 (m, 1H), 2.11-1.82 (m, 5H), 1.75 (s, 3H), 1.72-1.14 (m, 16H), 1.32 (s., 3H), 1.23 (s., 3H), 1.11 (s, 3H), 1.06 (s, 3H), 0.97 (s, 3H), 0.97 (s, 3H), 0.93-0.88 (m, 2H), 0.68-0.58 (m, 2H).

Ejemplo B64

Preparación de ácido 4-

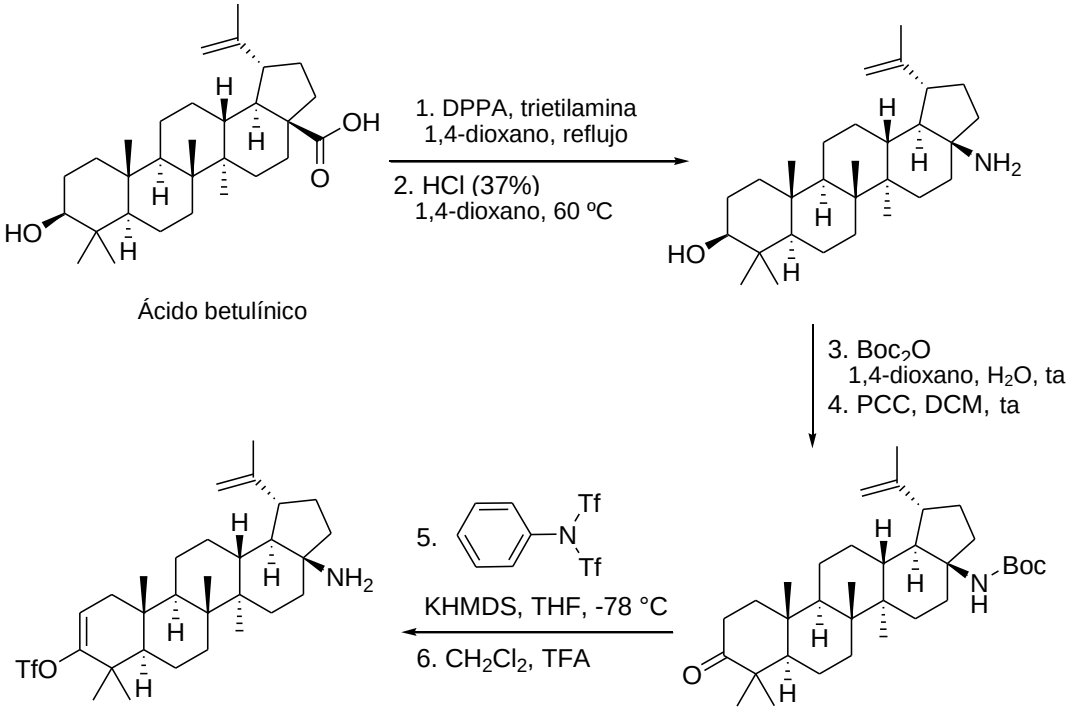
((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-3a-((2-(4-isobutirilpiperazin-1-il)etil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoico



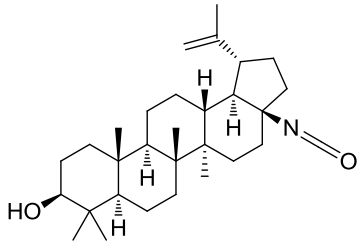
El compuesto del título (0.4 mg) se preparó de 4-((1R,3aS,5aR,5bR,7aR,11aS,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-3a-((2-(piperazin-1-il)etil)amino)-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-il)benzoato de metilo de acuerdo con el procedimiento general descrito anteriormente usando ácido isobutírico como agente de acilación. LCMS: m/e 712.8 $(M+H)^+$, 4.46 min (método 15). ^1H NMR (500MHz, METANOL-d_4) δ 7.88 (d, *J*= 8.2 Hz, 2H), 7.15 (d, *J*= 7.9 Hz, 2H), 5.30 (d, *J*= 4.9 Hz, 1H), 4.78 (s, 1H), 4.67 (s, 1H), 3.77-3.54 (m, 4H), 2.97 (dt, *J*= 13.4, 6.6 Hz, 2H), 2.86-2.71 (m, 3H), 2.70-2.51 (m, 4H), 2.46 (br. s., 1H), 2.15 (dd, *J*= 17.1, 6.4 Hz, 1H), 2.08-1.82 (m, 5H), 1.75 (s, 3H), 1.73-1.18 (m, 16H), 1.22 (s, 3H), 1.11 (d, *J*= 6.7 Hz, 6H), 1.10 (s, 3H), 1.05 (s, 3H), 0.97 (s., 3H), 0.97 (s., 3H),

Ejemplo B65

Preparación de trifluorometansulfonato de (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-ilo



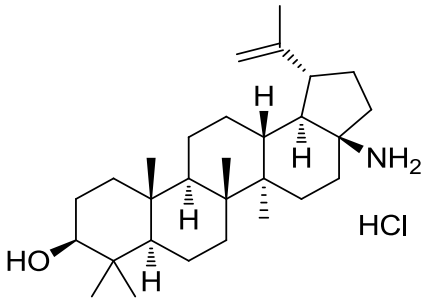
Etapa 1. Preparación de (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-isocianato-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)icosahidro-1H-ciclopenta[a]crisen-9-ol



A una suspensión de ácido betulínico (10 g, 21.90 mmol) en 1,4-dioxano (100 mL) se agregaron trietilamina (9.16 mL, 65.7 mmol) y fosforazidato de difenilo (7.08 mL, 32.8 mmol). La mezcla se calentó a reflujo. Después del calentamiento, se disolvieron todos los sólidos. Después de calentar la mezcla durante 26 h, la mezcla se enfrió a temperatura ambiente y se concentró a presión reducida. El residuo se diluyó con 100 mL de agua y se extrajo con diclorometano (3 x 100 mL). Las capas orgánicas combinadas se secaron con sulfato de sodio. El agente de secado se retiró mediante filtración, y el filtrado se concentró a presión reducida. El residuo se purificó mediante cromatografía instantánea en gel de sílice usando un gradiente de 0-15% de EtOAc en hexanos y una columna de gel de sílice Thomson de 240 g. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida. Un segundo lote de producto menos puro se concentró y se volvió a purificar usando una columna Thomson de 240 g y el mismo gradiente. Las fracciones que contenían el producto previsto se combinaron con el primer lote para obtener (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-isocianato-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)icosahidro-1H-ciclopenta[a]crisen-9-ol (7.76 g, 17.10 mmol, 78 % de rendimiento) como un sólido blanco. ^{1}H NMR (400MHz, *Cloroformo-d*) δ = 4.75 (s, 1H), 4.67-4.62 (m, 1H), 3.20

(dt, *J*= 11.3, 5.6 Hz, 1H), 2.55 (td, *J*= 10.9, 5.9 Hz, 1H), 2.17-2.03 (m, 1H), 1.92-1.76 (m, 5H), 1.69 (s, 3H), 1.06 (s, 3H), 0.98 (s, 3H), 0.95 (s, 3H), 0.85 (s, 3H), 0.78 (s, 3H), 1.74-0.66 (m, 19H).

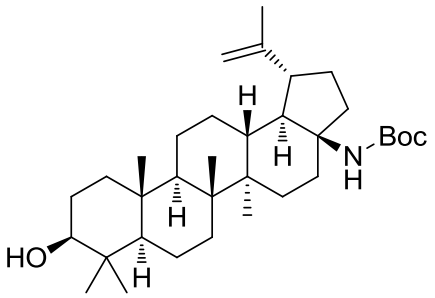
Etapa 2. Preparación de (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)icosahidro-1H-ciclopenta[a]crisen-9-ol, HCl



A una solución de (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-isocianato-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)icosahidro-1H-ciclopenta[a]crisen-9-ol (7.76 g, 17.10 mmol) en 1,4-dioxano (100 mL) se agregó HCl (37 %) (21.07 mL, 257 mmol). La mezcla se calentó a 60 °C durante 15 h, luego se enfrió a temperatura ambiente y se concentró a presión reducida. El residuo se disolvió en diclorometano y metanol, y se concentró dos veces más para obtener (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)icosahidro-1H-ciclopenta[a]crisen-9-ol, HCl (7.75 g, 16.70 mmol, 98 % de

rendimiento) como una espuma blancuzca. El producto crudo se usó en la siguiente etapa sin purificación.

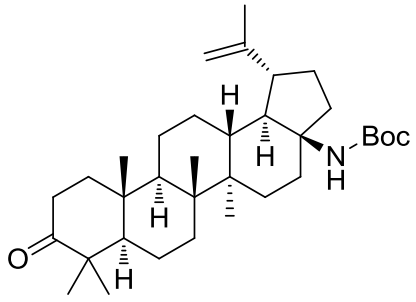
Etapa 3. Preparación de ((1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-9-hidroxi-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)icosahidro-1H-ciclopenta[a]crisen-3a-il)carbamato de terc-butilo



A una solución de (1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)icosahidro-1H-ciclopenta[a]crisen-9-ol, HCl (7.76 g, 16.72 mmol) en 1,4-dioxano (100 mL) se agregaron agua (25 mL), bicarbonato de sodio (4.21 g, 50.2 mmol) y anhídrido de Boc (5.82 mL, 25.08 mmol). La mezcla se agitó a temperatura ambiente durante 16 h, luego se diluyó la mezcla con 100 mL de agua y se extrajo con acetato de etilo (3 x 100 mL). Las capas orgánicas combinadas se lavaron con salmuera, se secaron en sulfato de magnesio, se filtraron y se concentraron a presión reducida para obtener ((1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-9-hidroxi-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)icosahidro-1H-ciclopenta[a]crisen-3a-il)carbamato de terc-

butilo como una espuma blancuzca. ^{1}H NMR (500MHz, *Cloroformo-d*) δ = 4.74 (d, *J*= 1.6 Hz, 1H), 4.64-4.62 (m, 1H), 4.34 (br. s., 1H), 3.24-3.18 (m, 1H), 2.63-2.35 (m, 3H), 2.06-1.93 (m, 1H), 1.71 (s, 3H), 1.46 (s, 9H), 1.04 (s, 3H), 0.99 (s, 3H), 0.98 (s, 3H), 0.86 (s, 3H), 0.79 (s, 3H), 1.77-0.68 (m, 22H).

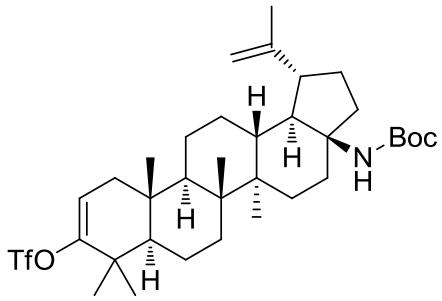
Etapa 4. Preparación de ((1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-9-oxo-1-(prop-1-en-2-il)icosahidro-1H-ciclopenta[a]crisen-3a-il)carbamato de terc-butilo



A una solución de ((1R,3aS,5aR,5bR,7aR,9S,11aR,11bR,13aR,13bR)-9-hidroxi-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)icosahidro-1H-ciclopenta[a]crisen-3a-il)carbamato de terc-butilo resultante en diclorometano (100 mL) se agregó clorocromato de piridinio (4.69 g, 21.74 mmol). La mezcla se agitó a temperatura ambiente durante 5 h, luego se agregó 1.0 g adicional de PCC, y la mezcla se agitó a temperatura ambiente durante 1 h. La mezcla se filtró a través de un tapón de gel de sílice y Celite, que se lavó con una solución de acetato de etilo al

25 % en hexanos. El filtrado se concentró a presión reducida para obtener ((1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-9-oxo-1-(prop-1-en-2-il)icosahidro-1H-ciclopenta[a]crisen-3a-il)carbamato de terc-butilo como una espuma amarilla clara. ^{1}H NMR (500MHz, CLOROFORMO-d) δ = 4.74 (d, *J*= 1.7 Hz, 1H), 4.63 (t, *J*= 1.7 Hz, 1H), 4.34 (br. s., 1H), 2.65-2.34 (m, 5H), 2.05-1.88 (m, 2H), 1.71 (s, 3H), 1.47 (s, 9H), 1.10 (s, 3H), 1.08 (s, 3H), 1.05 (s, 3H), 0.99 (s, 3H), 0.96 (s, 3H), 1.76-0.93 (m, 18H).

Etapa 5. Preparación de trifluorometansulfonato de (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((terbutoxicarbonil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-ilo

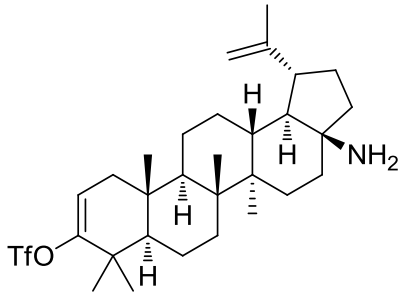


Una solución de ((1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-5a,5b,8,8,11a-pentametil-9-oxo-1-(prop-1-en-2-il)icosahidro-1H-ciclopenta[a]crisen-3a-il)carbamato de terc-butilo resultante en THF (100 mL) se enfrió a -78 °C. A la solución se agregó KHMDS (0.91 M en THF) (40.4 mL, 36.8 mmol). La mezcla se

agitó durante 20 minutos a -78 °C, y luego se agregó una solución de 1,1,1-trifluoro-N-fenil-N-(trifluorometil)sulfonilmetansulfonamida (7.47 g, 20.90 mmol) en THF (100 mL) mediante una cánula. La mezcla se agitó a -78 °C durante 5 h, luego se inactivó con 100 mL de agua y se extrajo con acetato de etilo (3 x 75 mL). Las capas orgánicas combinadas se secaron con sulfato de magnesio. El agente de secado se retiró mediante filtración, y el filtrado se concentró a presión reducida. El residuo se absorbió en una pequeña cantidad de DCM y metanol, y los sólidos amarillos que se habían formado se retiraron mediante filtración. El filtrado se volvió a concentrar y se trató con metanol, y los sólidos que se habían formado se retiraron nuevamente mediante filtración. El filtrado se concentró, se adsorbió en gel de sílice y luego se purificó mediante cromatografía instantánea usando un gradiente de 0-50% de acetato de etilo en hexanos y una columna de gel de sílice Thomson de 240 g. Las fracciones que contenían el producto desprotegido se combinaron y se concentraron a presión reducida para obtener una mezcla de productos. El producto previsto se volvió a purificar mediante cromatografía instantánea usando un gradiente de 0-10% de EtOAc en hexanos y una columna de gel de sílice Thomson de 240 g. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida para obtener trifluorometansulfonato de

(1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((ter-butoxicarbonil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-ilo (1.31g, 1.99 mmol, 11.9 % en 3 etapas). ^{1}H NMR (500MHz, CLOROFORMO-d) δ = 5.57 (dd, *J*= 6.7, 1.8 Hz, 1H), 4.73 (s, 1H), 4.62 (s, 1H), 4.32 (br. s., 1H), 2.64-2.31 (m, 3H), 2.16 (dd, *J*= 17.0, 6.8 Hz, 1H), 2.04-1.94 (m, 1H), 1.70 (s, 3H), 1.45 (s, 9H), 1.13 (s, 3H), 1.06 (s, 3H), 1.03 (s, 3H), 0.97 (s, 3H), 0.93 (s, 3H), 1.82-0.86 (m, 18H).

Etapa 6. Preparación de trifluorometansulfonato de (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-ilo



A una solución de trifluorometansulfonato de (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-((ter-butoxicarbonil)amino)-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-ilo (0.2 g, 0.304

mmol) en diclorometano (2 mL) se agregó ácido trifluoroacético (0.5 mL, 6.49 mmol). La mezcla se agitó a temperatura ambiente durante 1.5 h y luego se concentró a presión reducida. El residuo se diluyó con bicarbonato de sodio acuoso saturado (20 mL) y se extrajo con diclorometano (3 x 20 mL). Las capas orgánicas combinadas se secaron con Na_2SO_4. El agente de secado se retiró mediante filtración, y el filtrado se concentró, se adsorbió en gel de sílice y luego se purificó mediante cromatografía instantánea usando un gradiente de 12-100 % de acetato de etilo en hexanos y una columna de gel de sílice Thomson de 12 g. Las fracciones que contenían el producto previsto se combinaron y se concentraron a presión reducida para obtener trifluorometansulfonato de (1R,3aS,5aR,5bR,7aR,11aR,11bR,13aR,13bR)-3a-amino-5a,5b,8,8,11a-pentametil-1-(prop-1-en-2-il)-2,3,3a,4,5,5a,5b,6,7,7a,8,11,11a,11b,12,13,13a,13b-octadecahidro-1H-ciclopenta[a]crisen-9-ilo (0.109 g, 0.195 mmol, 64.3 % de rendimiento) como un sólido blancuzco. ^{1}H NMR (500MHz, *Cloroformo-d*) δ = 5.57 (dd, *J*= 6.8, 1.9 Hz, 1H), 4.73 (d, *J*= 1.6 Hz, 1H), 4.63-4.60 (m, 1H), 2.54 (td, *J*= 10.9, 5.3 Hz, 1H), 2.17 (dd, *J*= 17.1, 6.9 Hz, 1H), 2.08-1.99 (m, 1H), 1.70 (s, 3H), 1.13 (s, 3H), 1.08 (s, 3H), 1.03 (s, 3H), 0.97 (s, 3H), 0.93 (s, 3H), 1.82-0.91 (m, 20H).

Datos biológicos para los ejemplos

- "µM" significa micromolar;
- "mL" significa mililitro;
- "µl" significa microlitro;
- "mg" significa miligramo;
- "µg" significa microgramo;

Los materiales y procedimientos experimentales que se usan para obtener los resultados informados en las Tablas 1-2 se describen a continuación.

Ensayo de cultivo celular con VIH-se obtuvieron células MT-2 y 293T del NIH AIDS Research and Reference Reagent Program. Las células MT-2 se propagaron en un medio RPMI 1640 enriquecido con 10 % de suero bovino fetal termoinactivado, 100 µg/ml de penicilina G y hasta 100 unidades/ml de estreptomicina. Las células 293T se propagaron en un medio DMEM enriquecido con 10 % de suero bovino fetal termoinactivado (FBS, por sus siglas en inglés), 100 unidades/ml de penicilina G y 100 µg/ml de estreptomicina. El clon de ADN proviral de NL_{4-3} se obtuvo de NIH AIDS Research and Reference Reagent Program. Como virus de referencia se usó un virus NL_{4-3} recombinante, en el cual una sección del gen nef de NL4-3 se reemplazó con el gen luciferasa *Renilla*. Asimismo, el Gag P373 residual se convirtió en P373S. En síntesis, el virus recombinante se preparó mediante transfección del clon proviral alterado de NL_{4-3}. Se

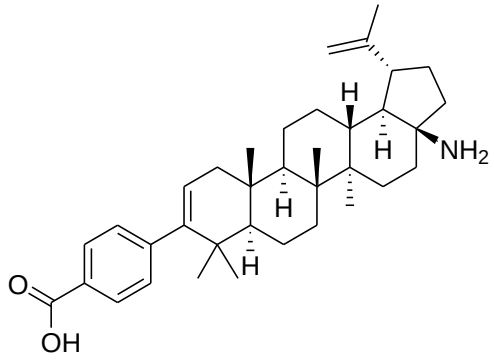
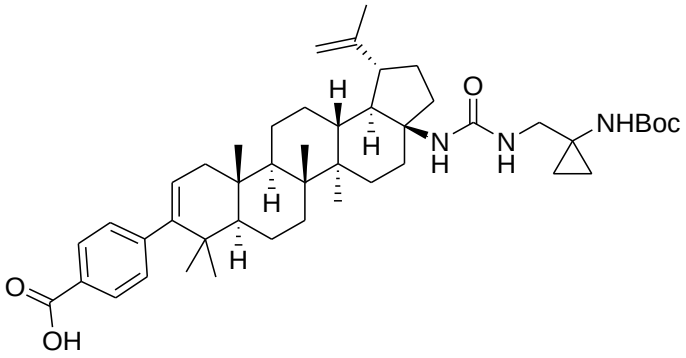
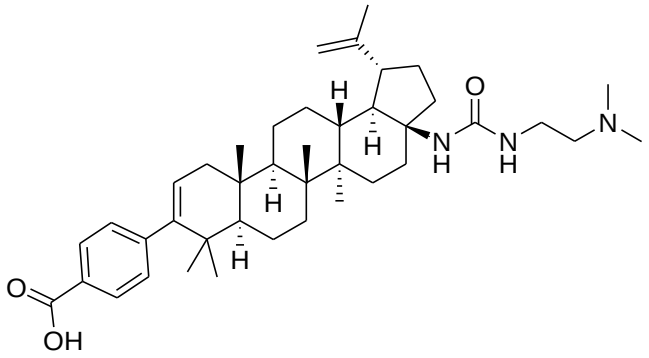
realizaron transfecciones en células 293T con LipofectAMINE PLUS de Invitrogen (Carlsbad, CA), de acuerdo con las instrucciones del fabricante. El virus se tituló en células MT-2 usando la actividad de la enzima luciferasa como marcador. La luciferasa se cuantificó con el kit Dual Luciferase de Promega (Madison, WI), con modificaciones al protocolo del fabricante. La solución de lisis pasiva diluida se mezcló previamente con el reactivo del ensayo de luciferasa resuspendido y el sustrato de Stop & Glo resuspendido (relación 2:1:1). Se agregaron cincuenta (50) µL de la mezcla a cada cavidad aspirada en placas de ensayo, y se midió inmediatamente la actividad de luciferasa en Wallac TriLux (Perkin-Elmer). Las actividades antivirales de los inhibidores con respecto al virus recombinante se cuantificaron midiendo la actividad de luciferasa en las células infectadas durante 4-5 días con recombinantes NLRluc en presencia de diluciones en serie del inhibidor. Los datos EC_{50} de los compuestos se muestran en la Tabla 2. La Tabla 1 es clave para los datos de la Tabla 2.

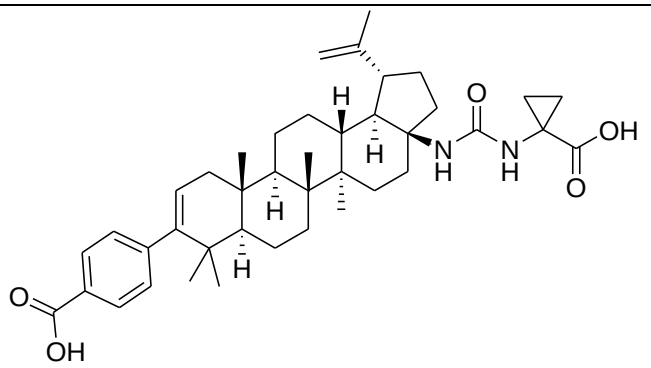
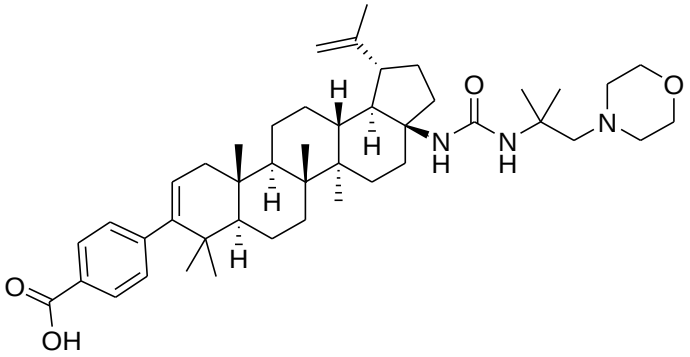
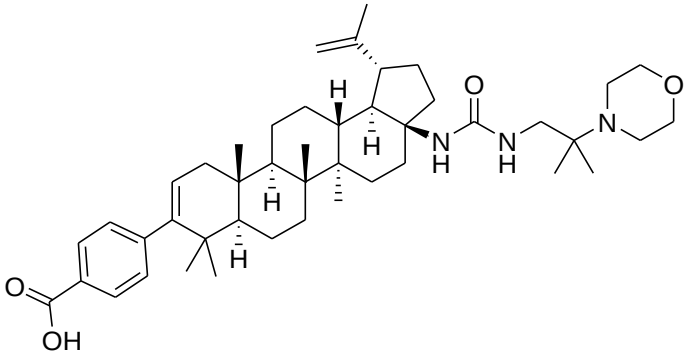
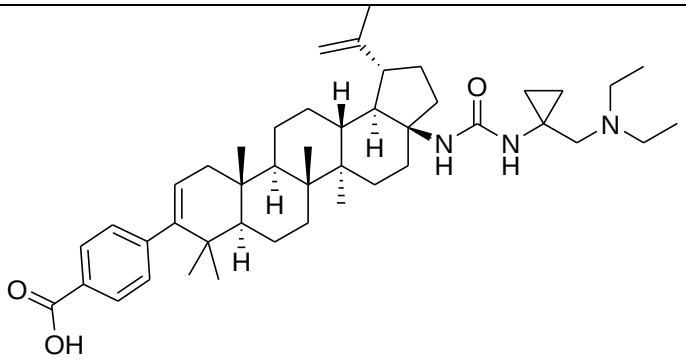
Resultados

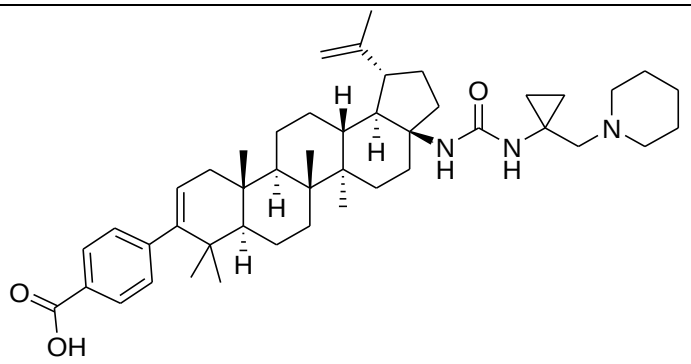
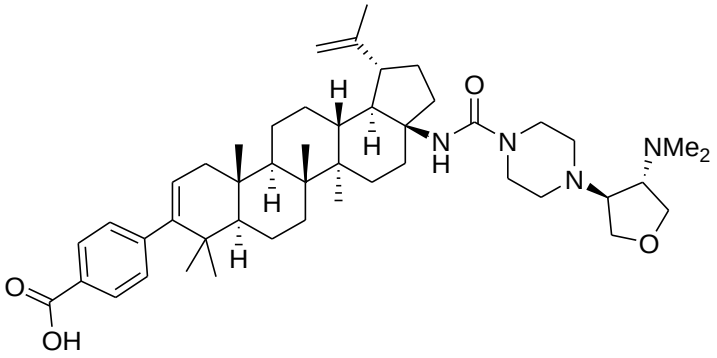
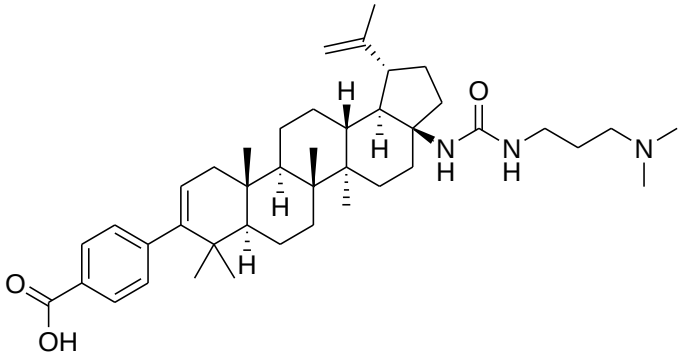
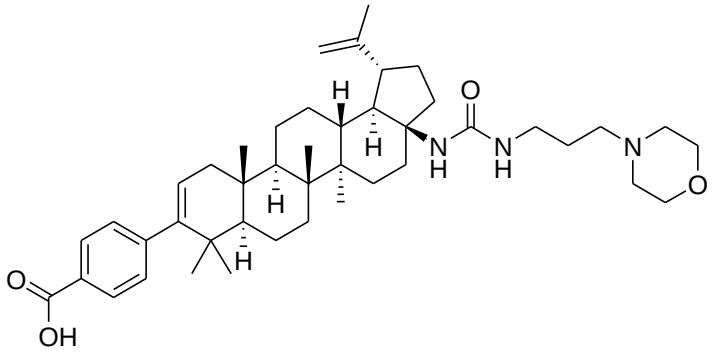
Tabla 1. Datos biológicos clave para EC_{50}

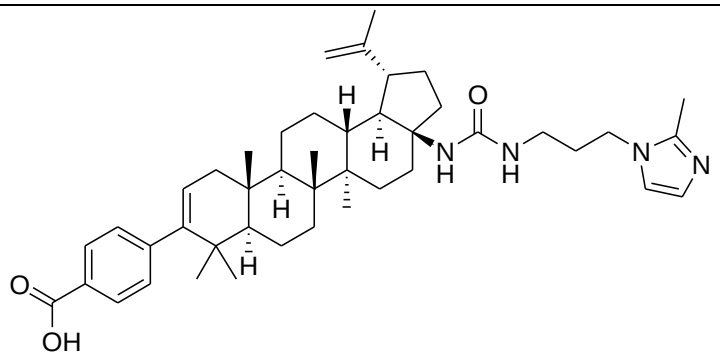
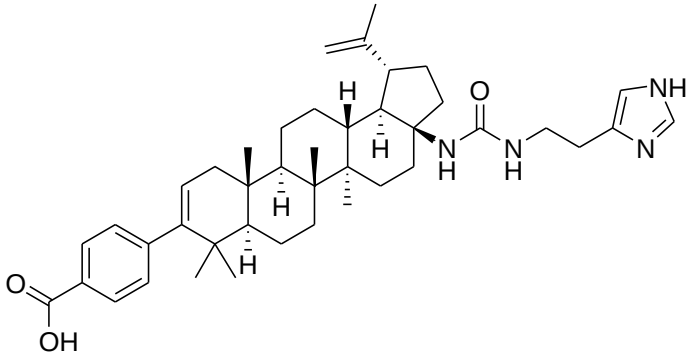
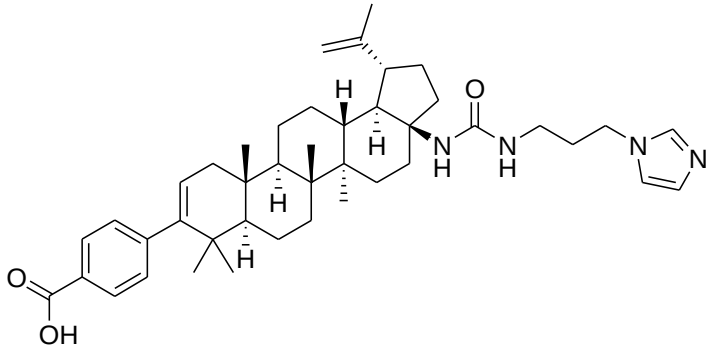
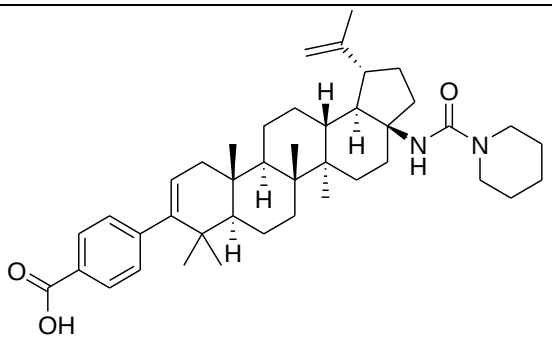
Compuestos con EC_{50} >0.1 µM	Compuestos con EC_{50} < 0.1 µM
Grupo "B"	Grupo "A"

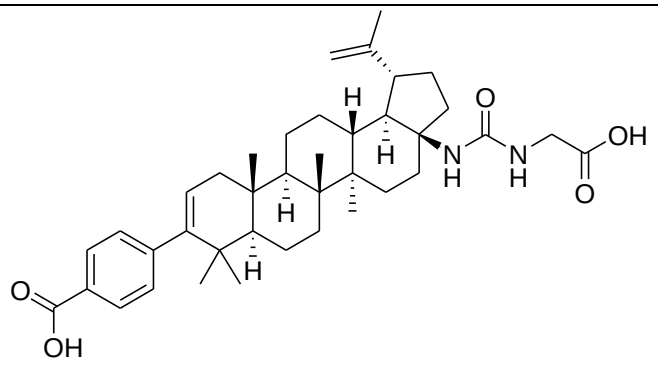
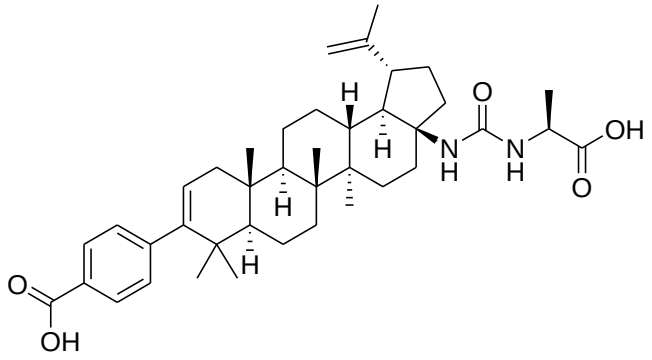
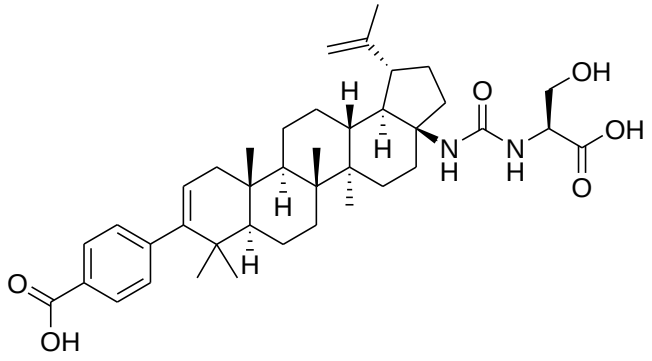
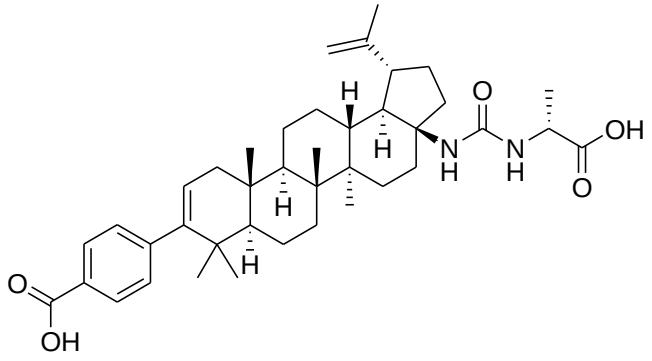
Tabla 2

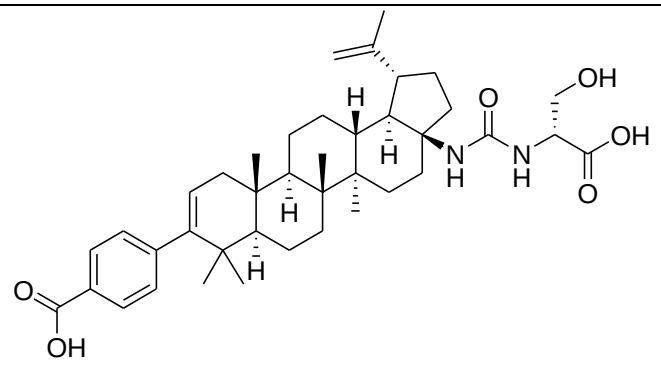
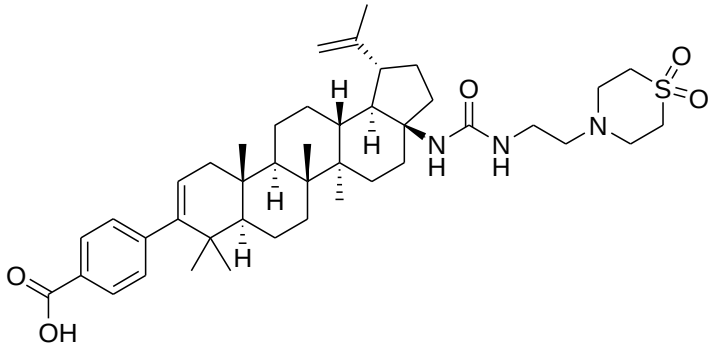
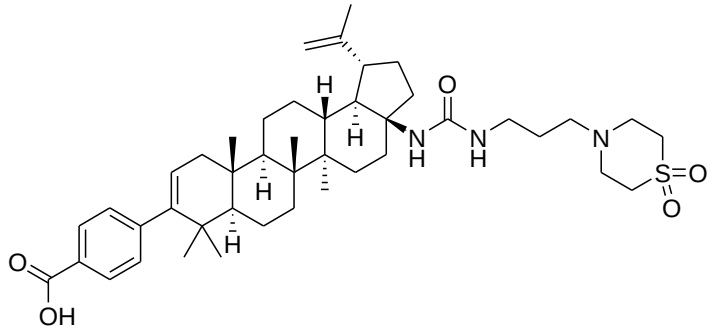
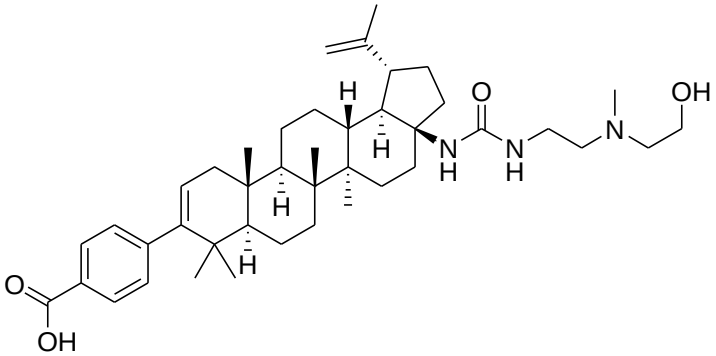
Ejemplo #	Estructura	EC_{50} (µM)
1		A
2		A
3		0.004

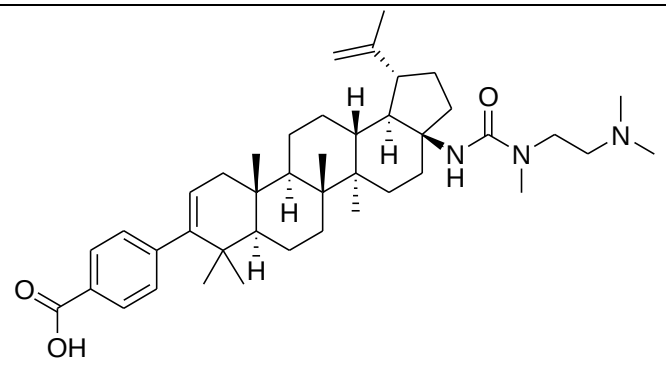
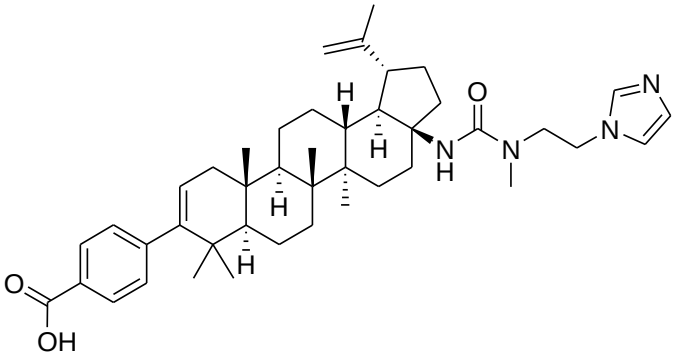
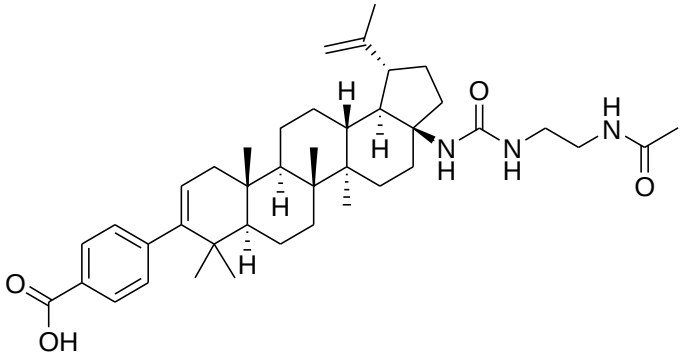
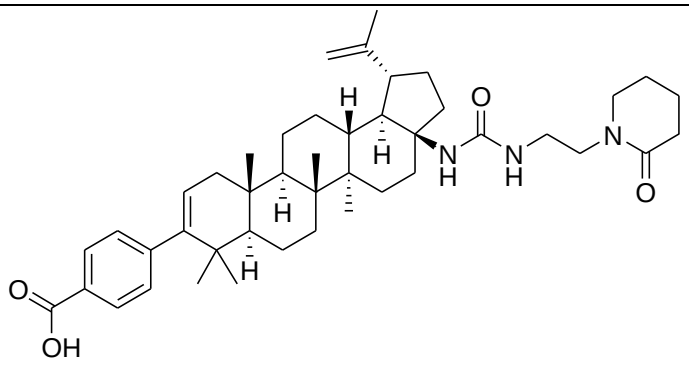
4		B
5		A
6		A
7		A

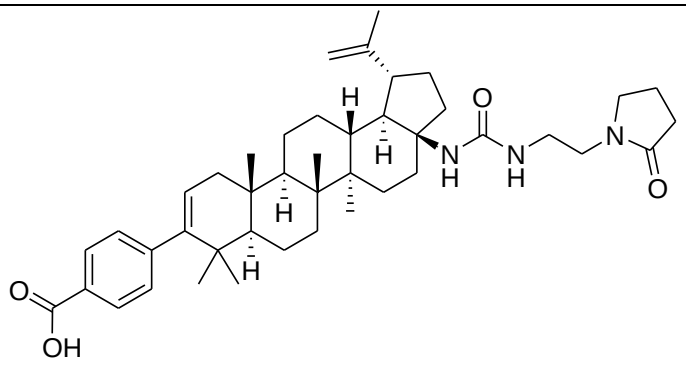
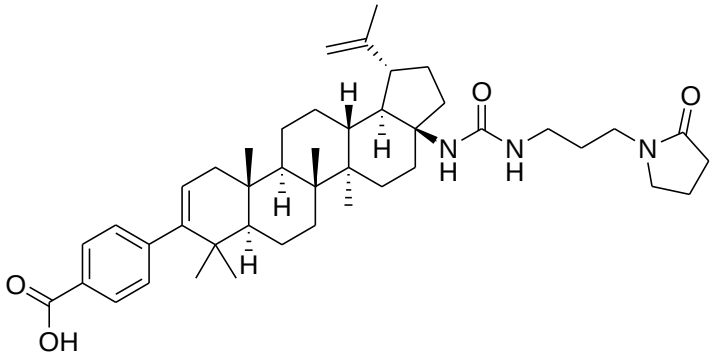
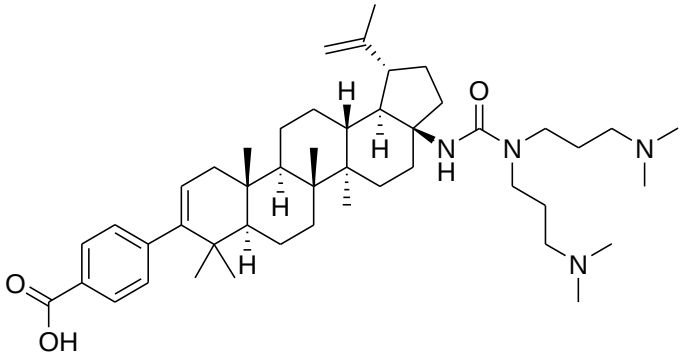
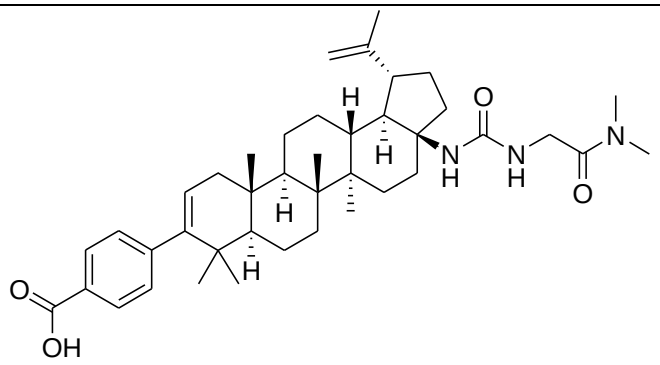
8		A
9		0.003
10		A
11		A

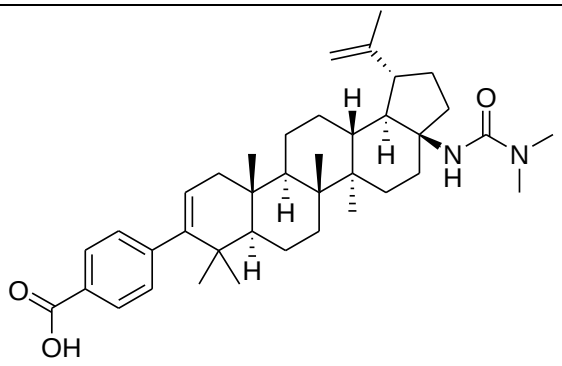
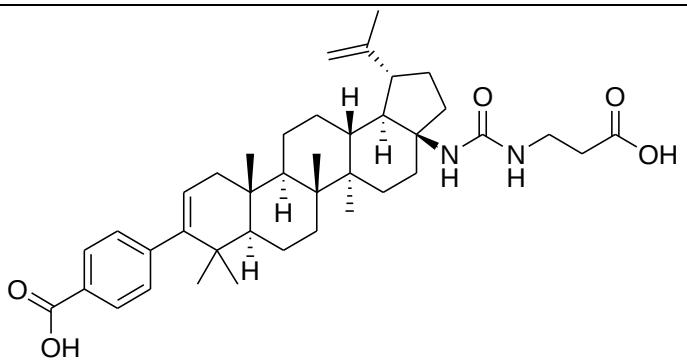
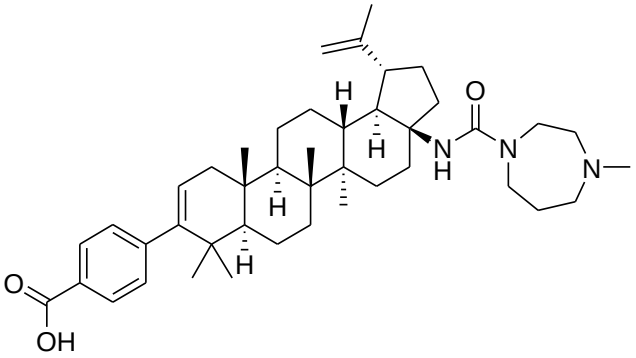
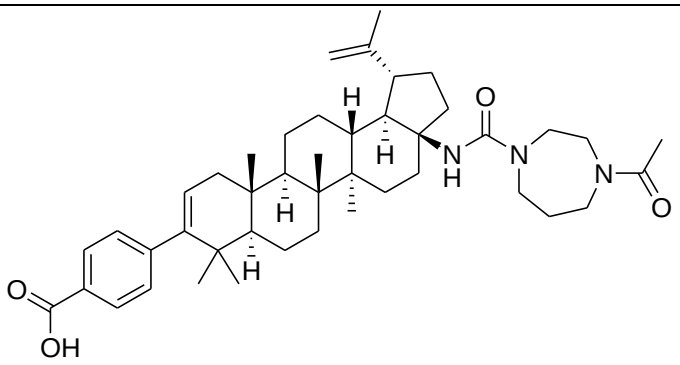
12		A
13		A
14		A
15		A

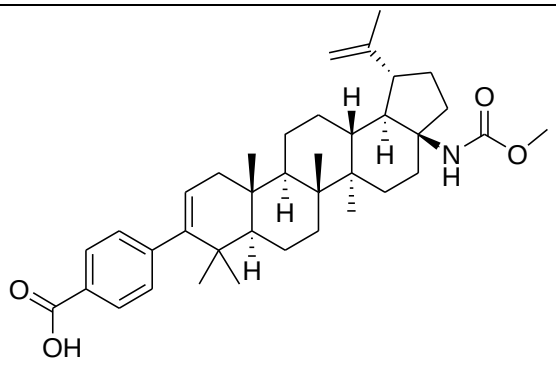
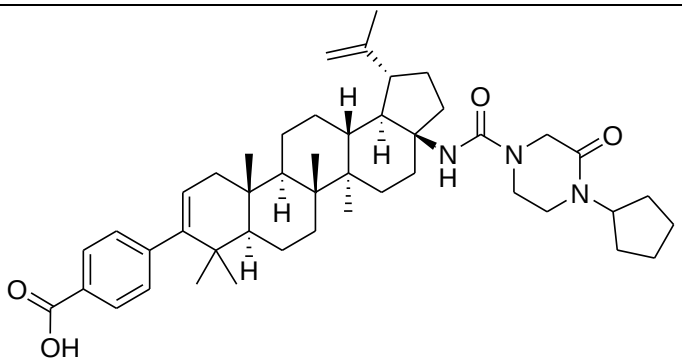
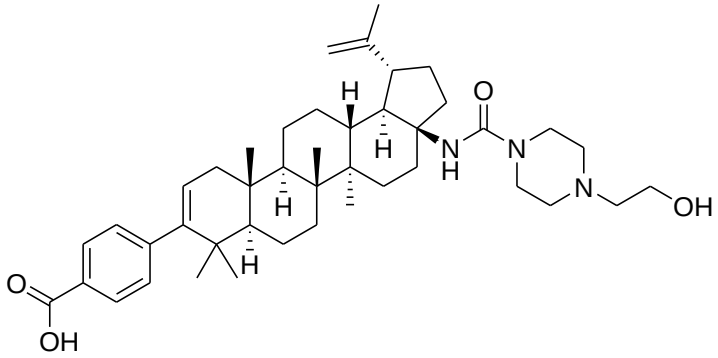
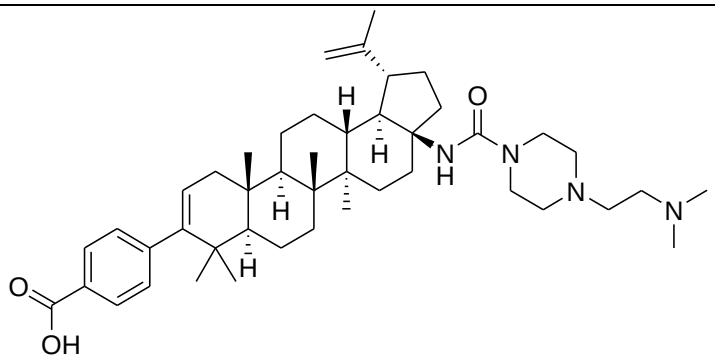
16		A
17		A
18		0.25
19		A

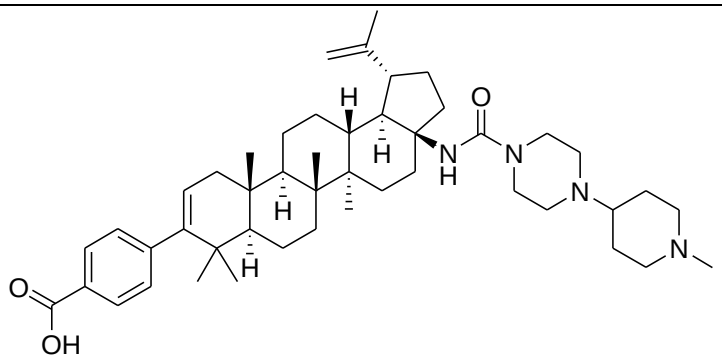
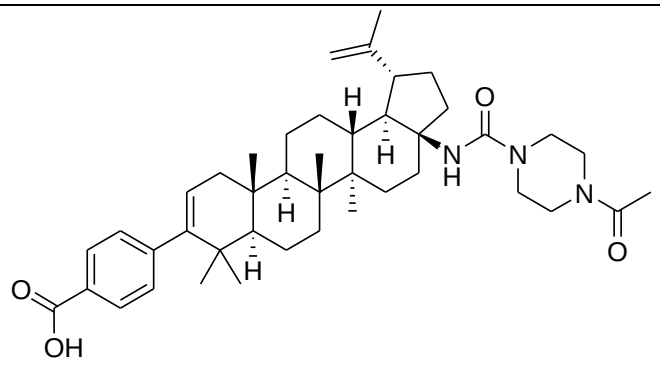
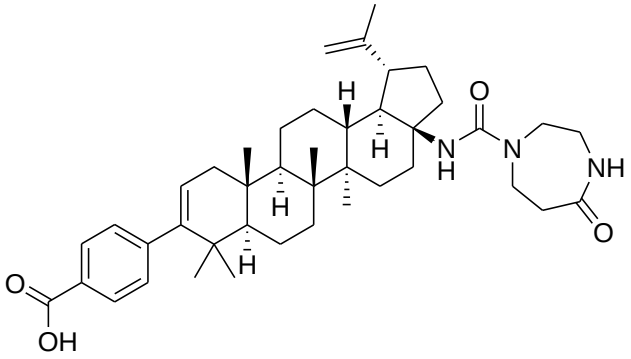
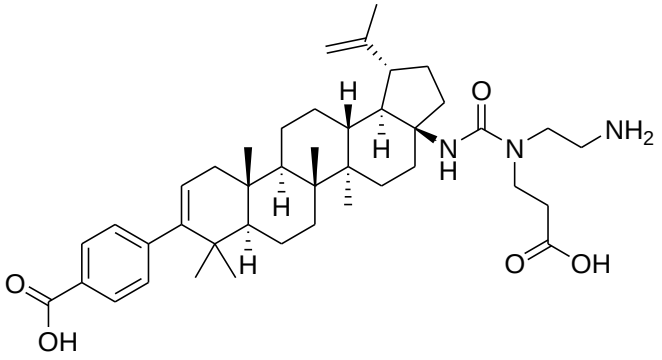
20		0.4
21		A
22		A
23		A

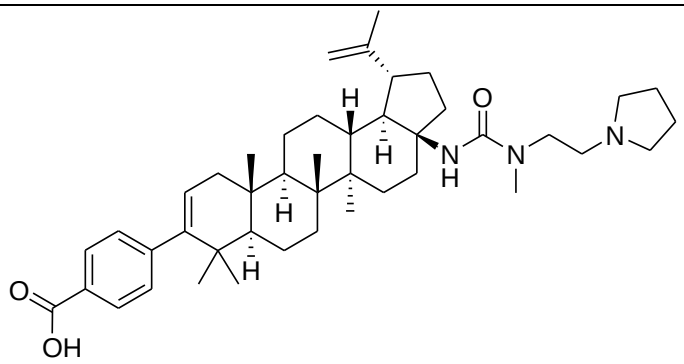
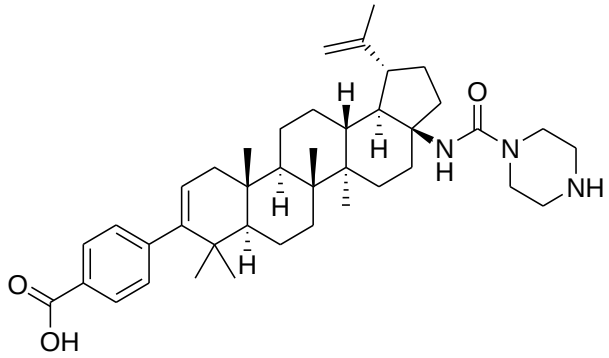
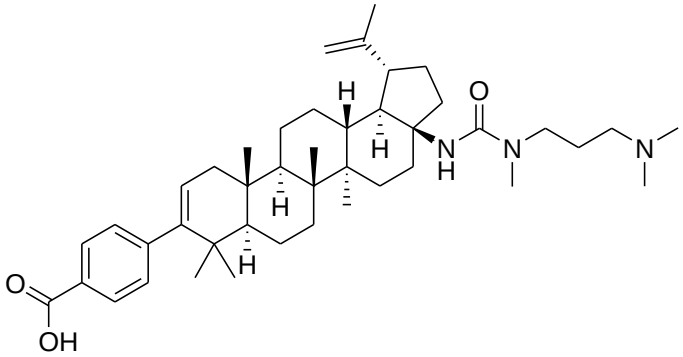
24		A
25		A
26		A
27		A

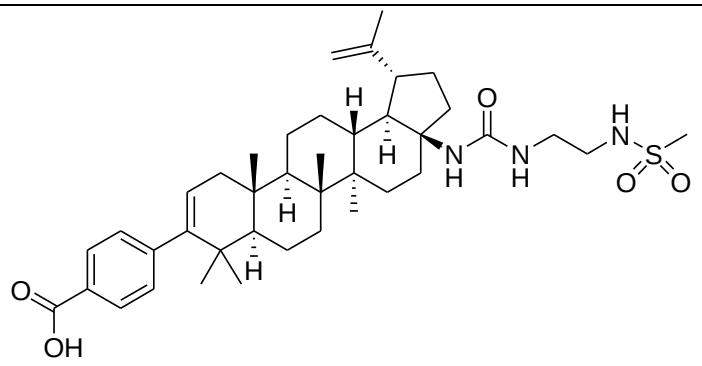
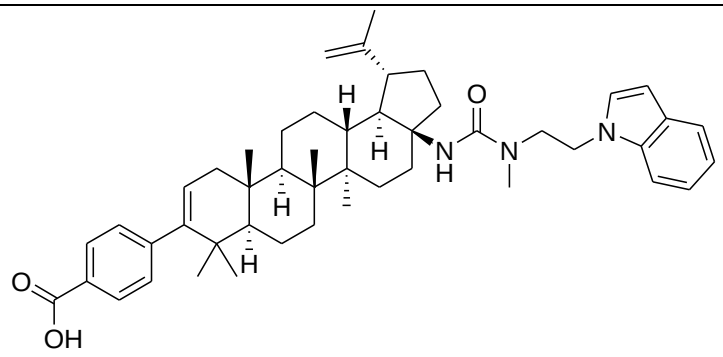
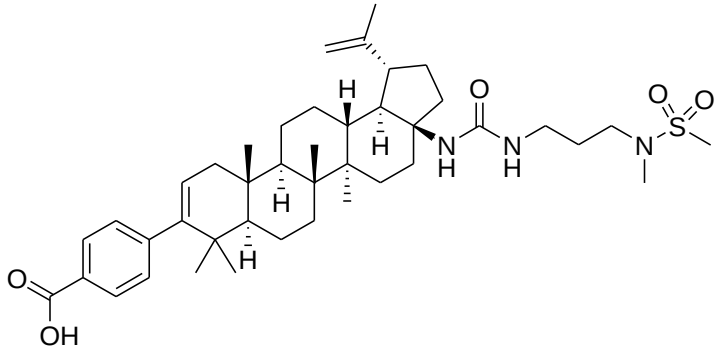
28		0.004
29		0.01
30		A
31		A

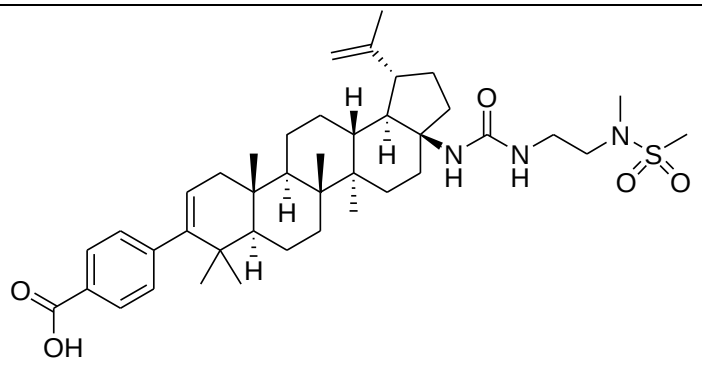
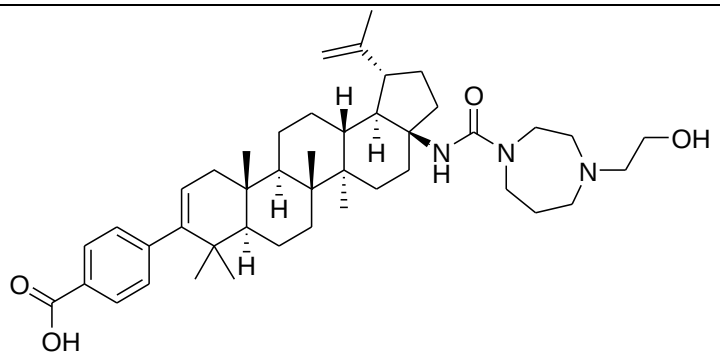
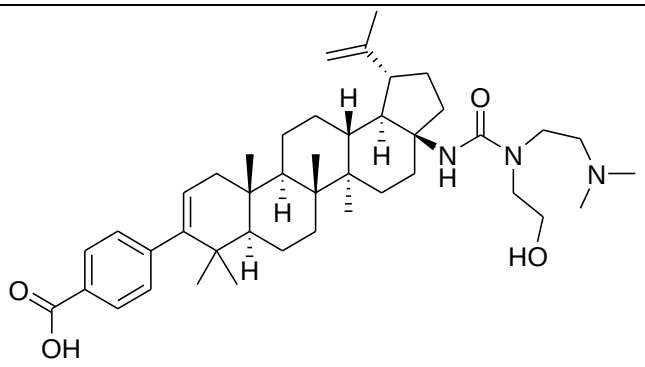
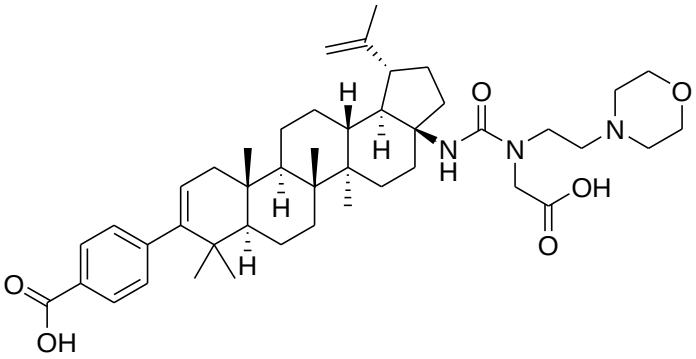
32		0.01
33		A
34		0.002
35		A

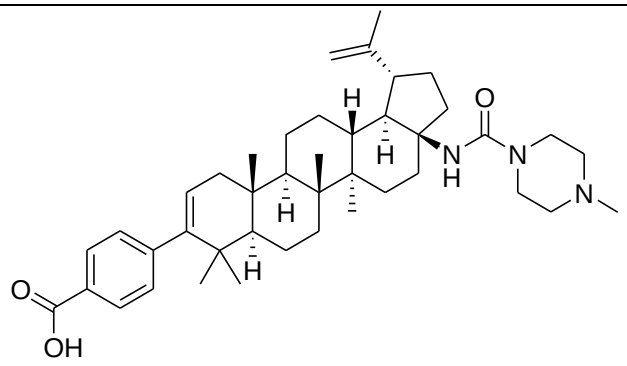
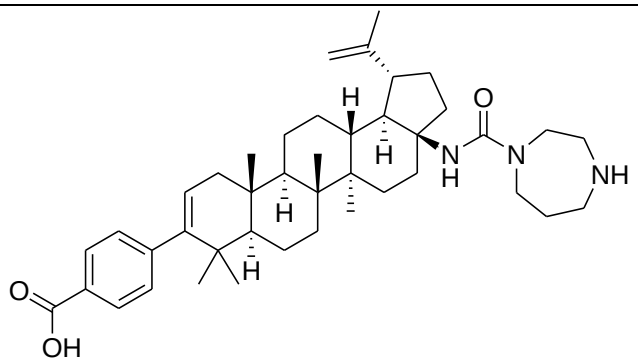
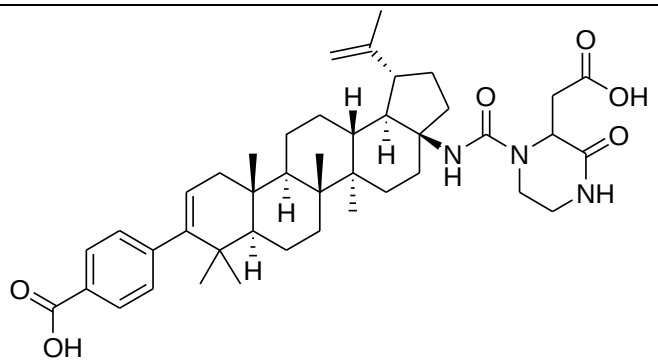
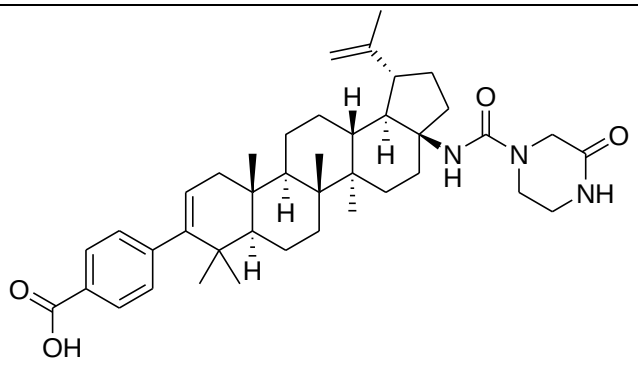
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38		A
39		A

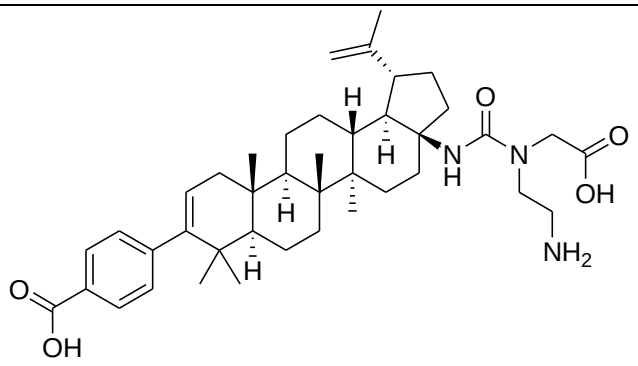
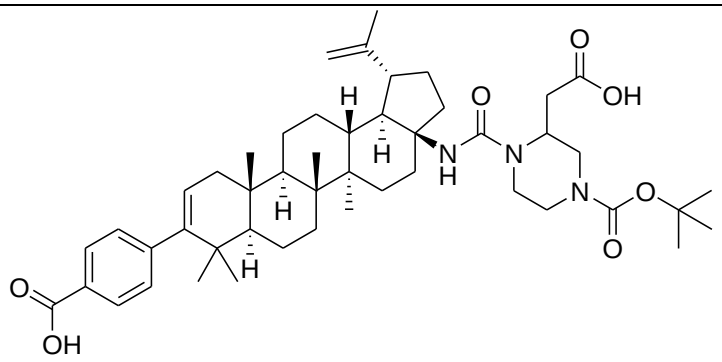
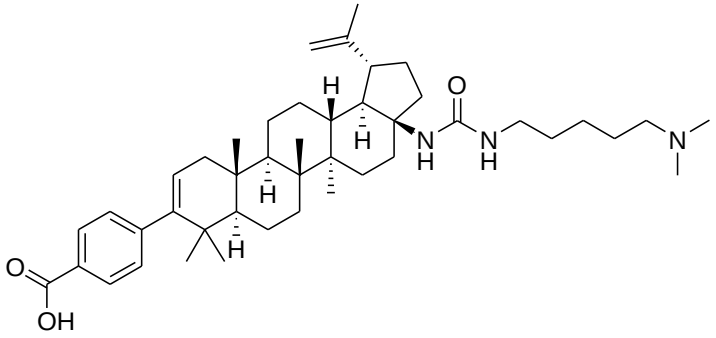
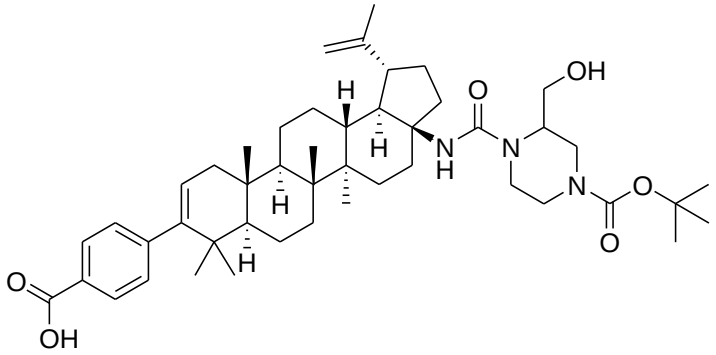
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42		A
43		0.03

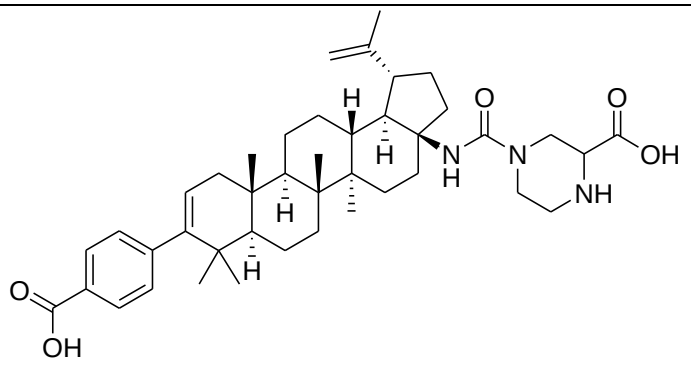
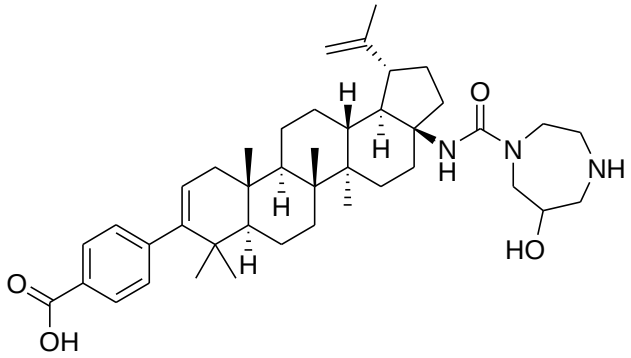
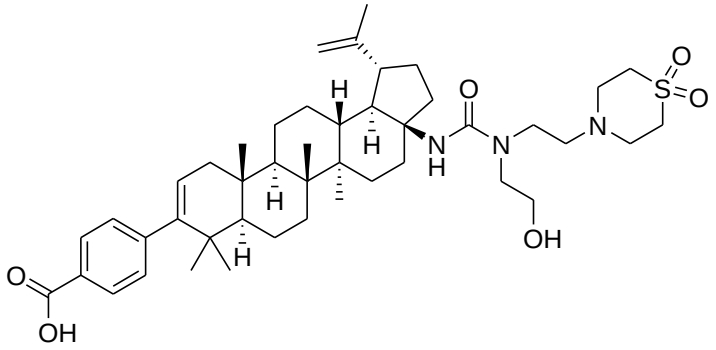
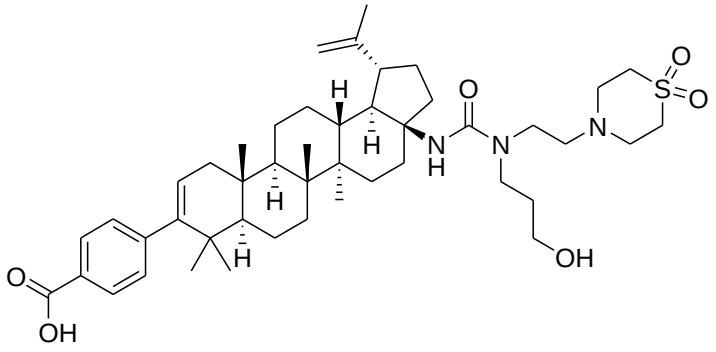
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46		A

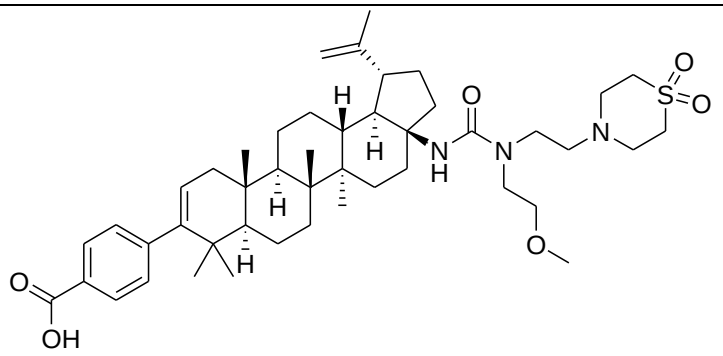
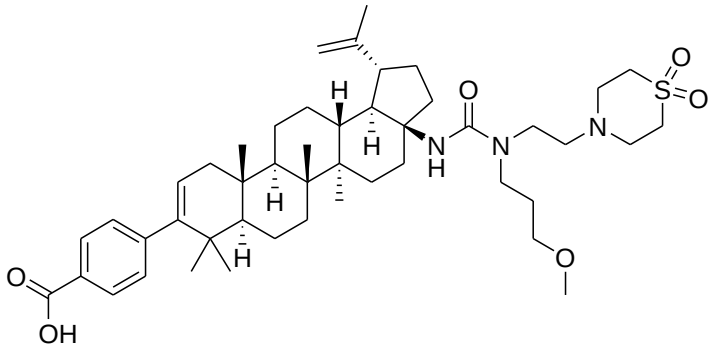
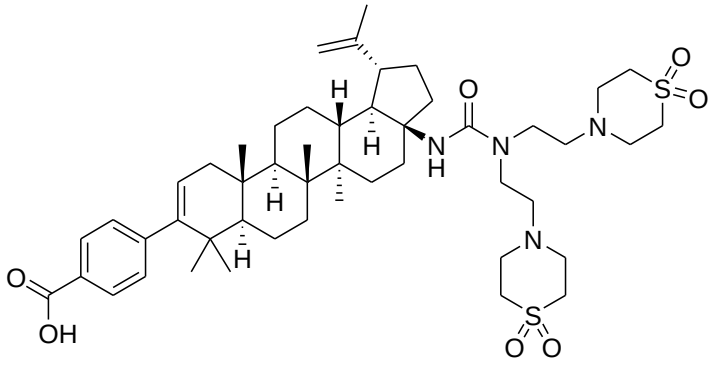
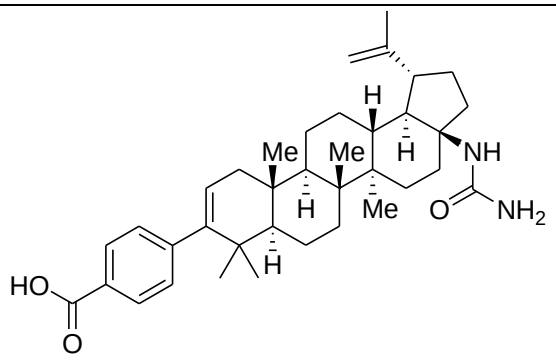
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48		A
49		A

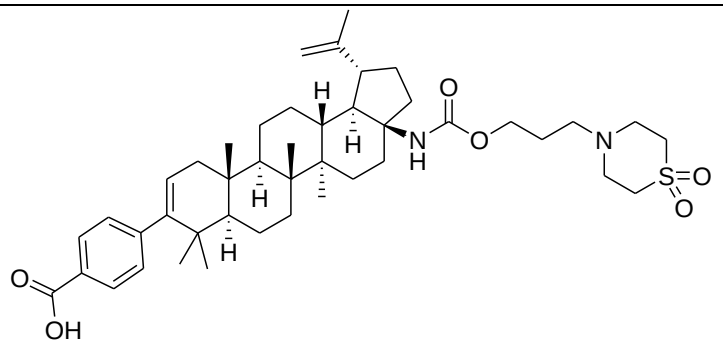
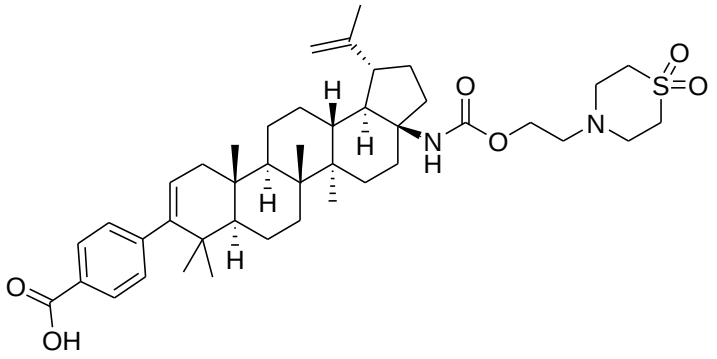
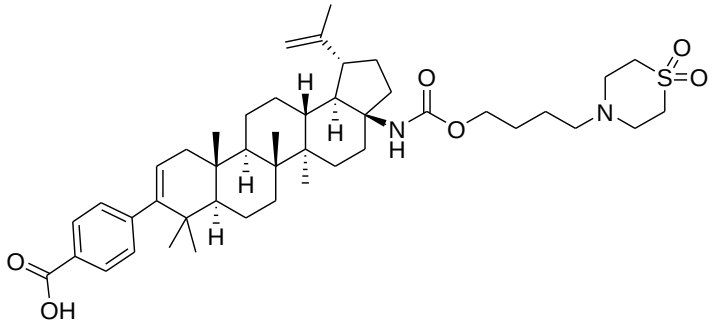
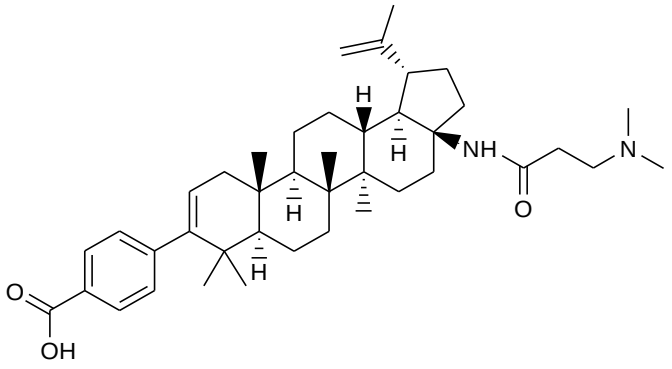
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52		A
53		A

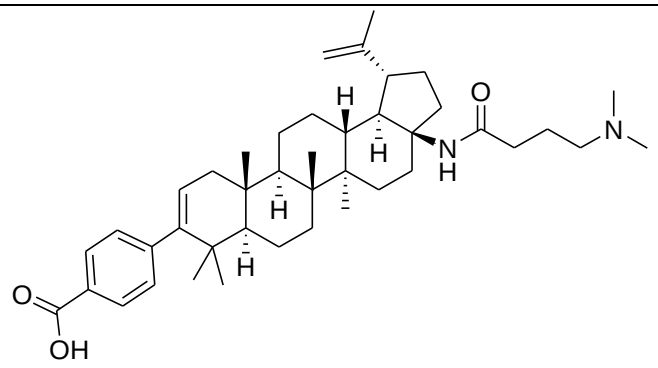
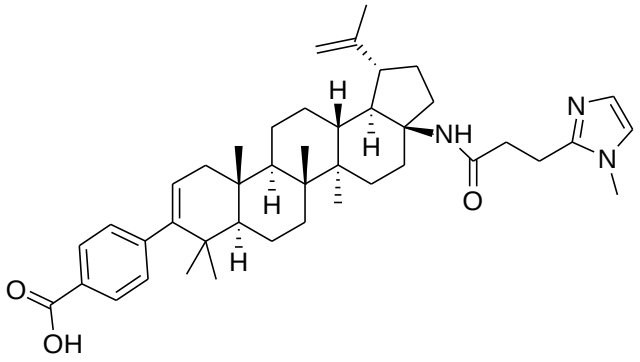
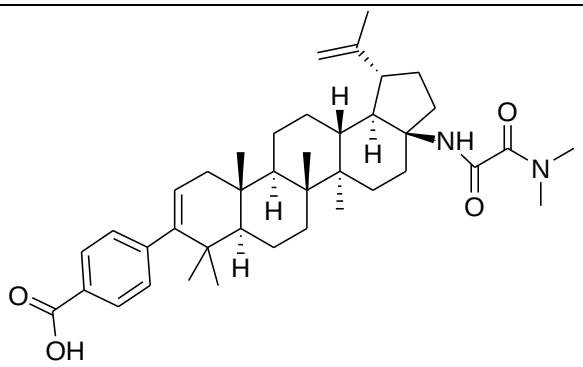
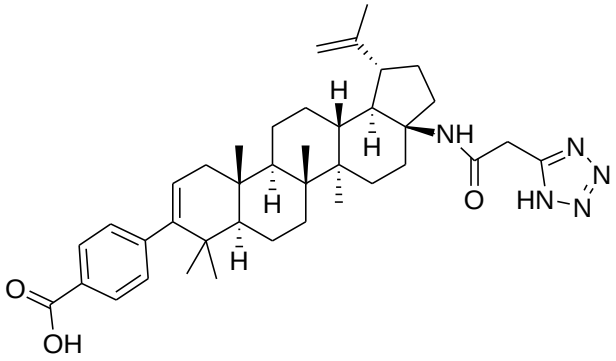
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56		A
57		A

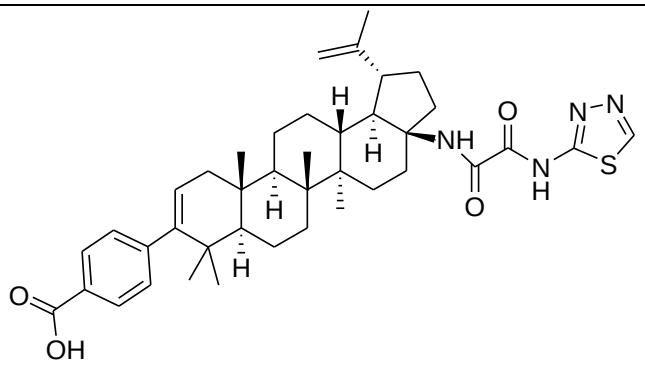
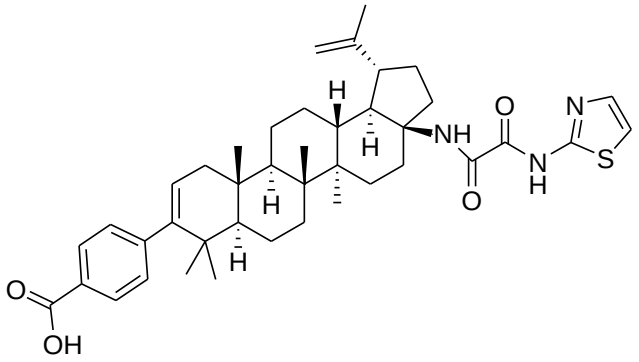
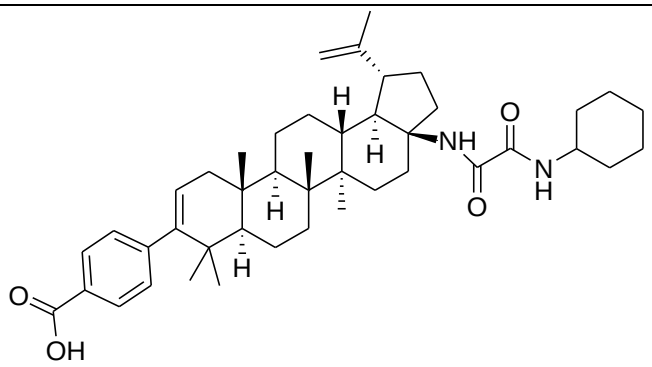
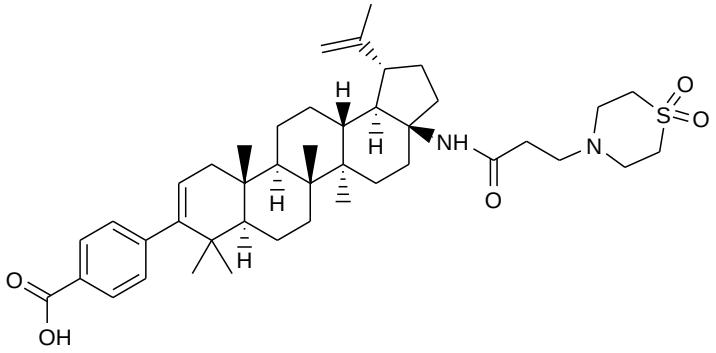
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62		A

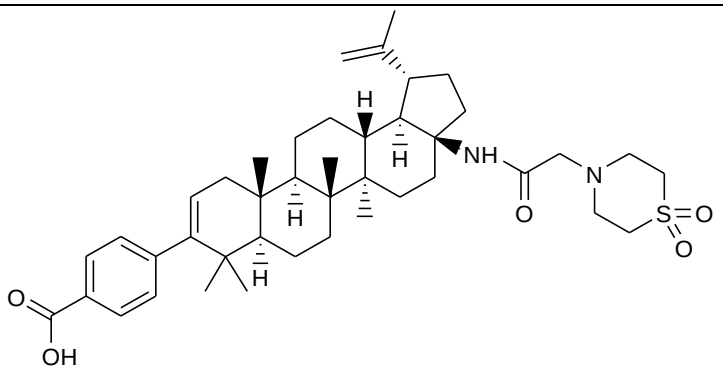
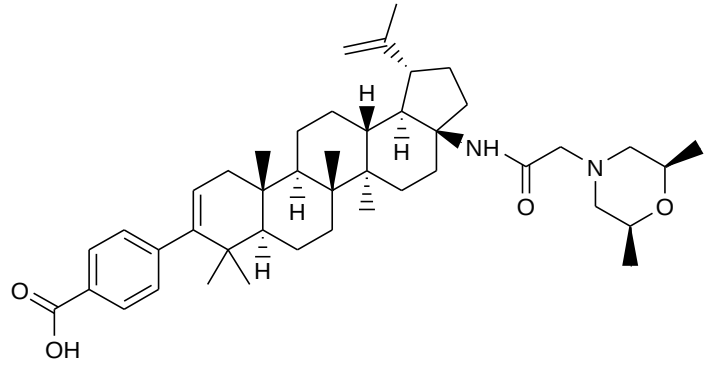
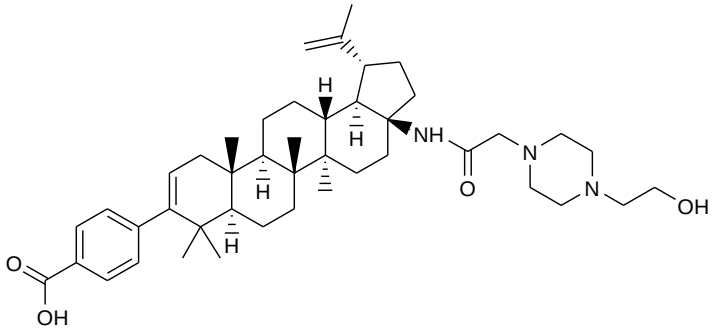
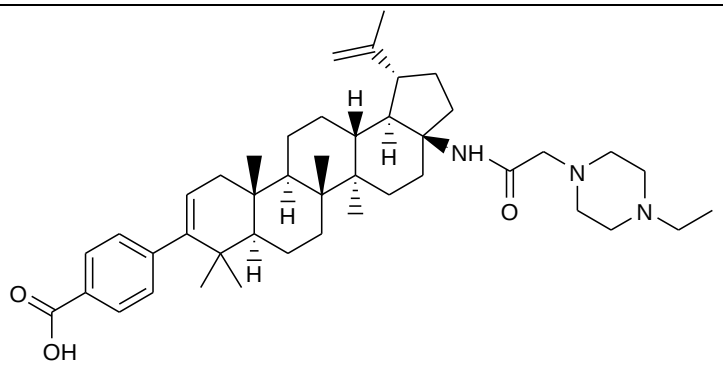
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65		A
66		A

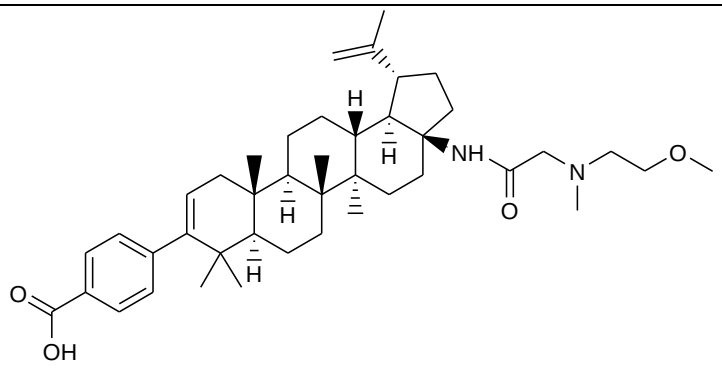
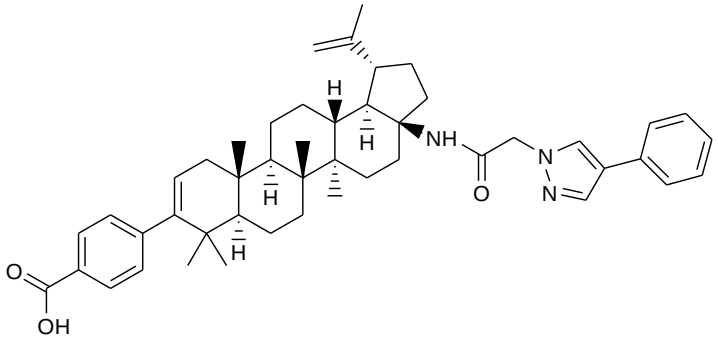
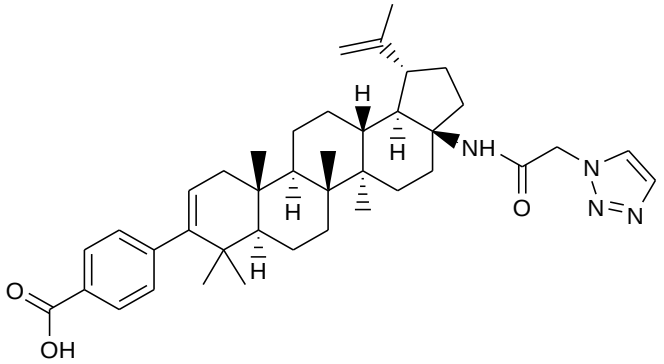
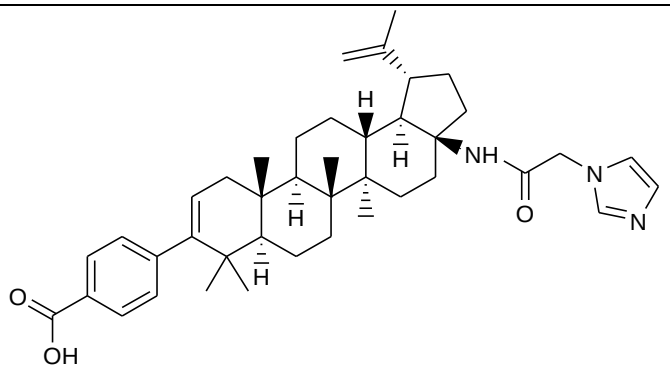
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68		A
69		A
69-1		A

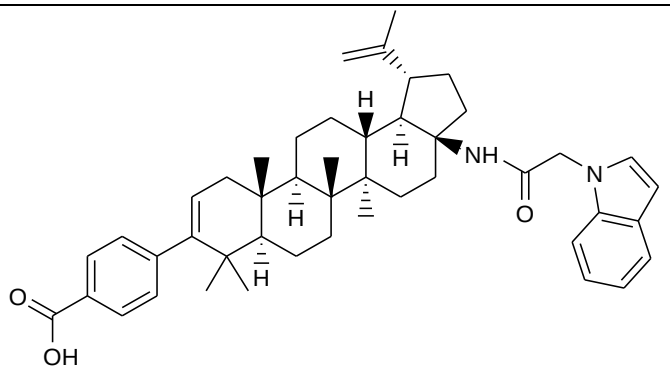
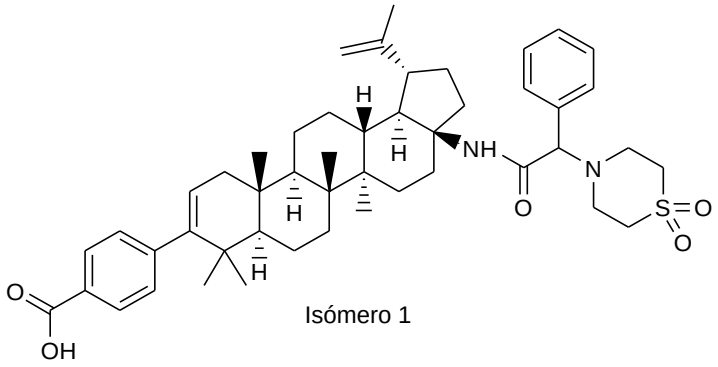
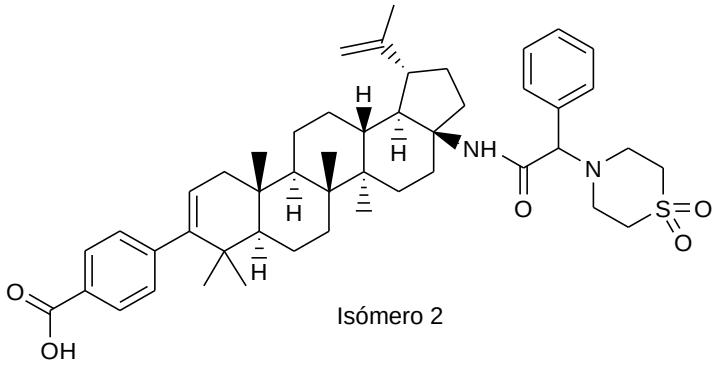
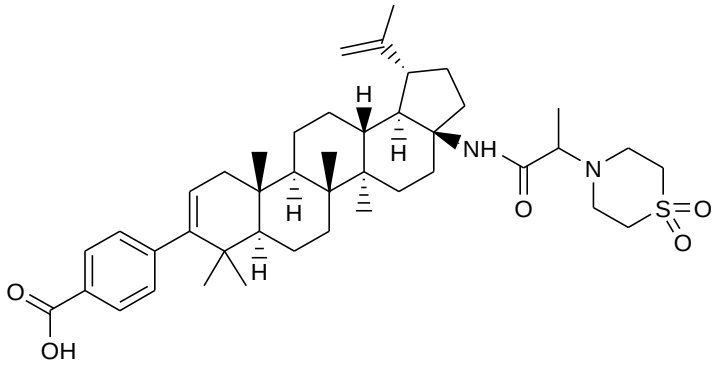
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71		A
72		A
73		A

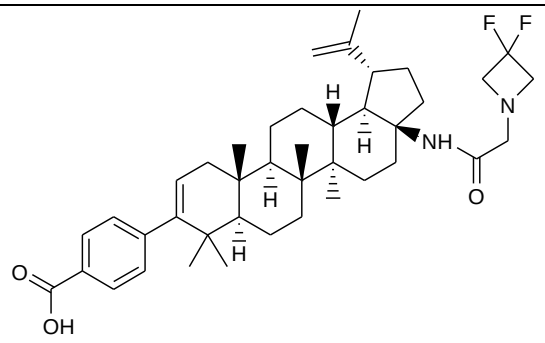
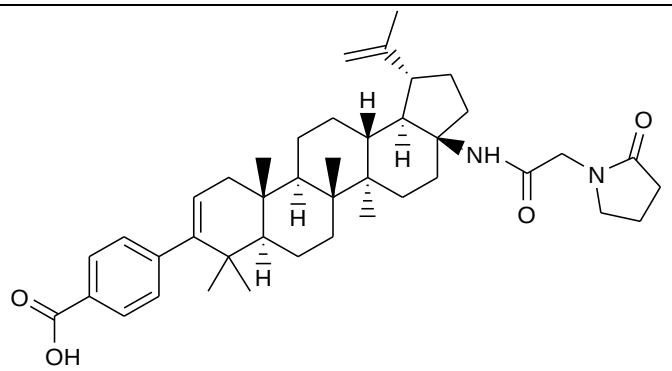
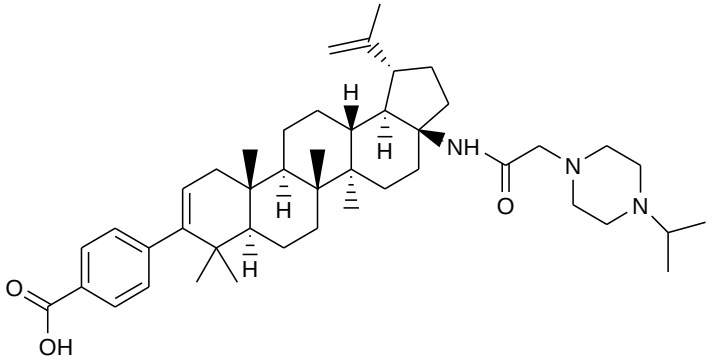
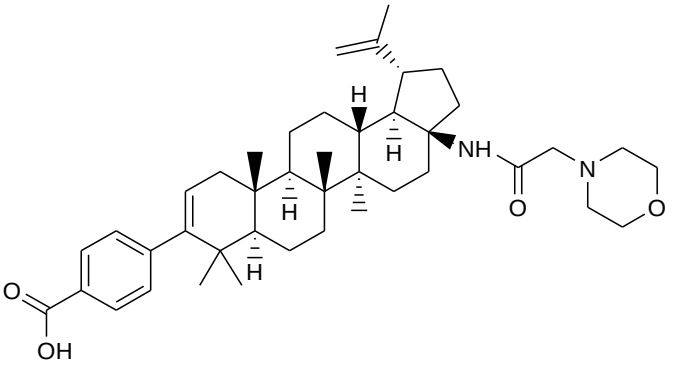
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76		A
77		A

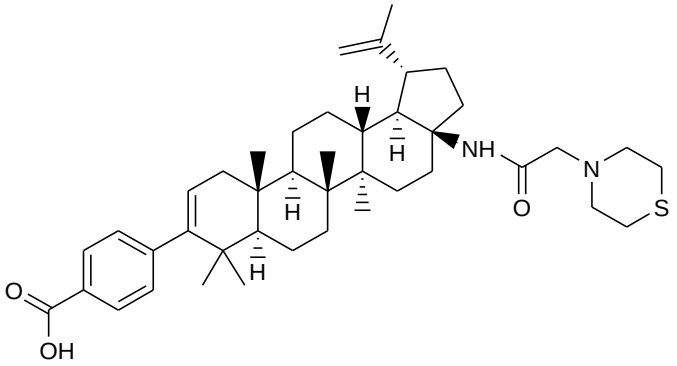
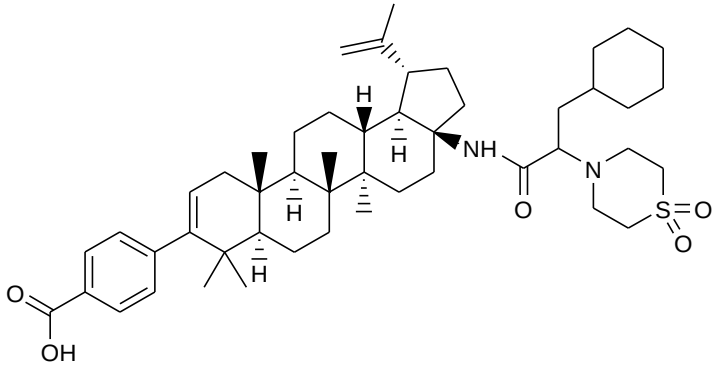
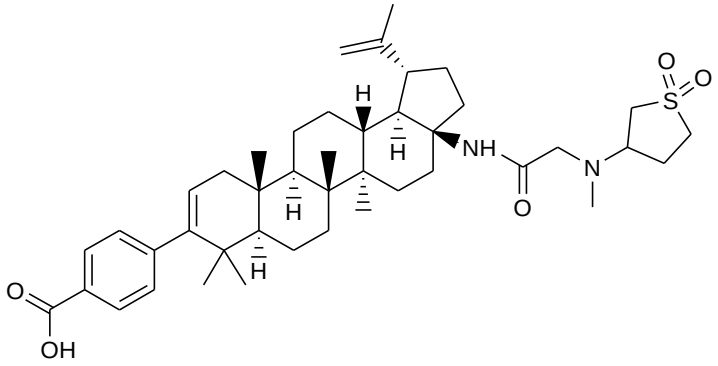
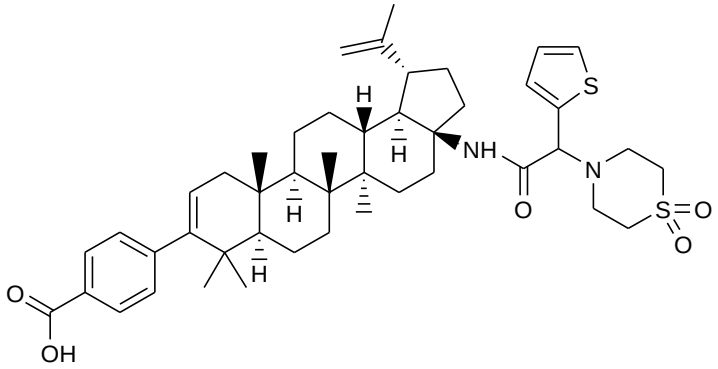
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79		A
80		0.11
81		A

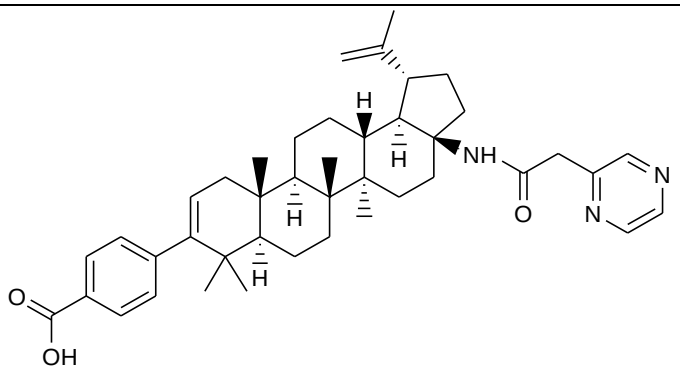
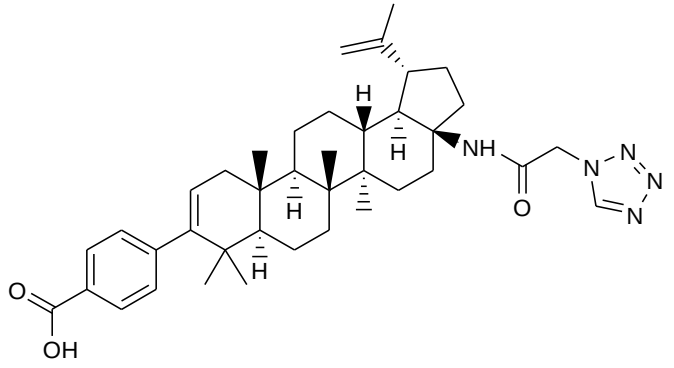
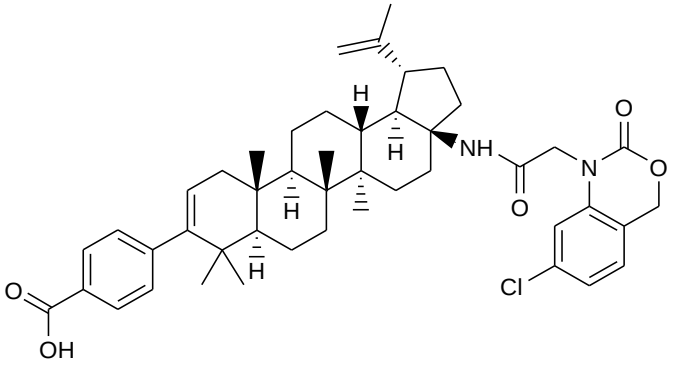
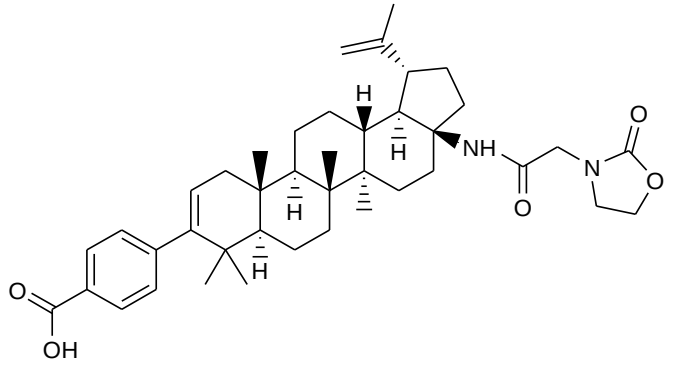
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83		A
84		A
85		A

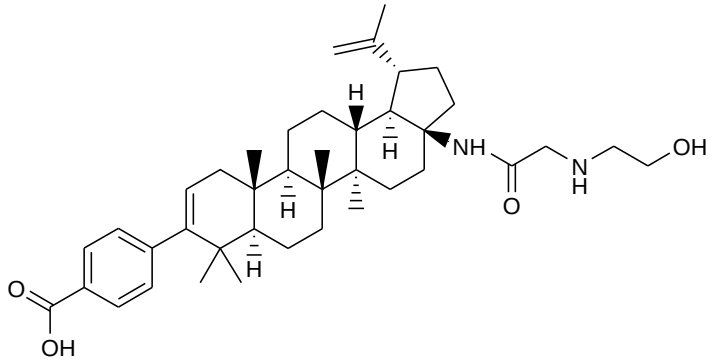
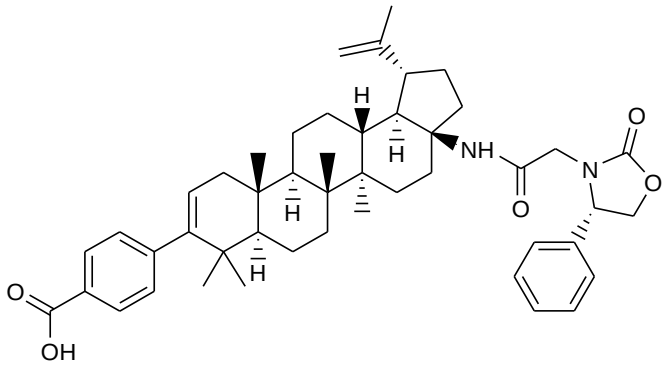
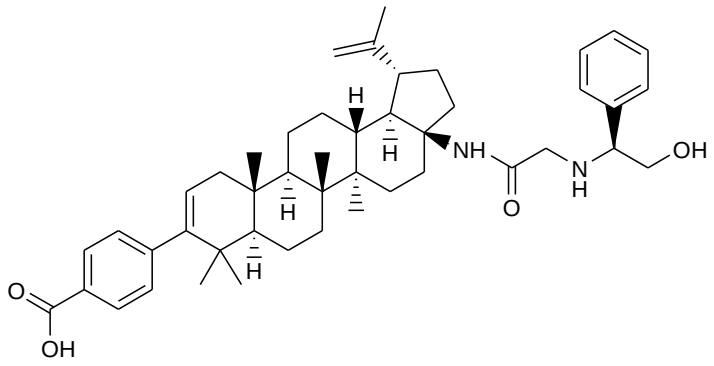
86		A
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88		A
89		A

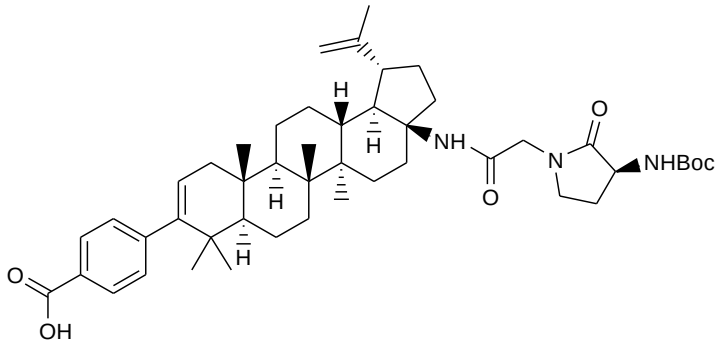
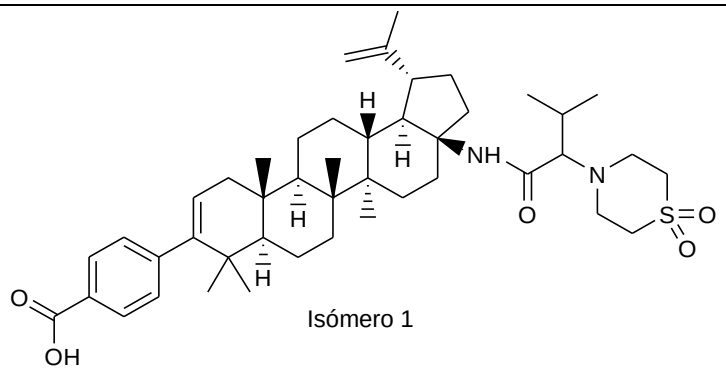
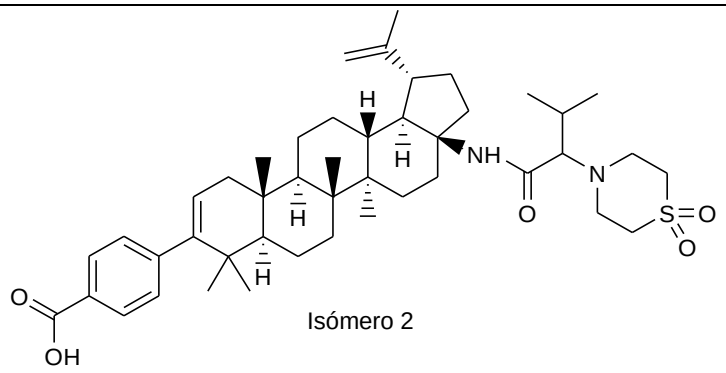
90		0.02
91	 Isómero 1	A
92	 Isómero 2	A
93		A

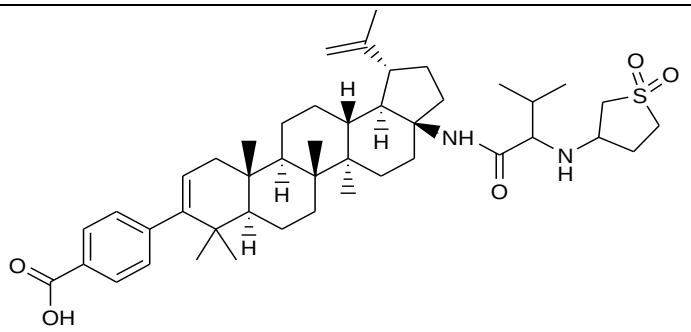
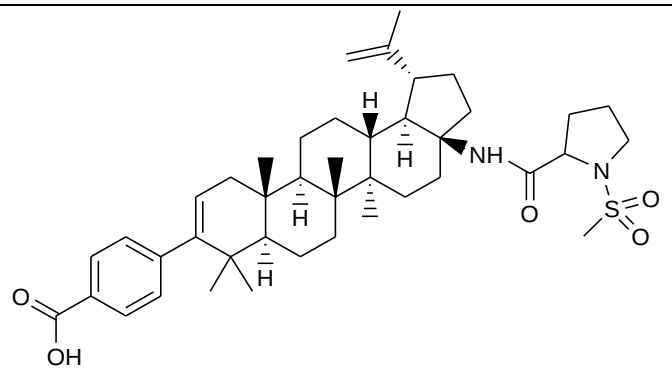
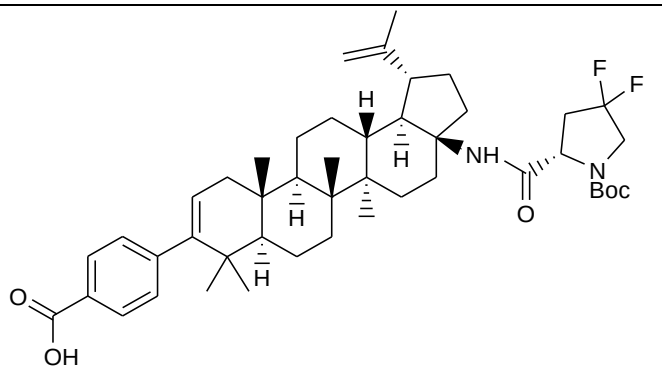
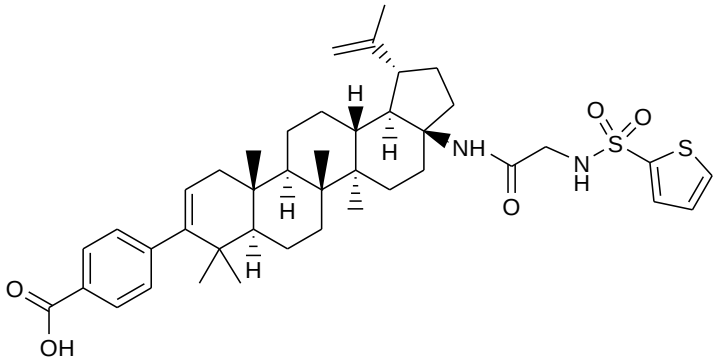
94		A
95		A
96		A
97		A

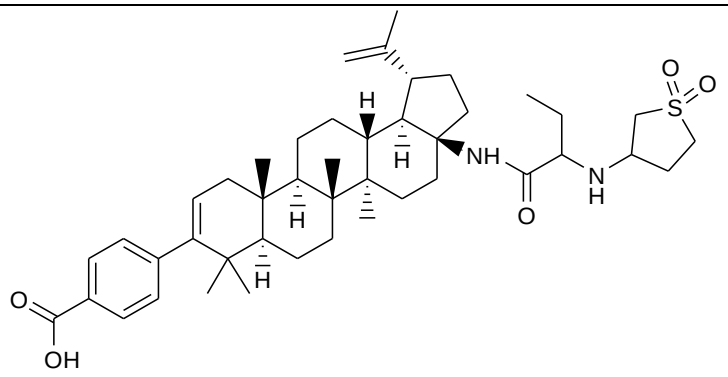
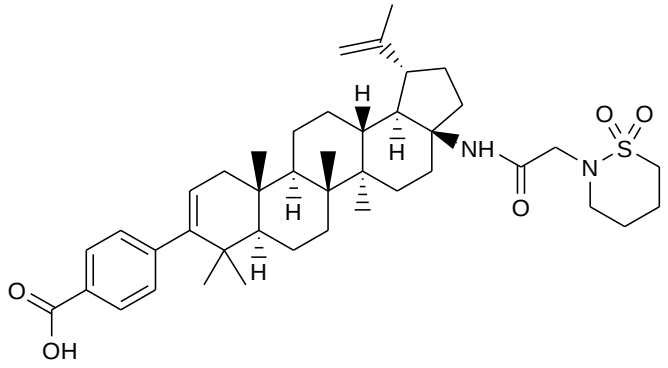
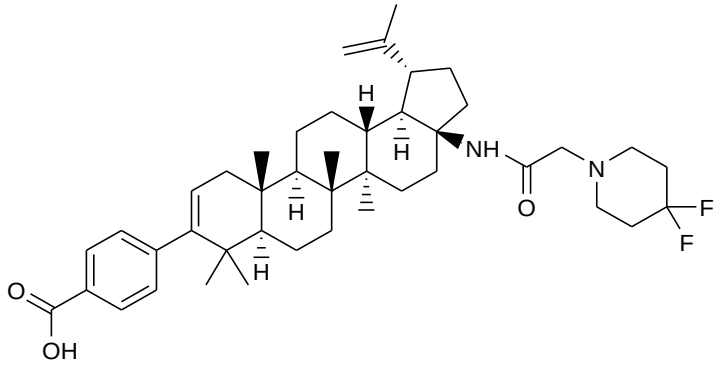
98		A
99		A
100		A
101		A

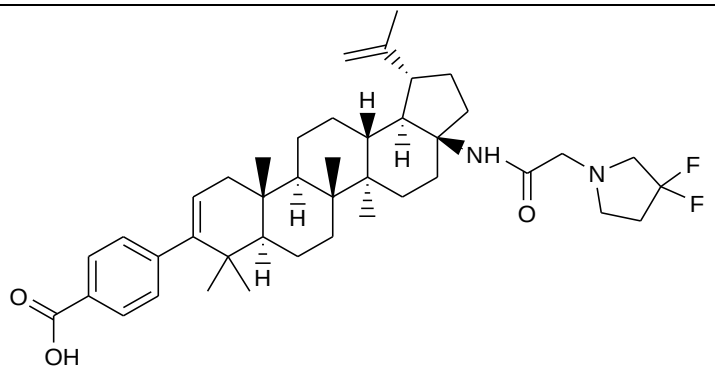
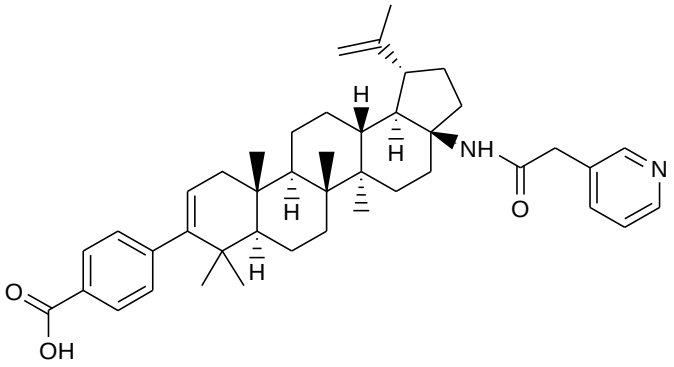
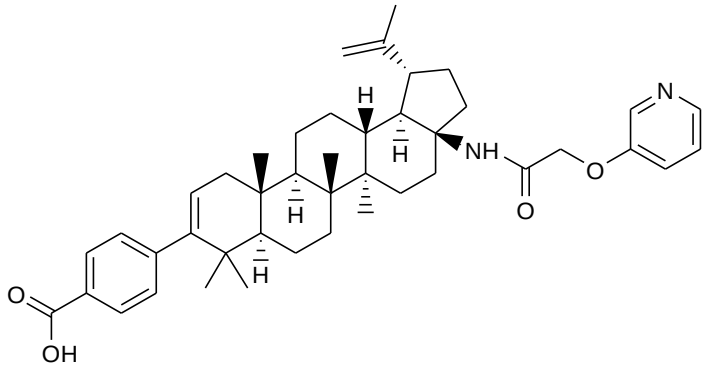
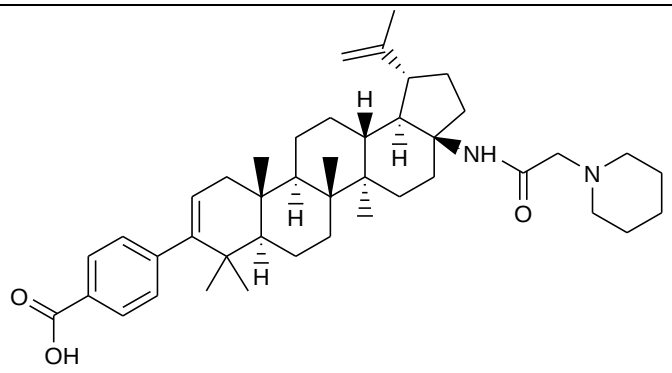
102		A
103		A
104		A
105		A

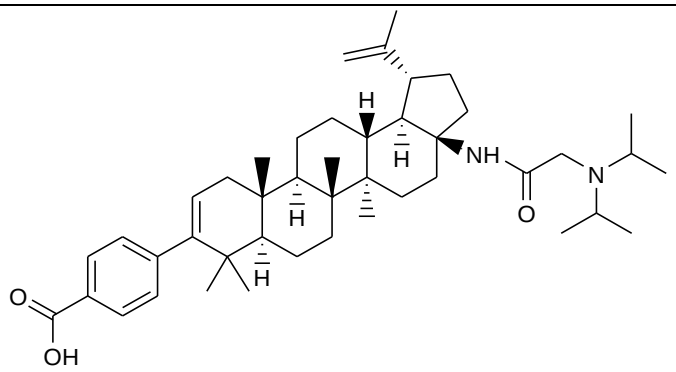
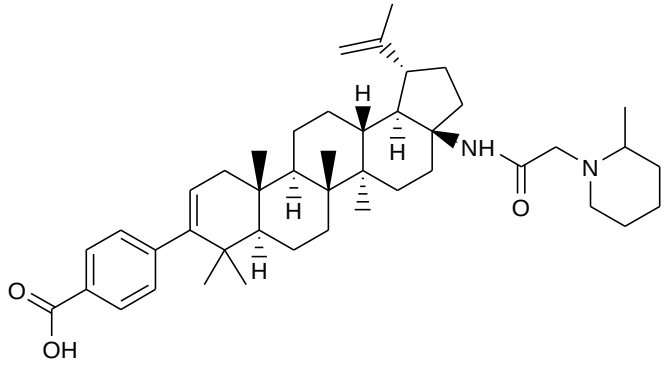
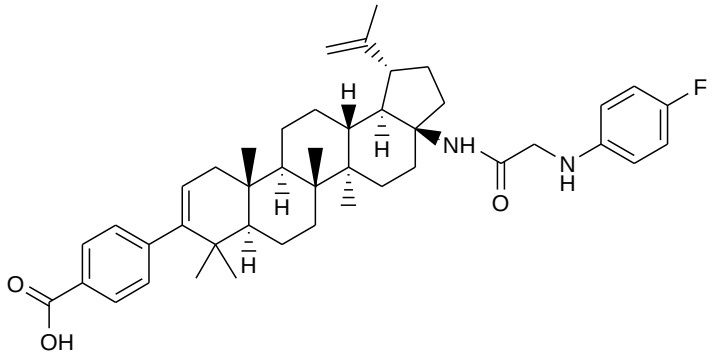
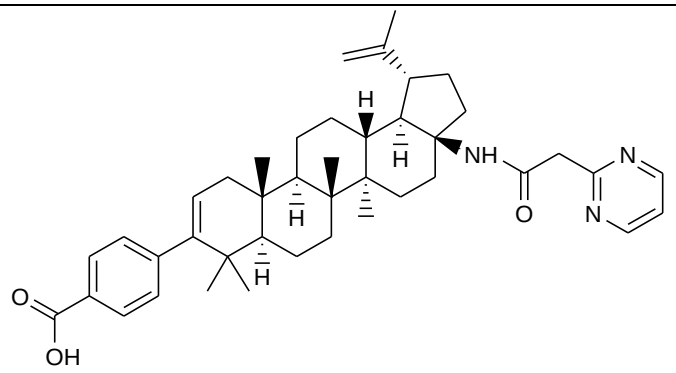
106		A
107		A
108		A

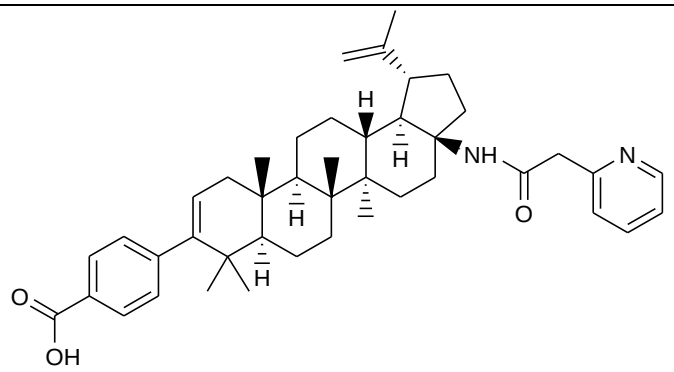
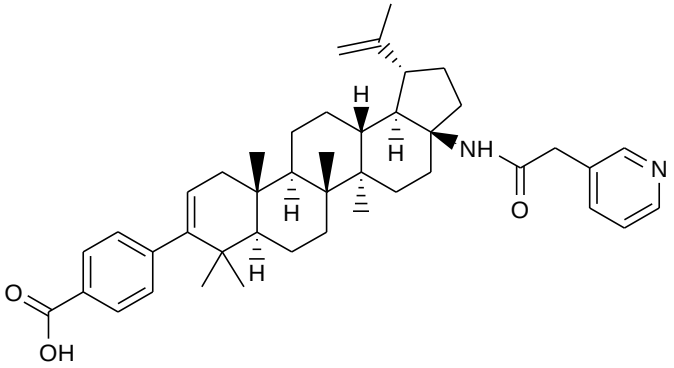
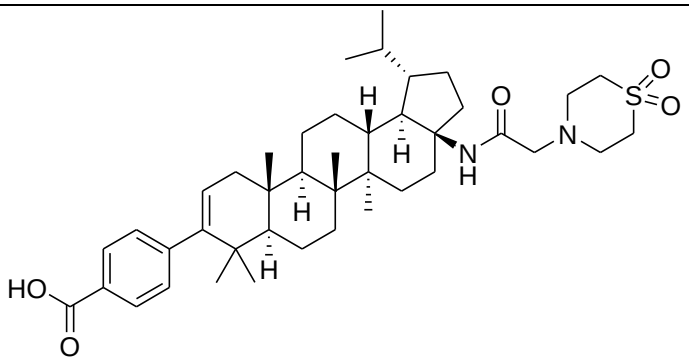
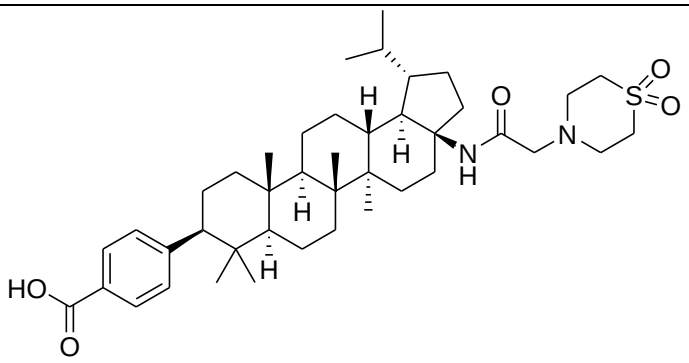
109		A
110	 Isómero 1	A
111	 Isómero 2	A

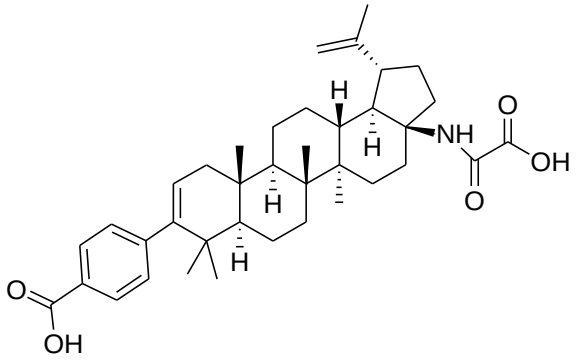
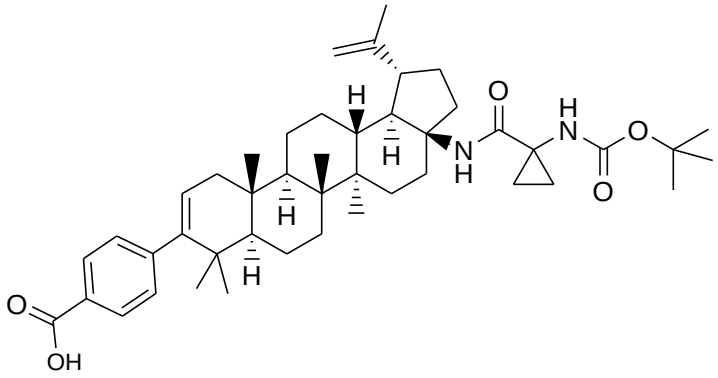
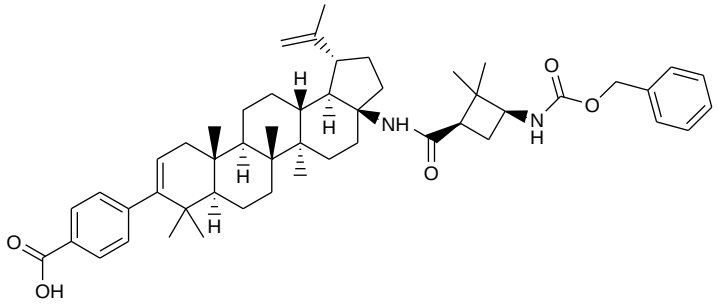
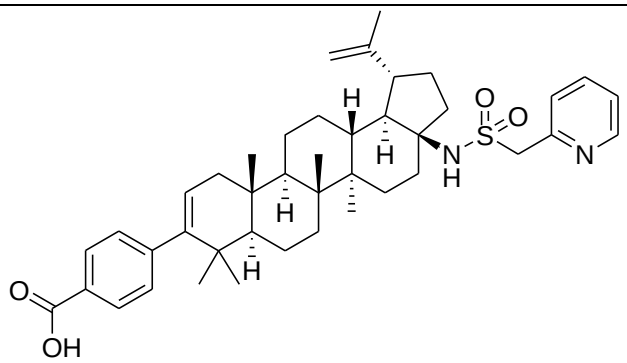
112		A
113		A
114		A
115		A

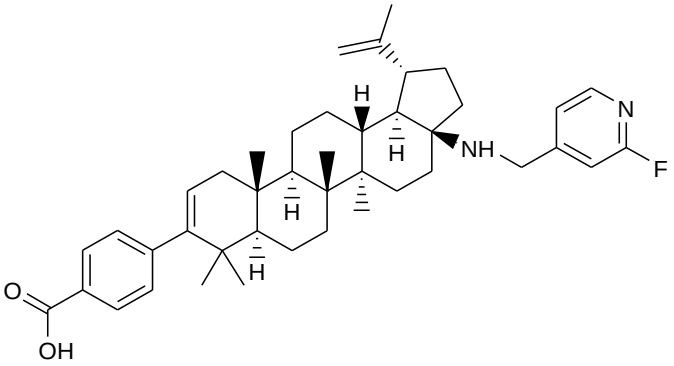
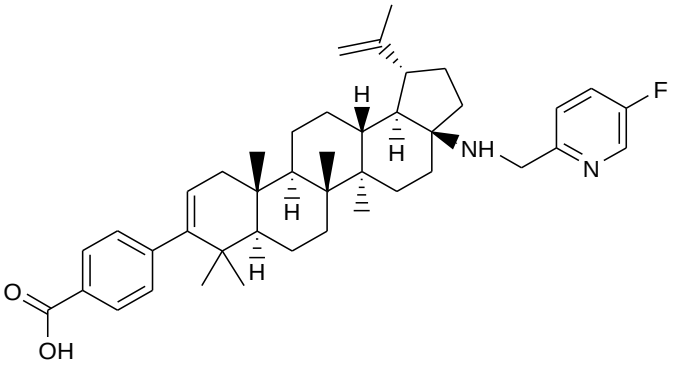
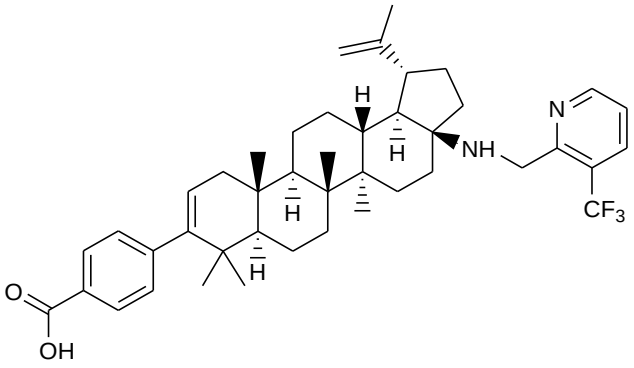
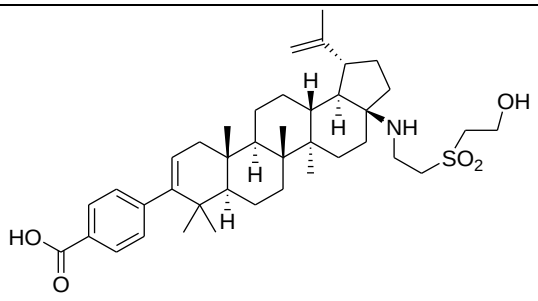
116		A
117		A
118		A

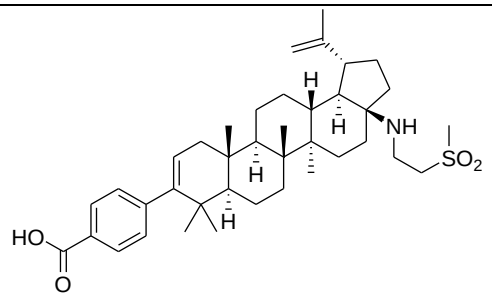
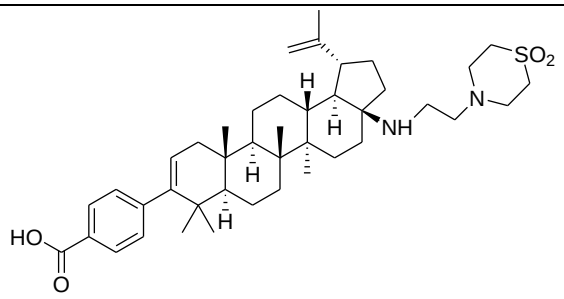
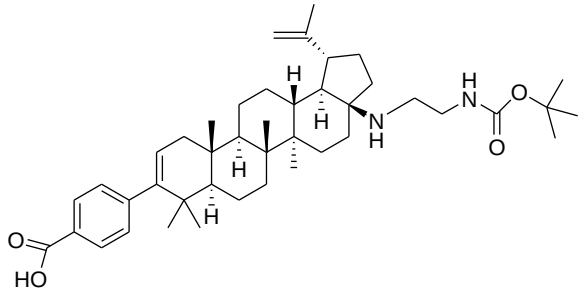
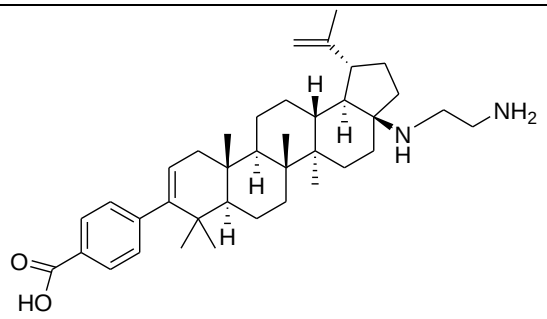
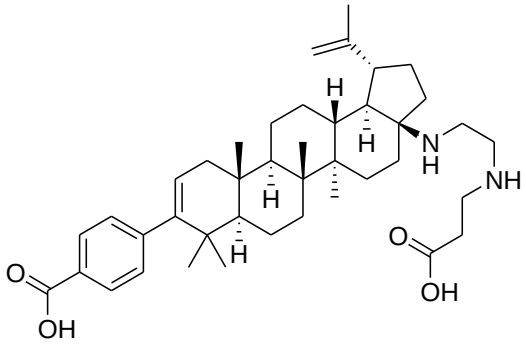
119		A
120		A
121		A
122		A

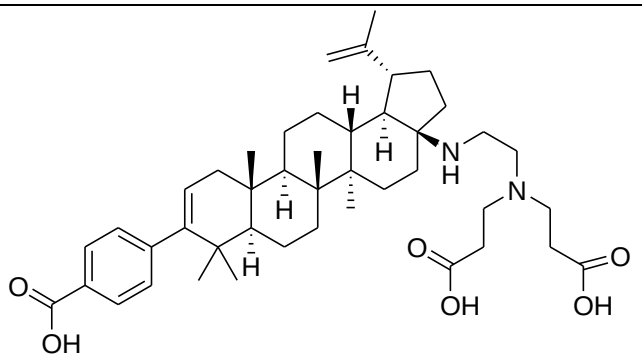
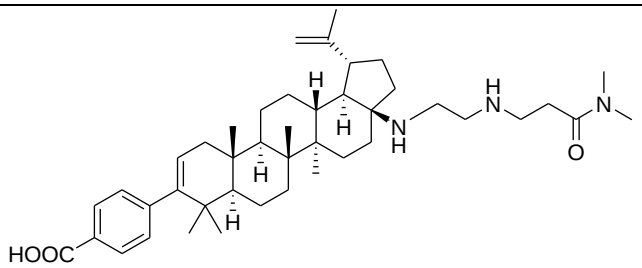
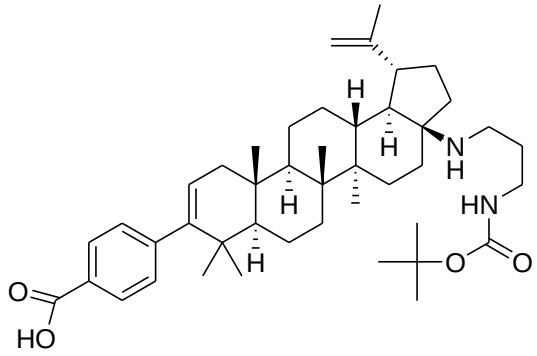
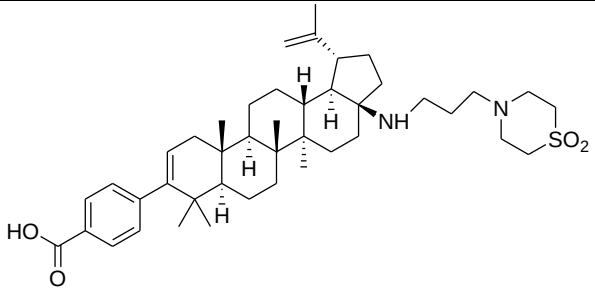
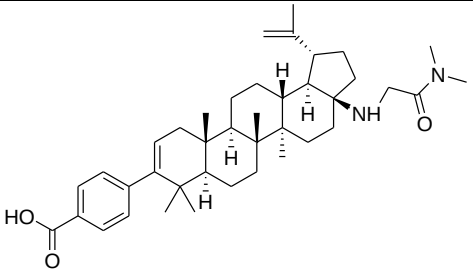
123		A
124		A
125		A
126		A

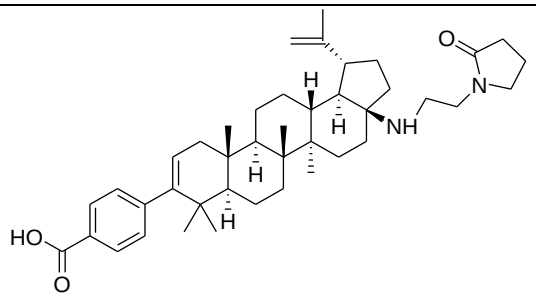
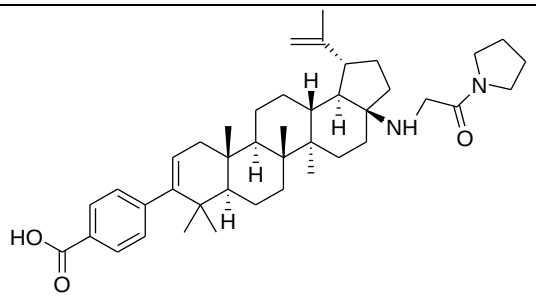
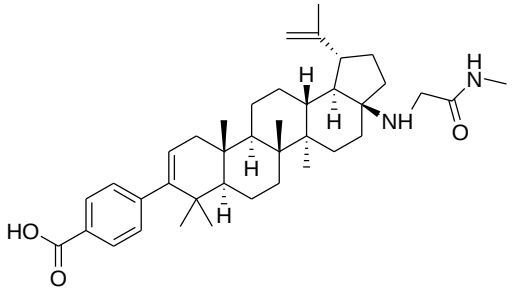
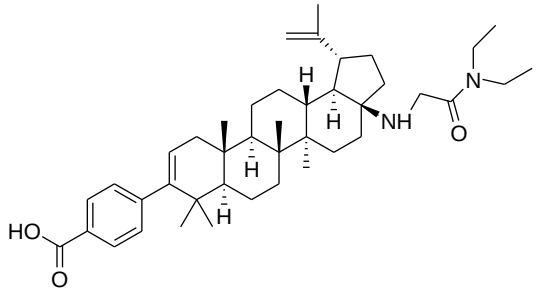
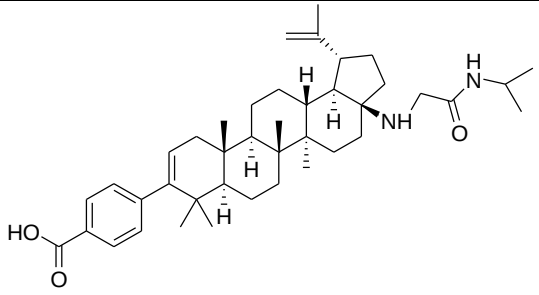
127		A
128		A
129		A
130		A

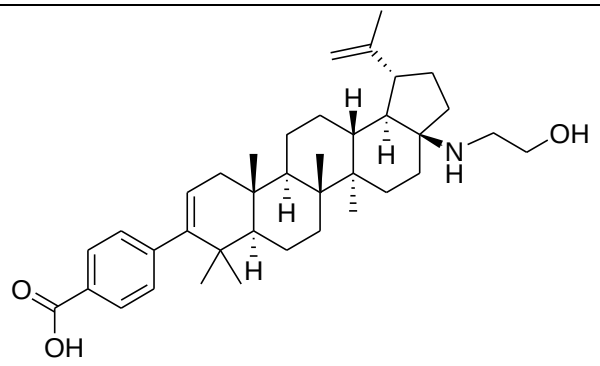
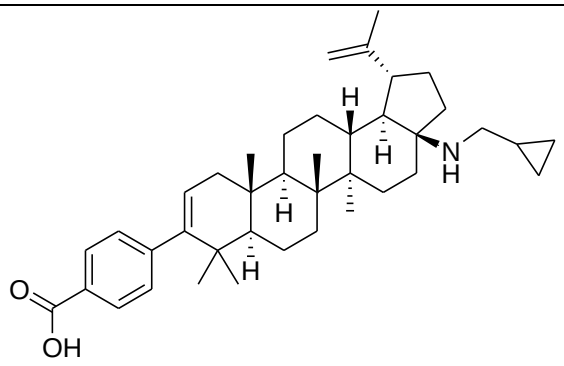
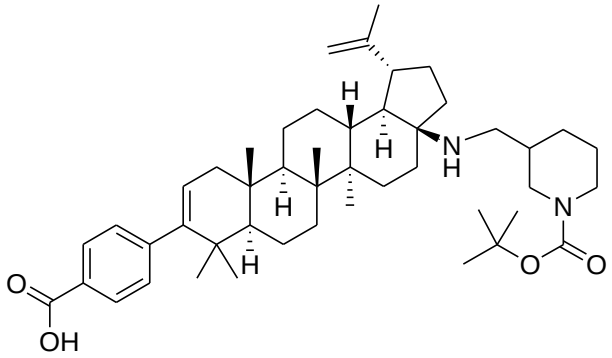
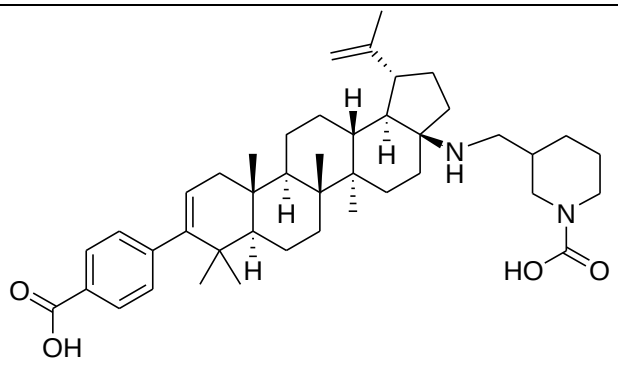
130-1		B
130-2		A
130-3		A
131		A

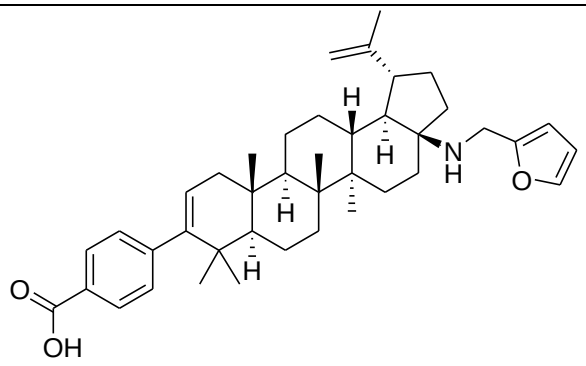
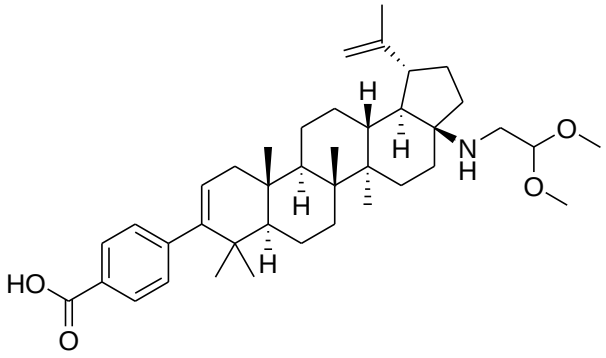
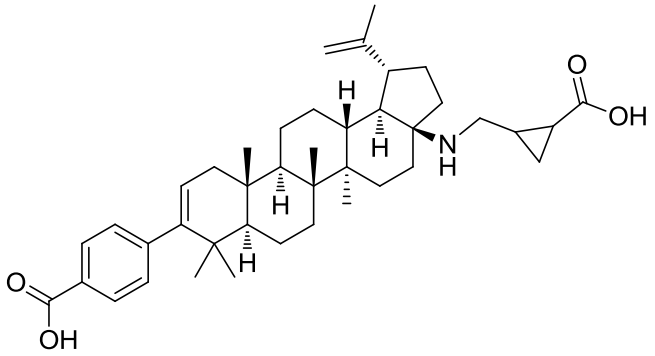
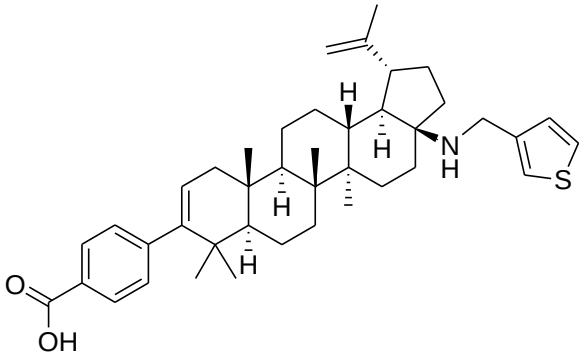
132		A
133		0.03
134		0.10
135		A

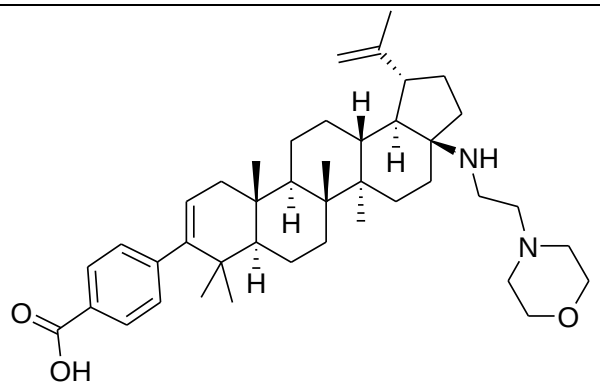
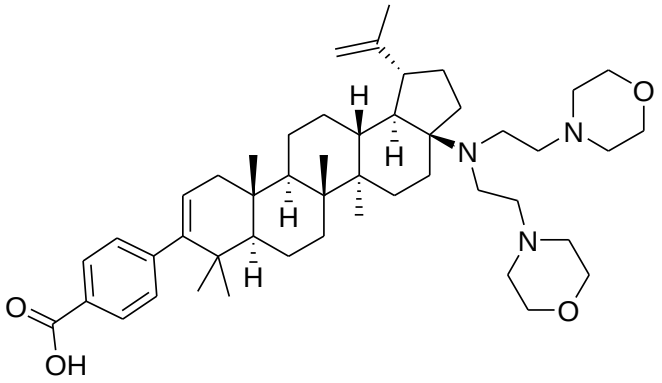
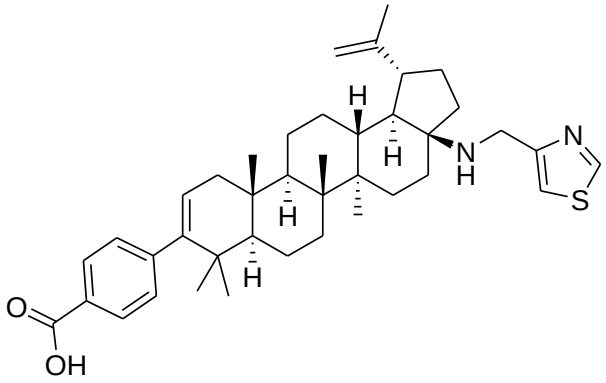
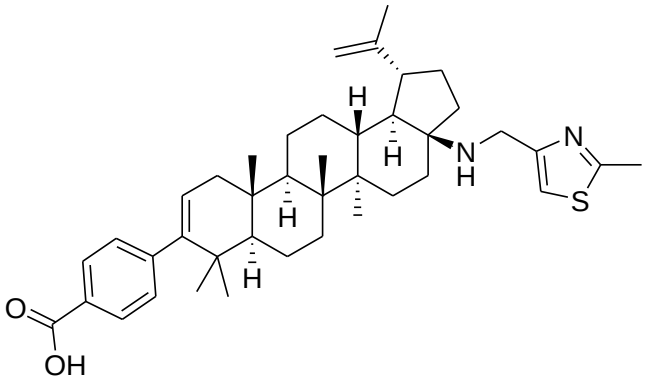
136		A
137		A
138		A
139		A
140		0.009

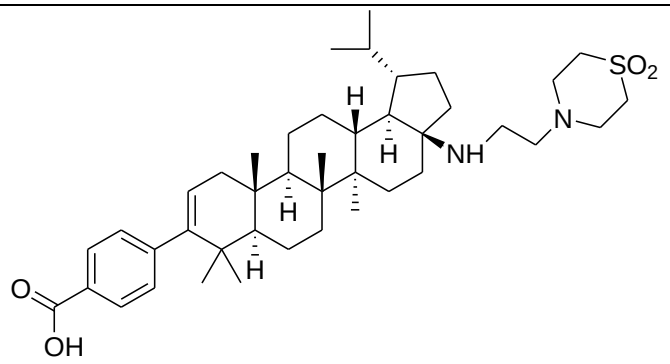
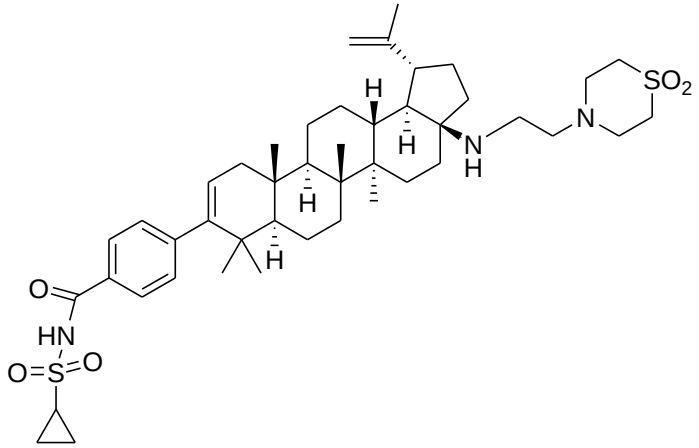
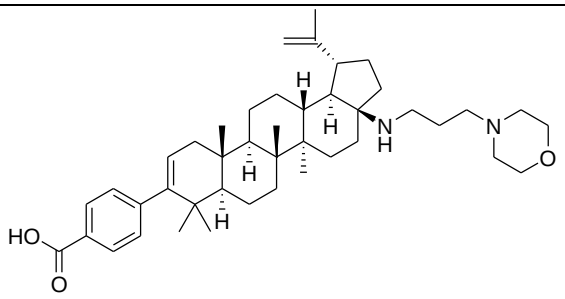
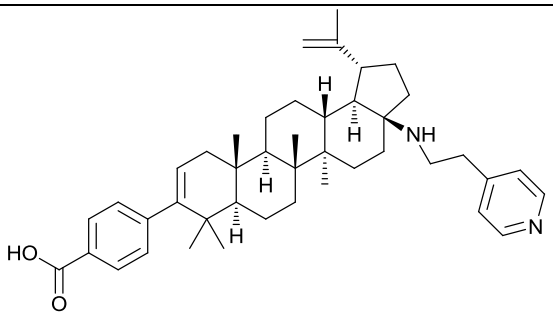
141		A
142		A
143		A
144		A
145		A

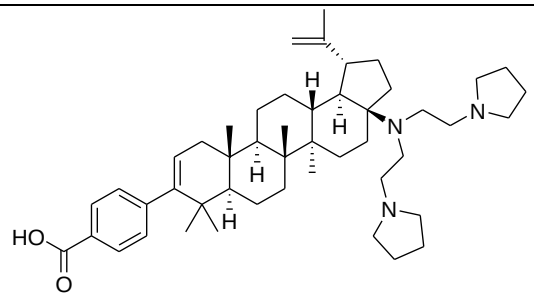
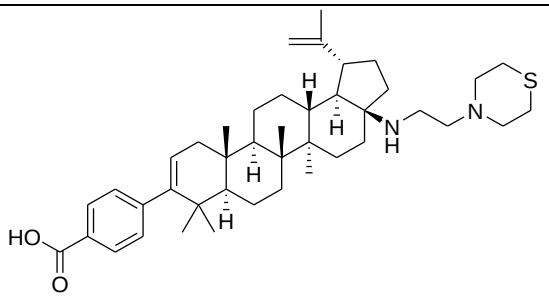
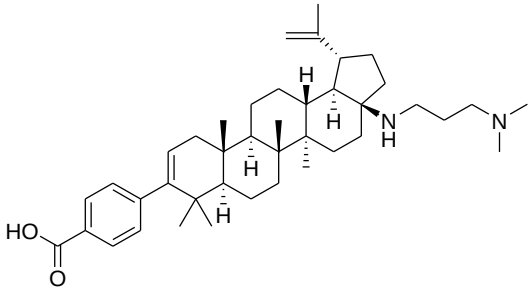
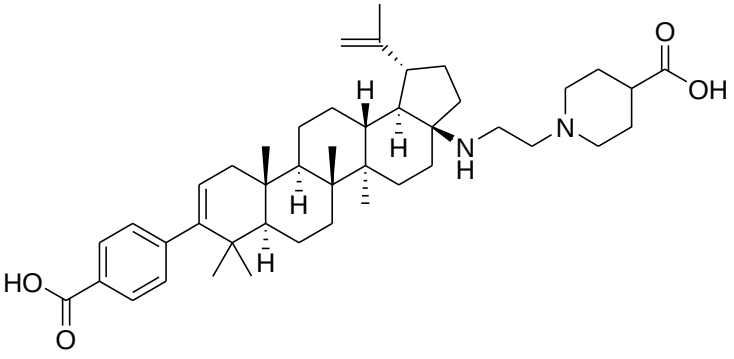
146		A
147		A
148		A
149		A
150		A

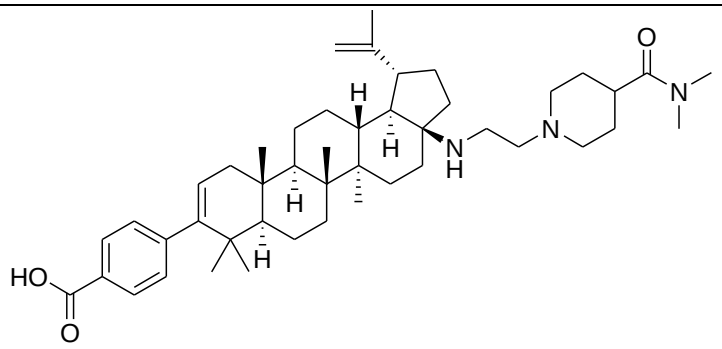
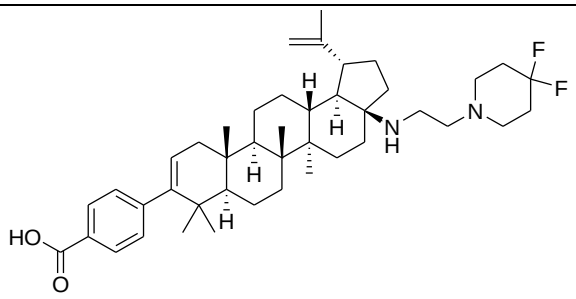
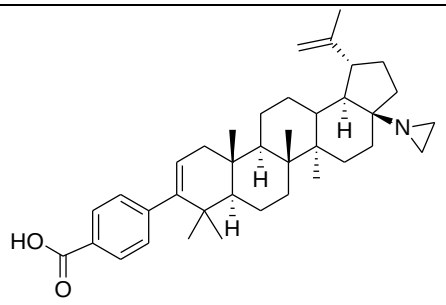
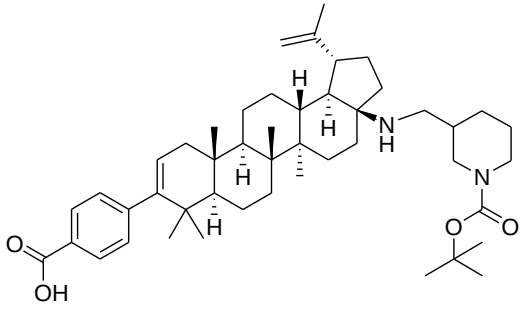
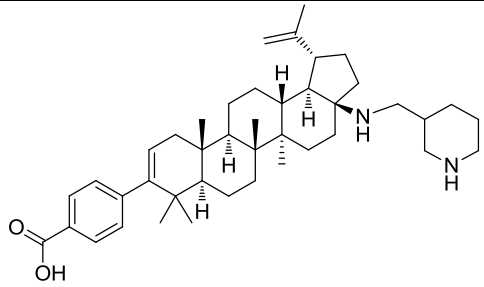
151		A
152		A
153		B
154		A

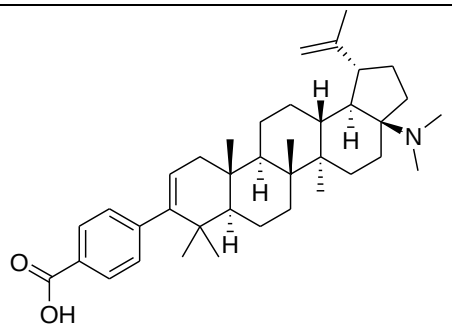
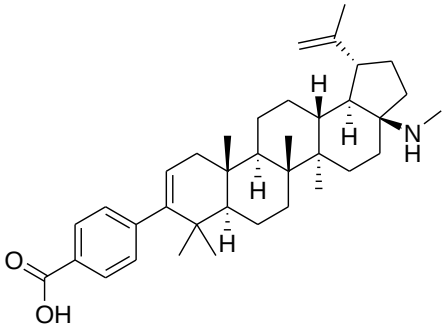
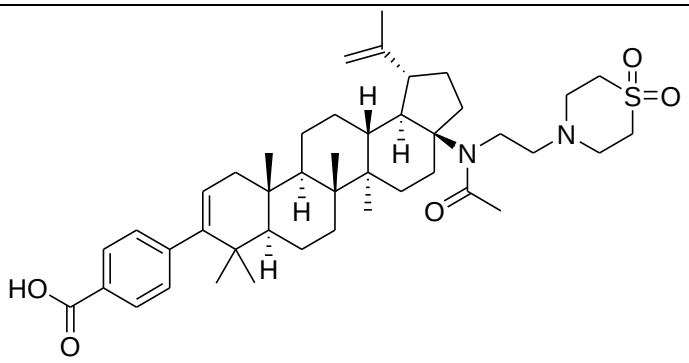
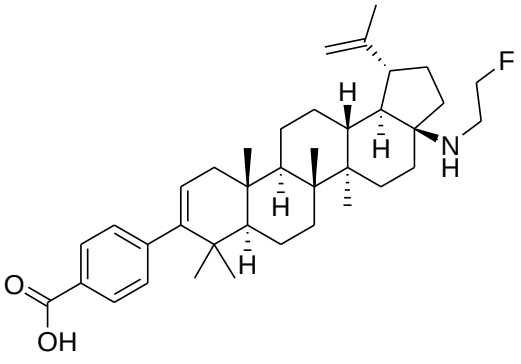
155		A
156		0.12
157		A
158		A

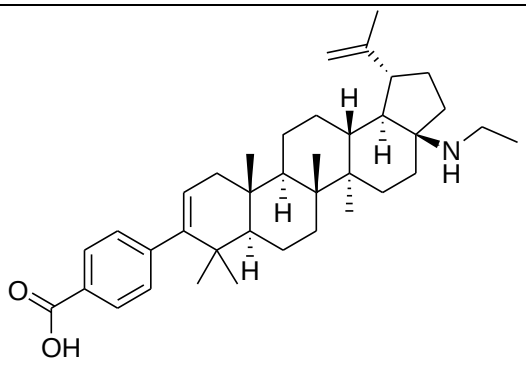
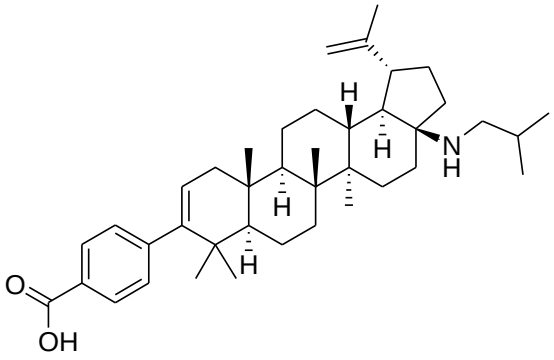
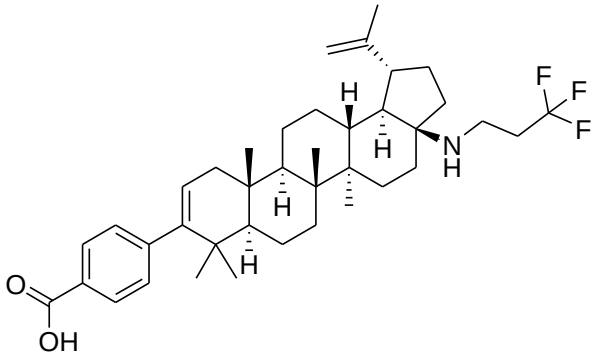
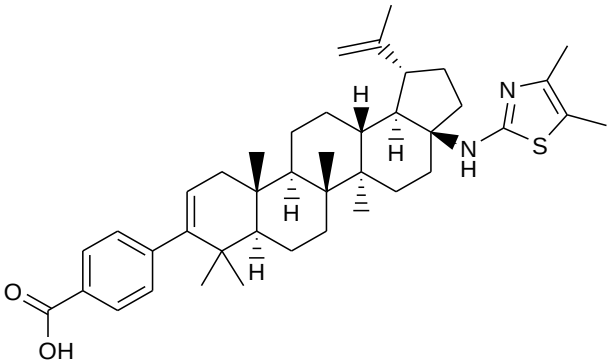
159		A
160		A
161		A
162		A

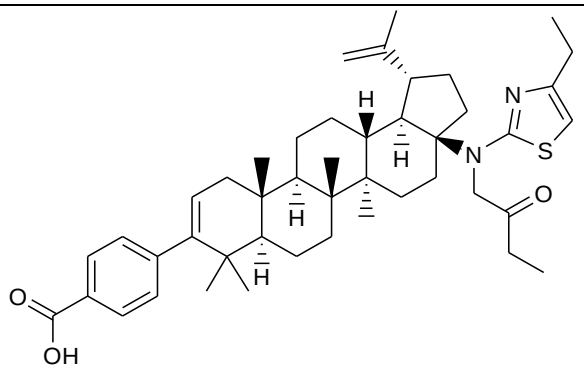
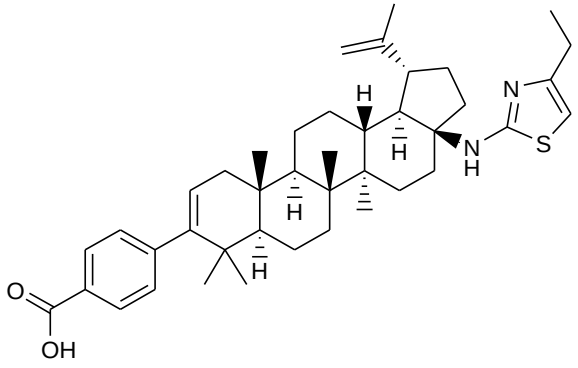
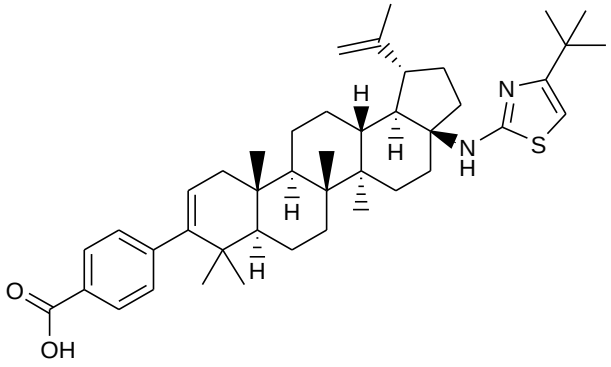
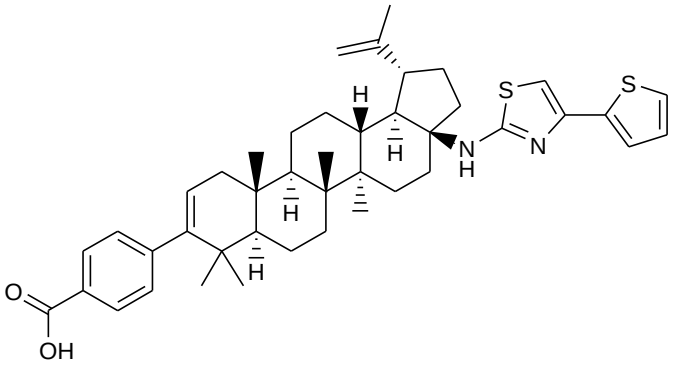
163		A
164		A
165		A
166		A

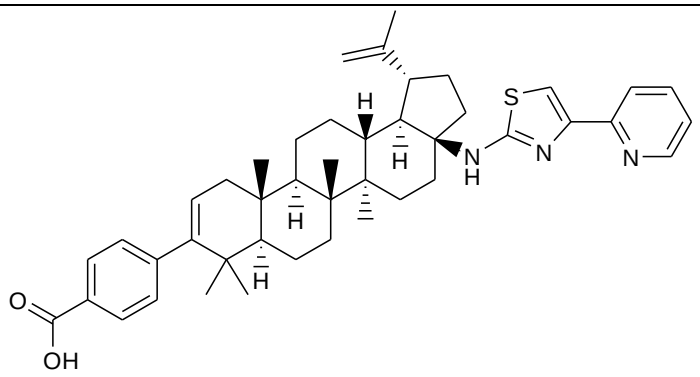
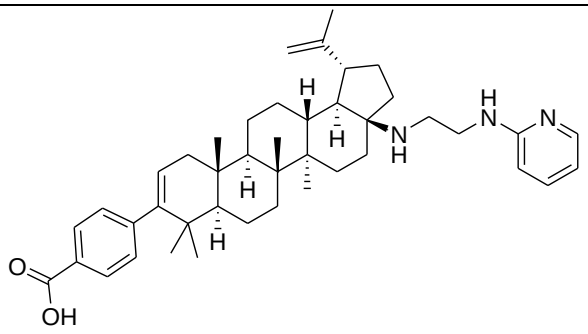
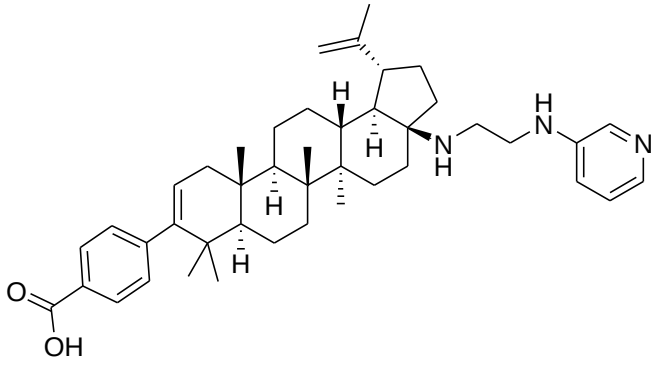
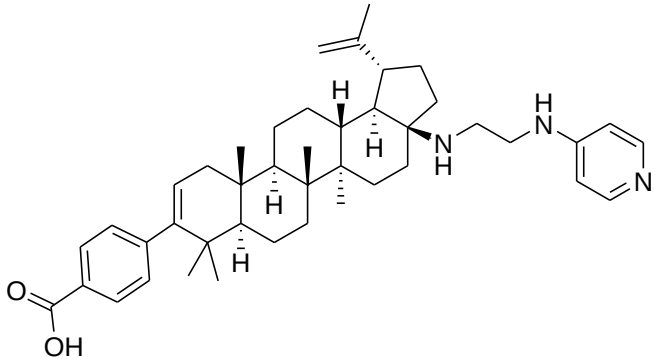
167		0.004
168		A
169		A
170		A

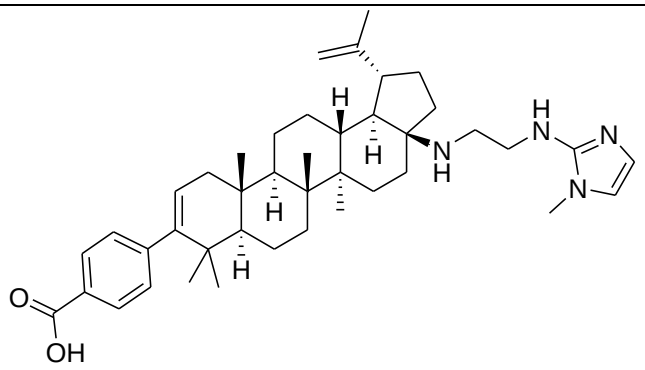
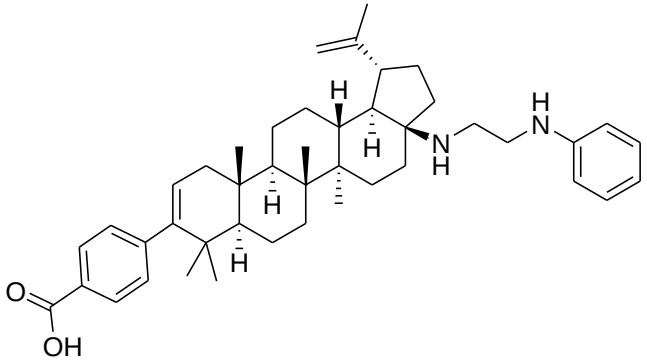
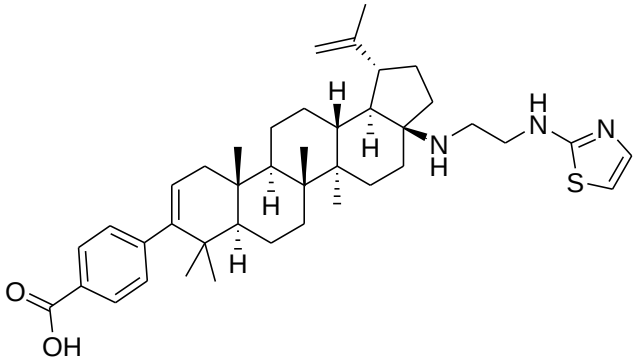
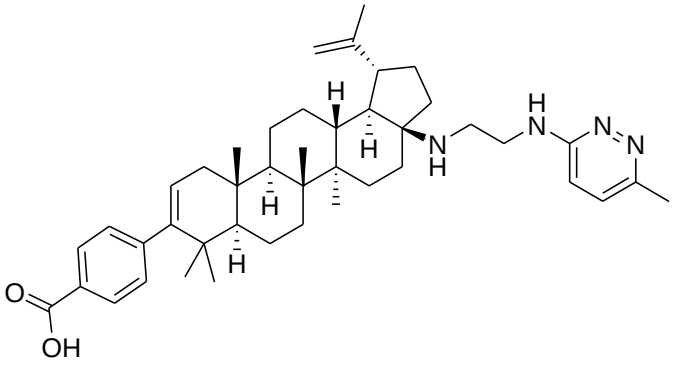
171		A
172		A
173		A
174		0.3
175		0.01

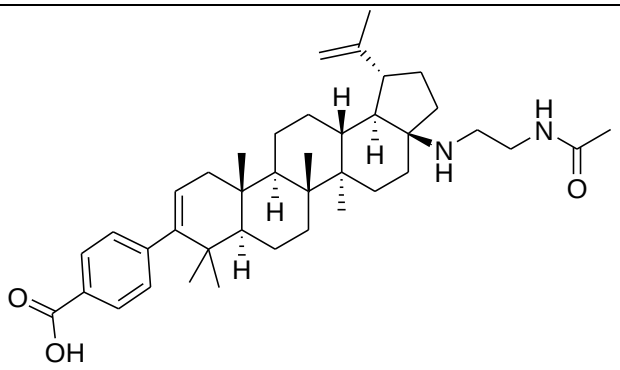
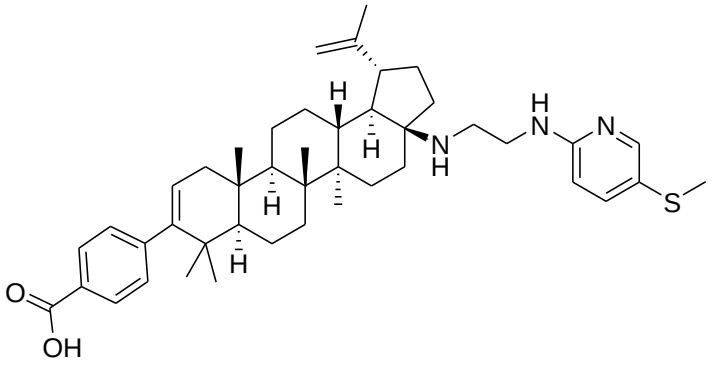
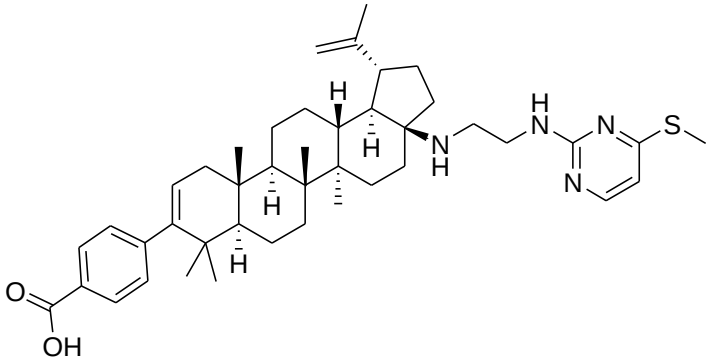
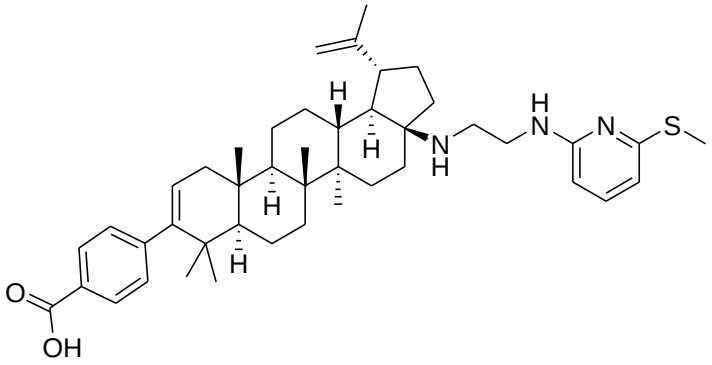
176		A
177		0.009
178		A
179		A

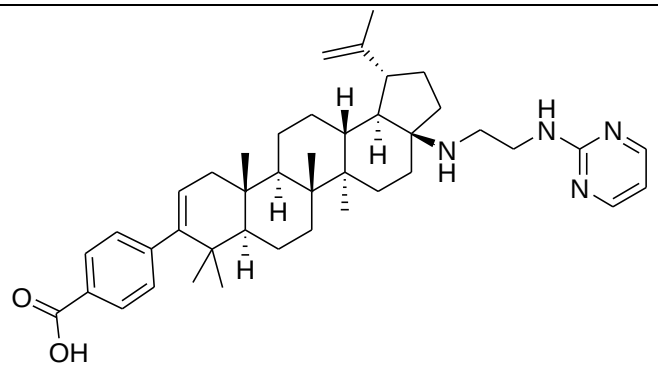
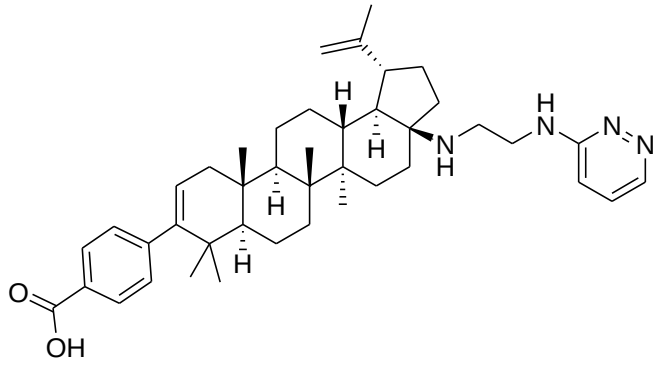
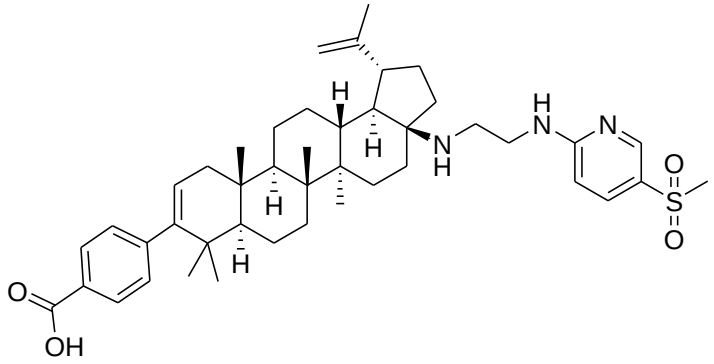
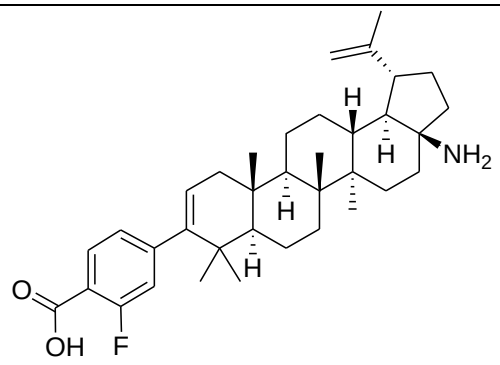
180		A
181		A
182		B
183		A

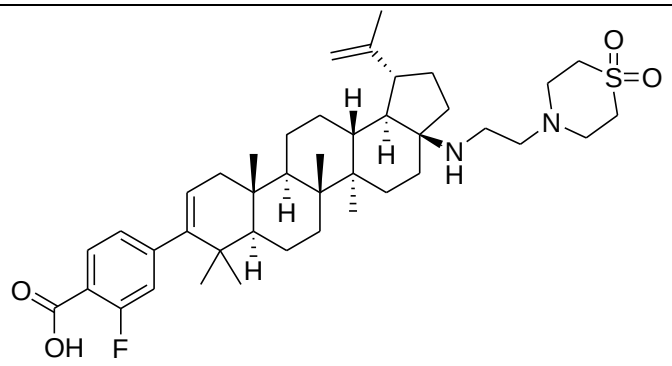
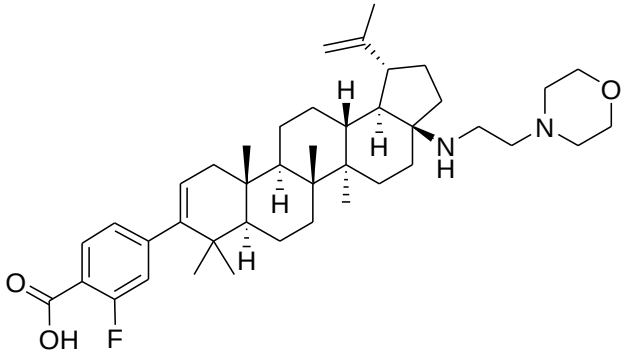
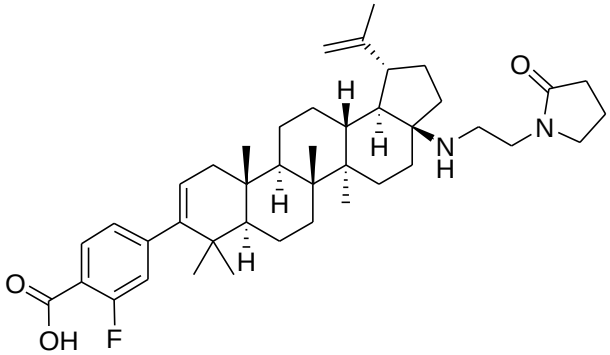
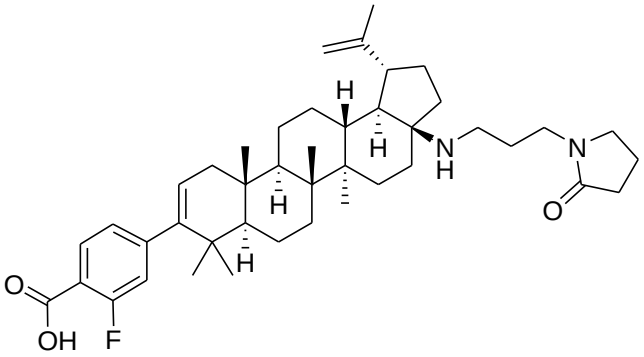
184A		0.39
184B		A
185		B
186		B

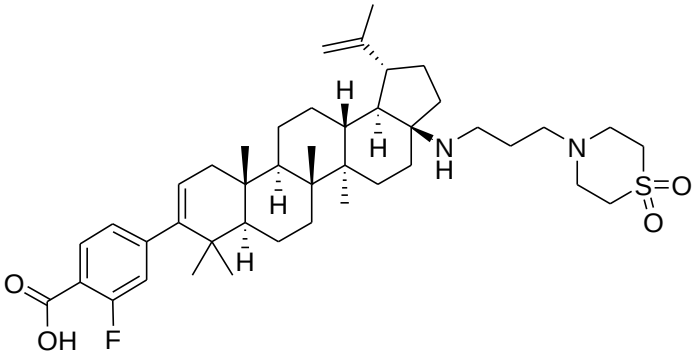
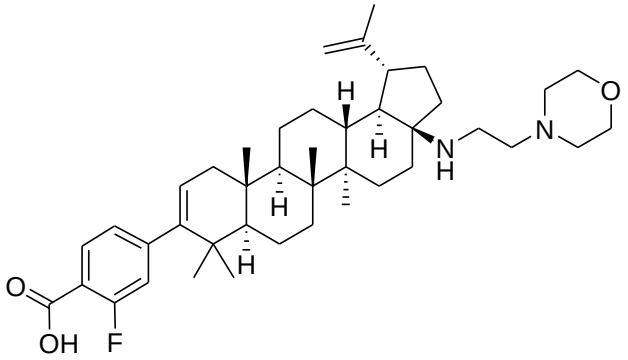
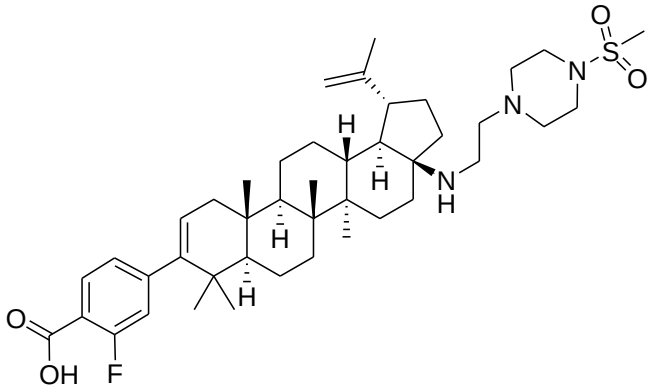
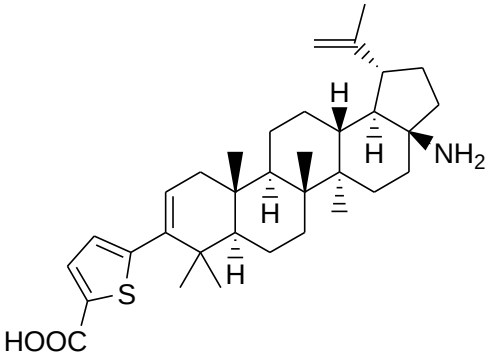
187		A
188		0.001
189		A
190		A

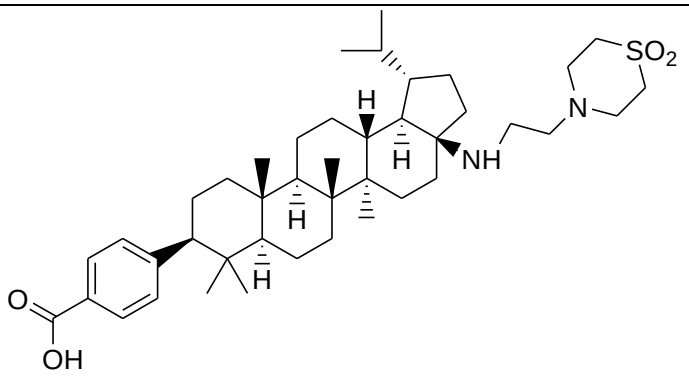
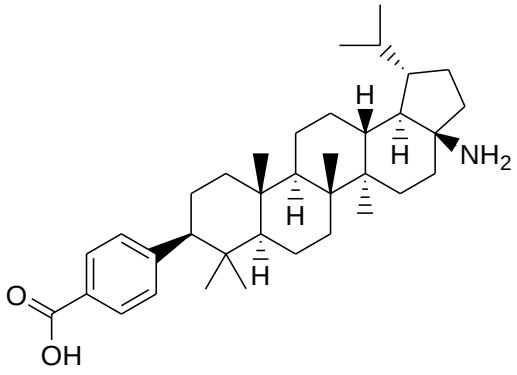
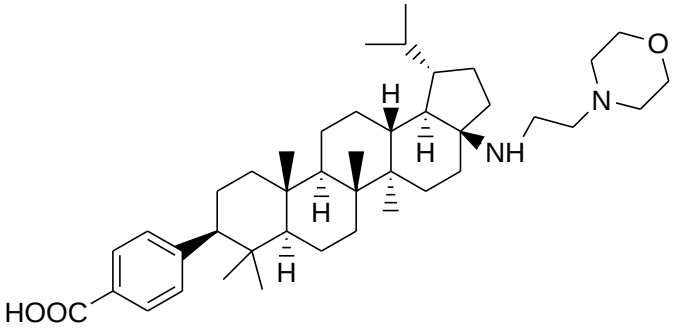
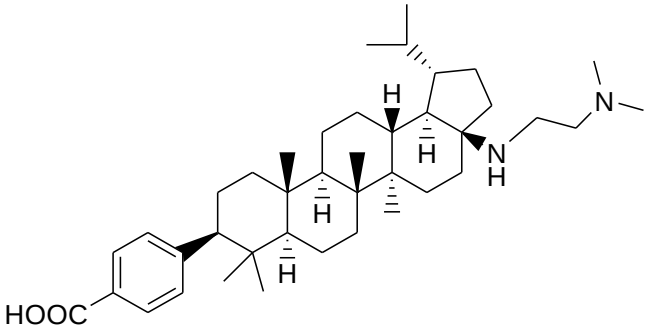
191		A
192		A
193		0.02
194		A

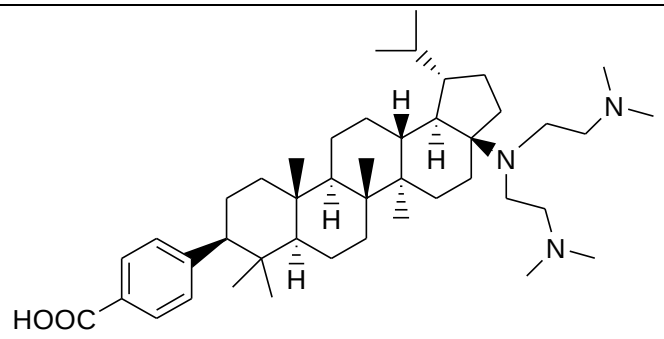
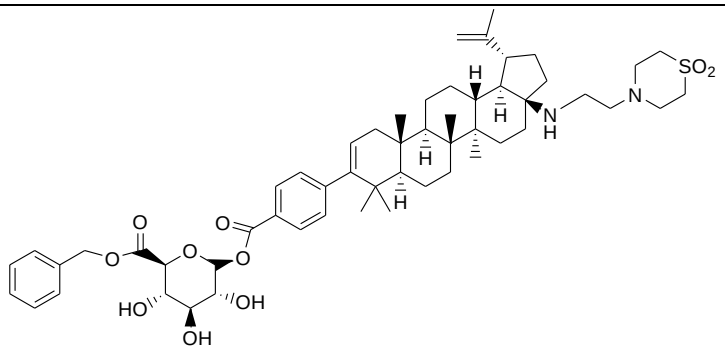
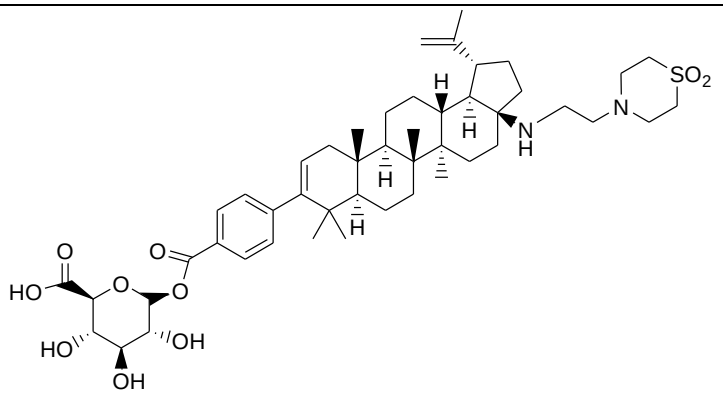
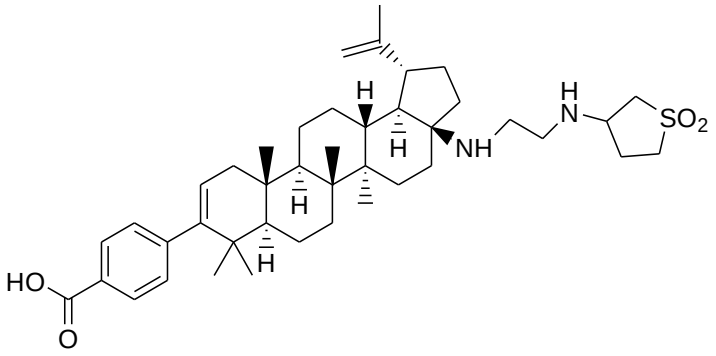
195		A
196		A
197		A
198		A

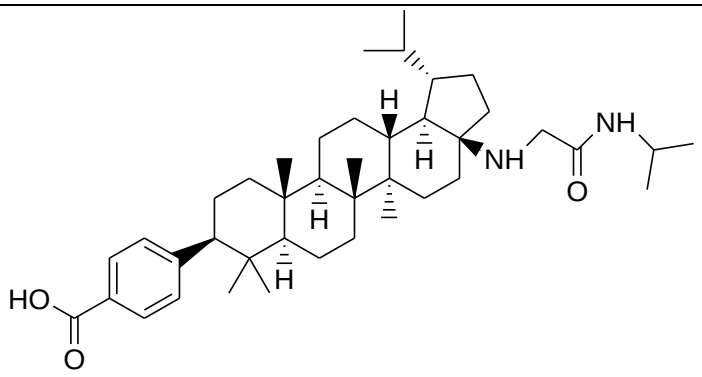
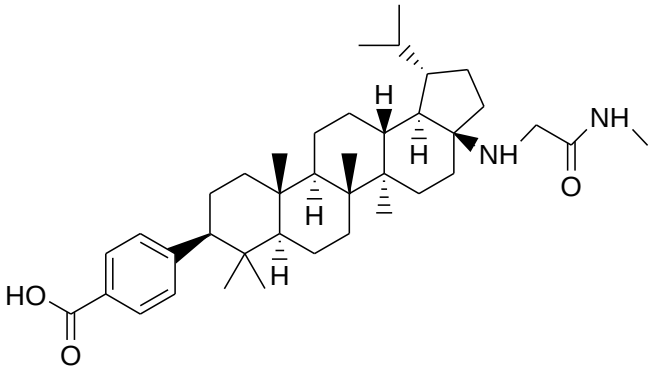
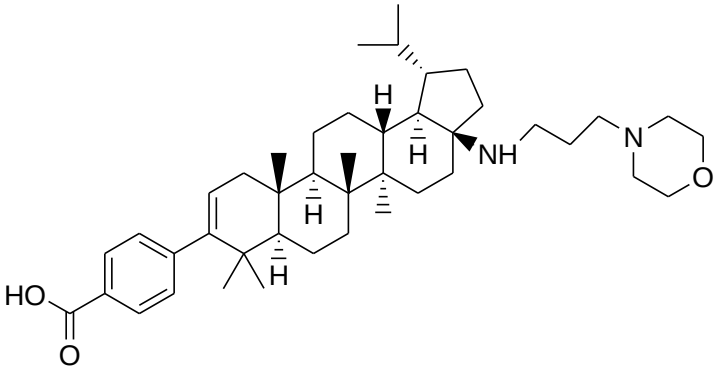
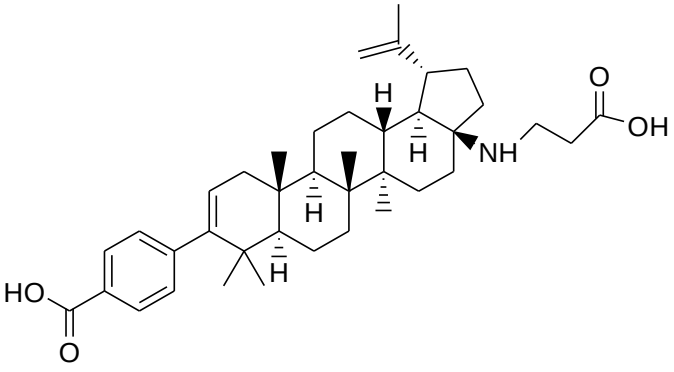
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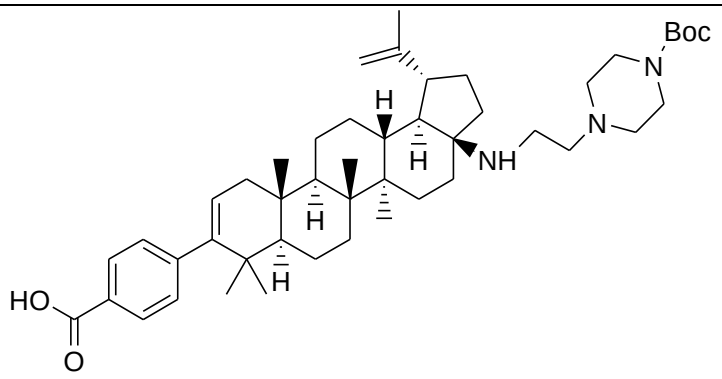
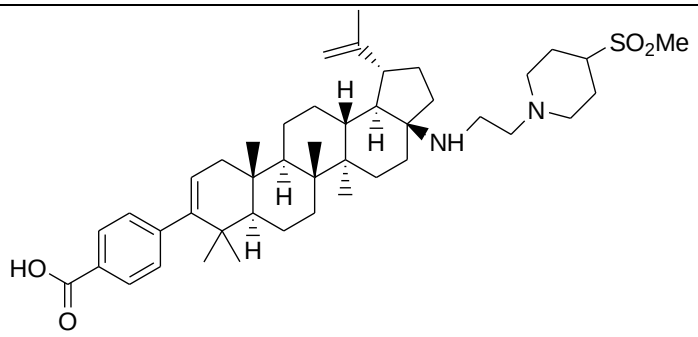
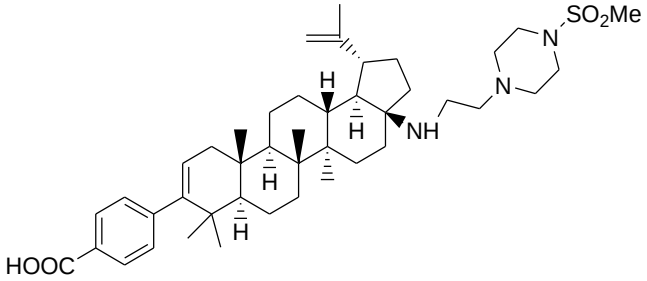
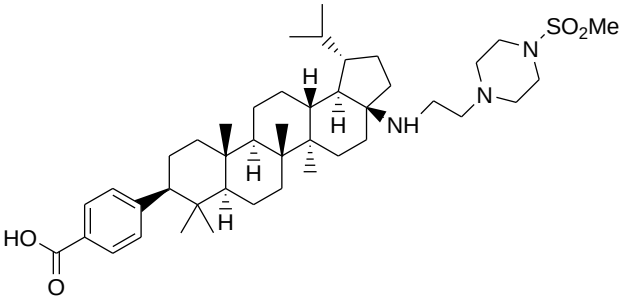
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A5		A

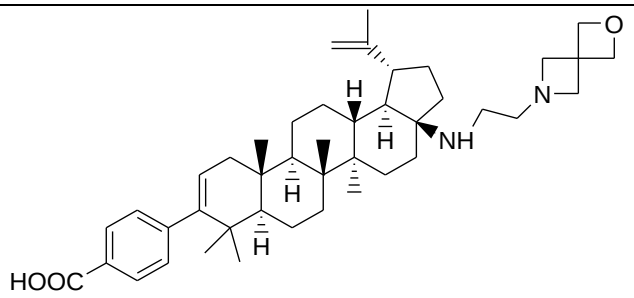
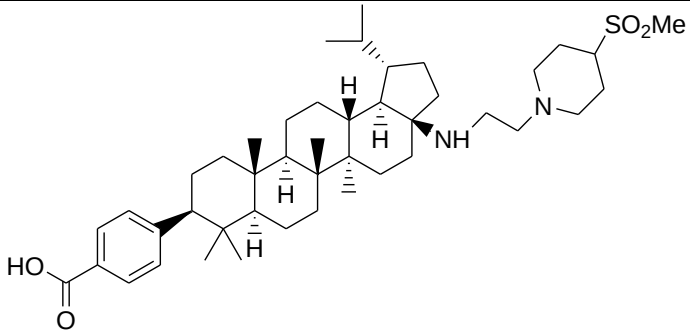
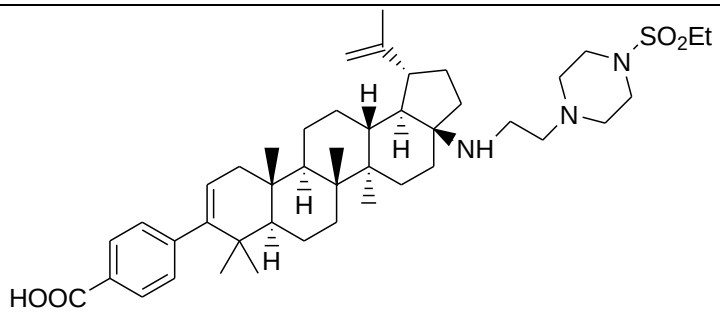
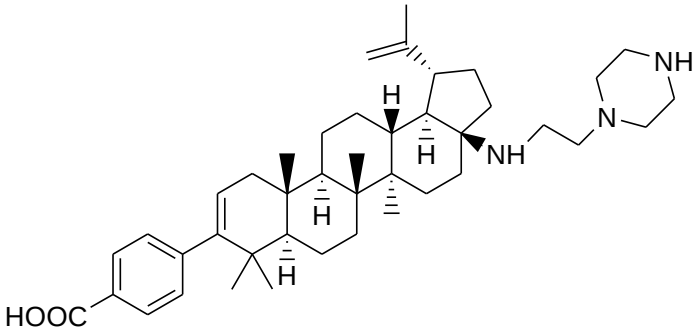
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B1		A

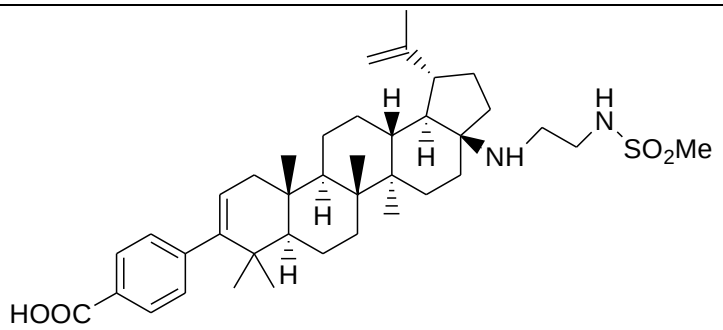
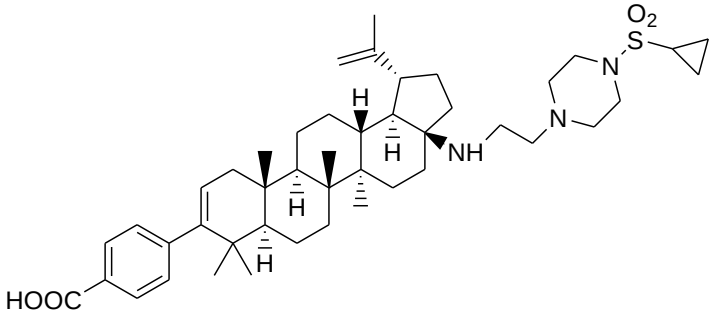
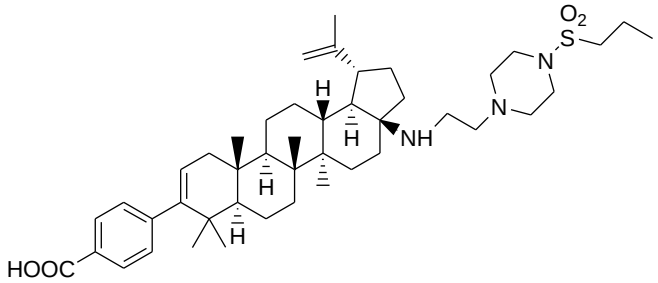
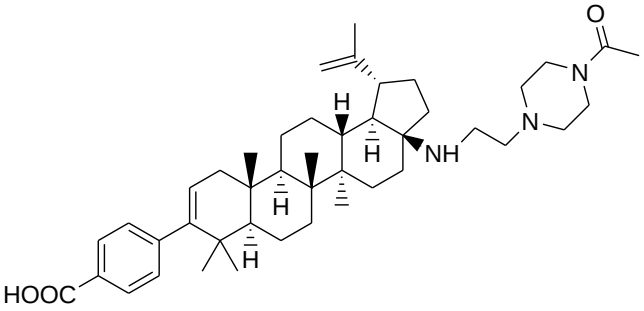
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B5		A

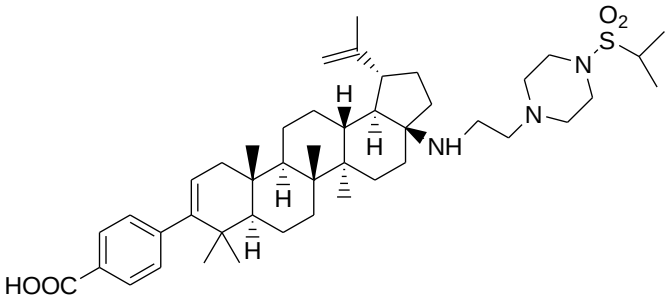
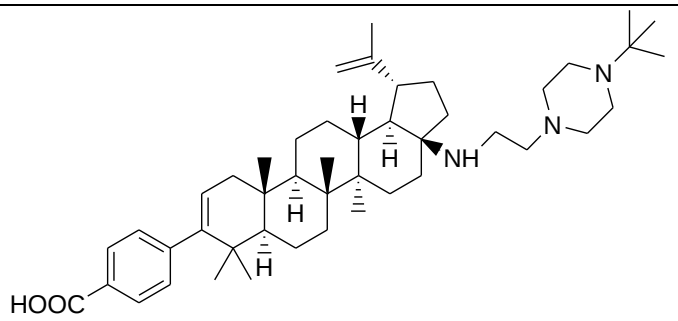
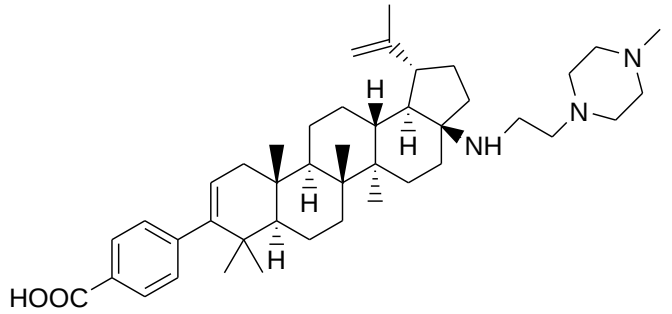
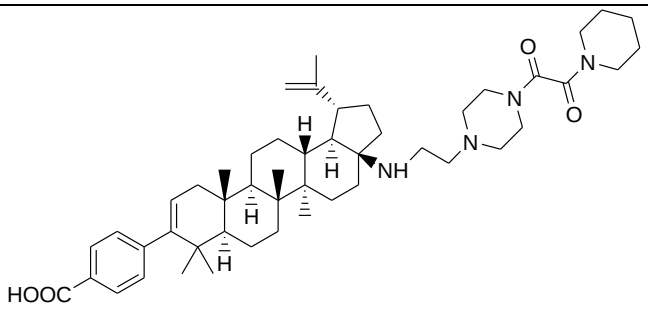
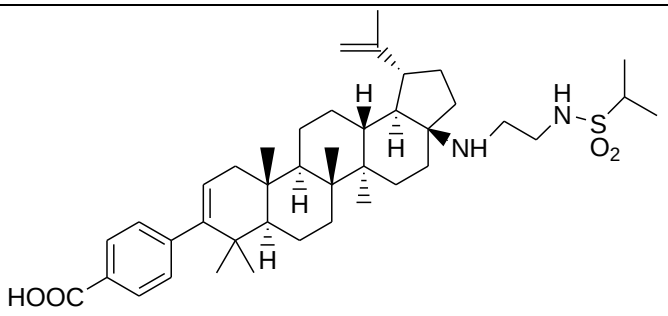
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B8		A

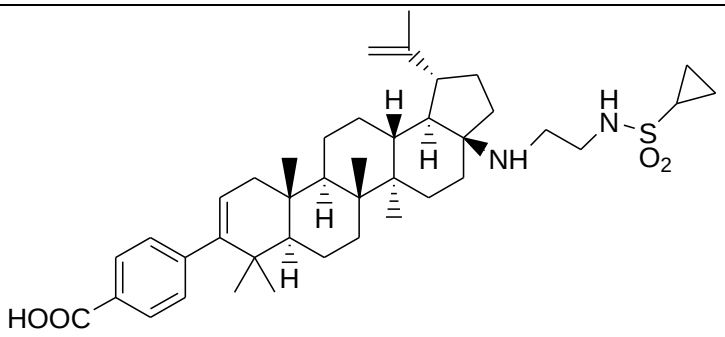
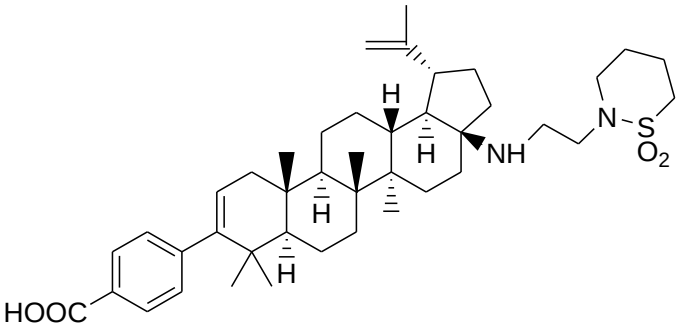
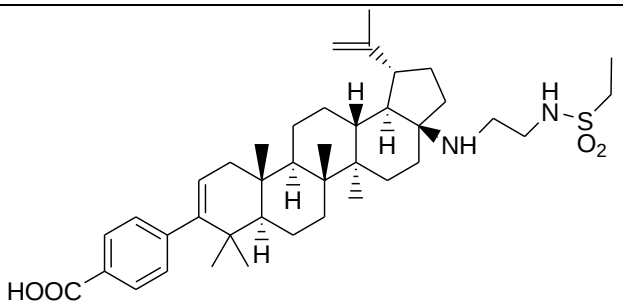
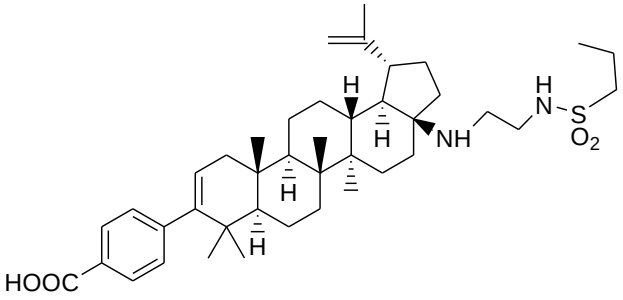
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B12		A

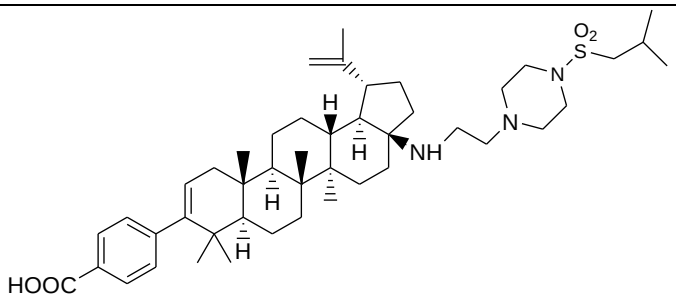
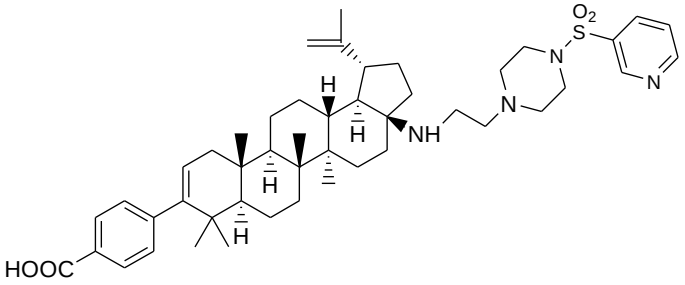
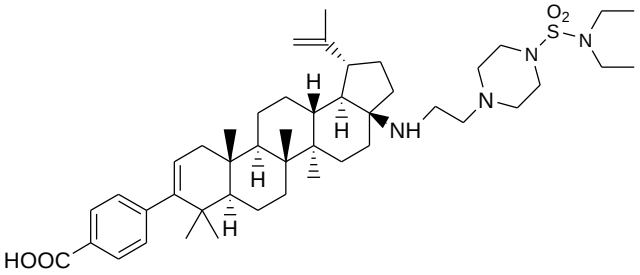
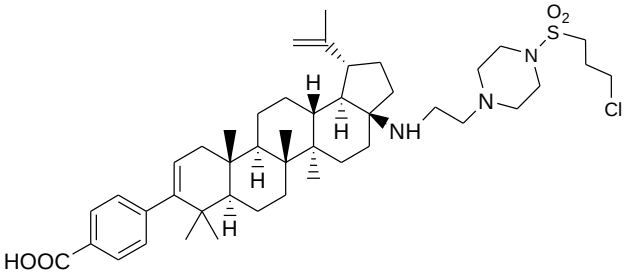
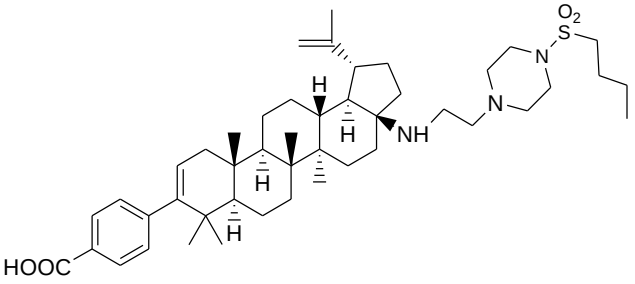
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B16		A

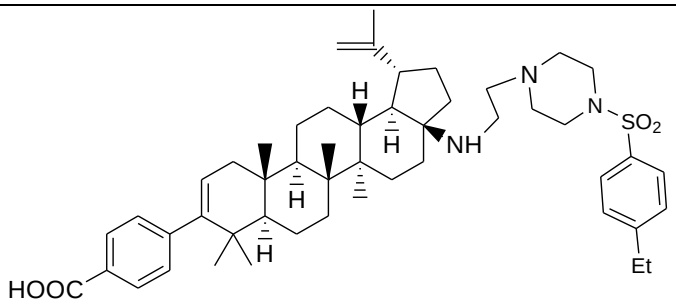
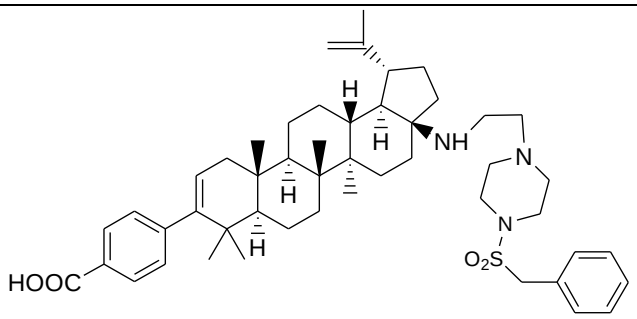
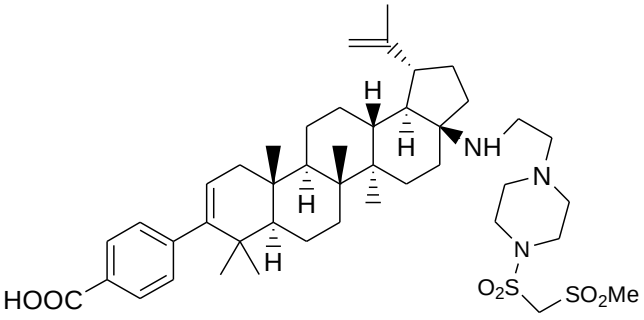
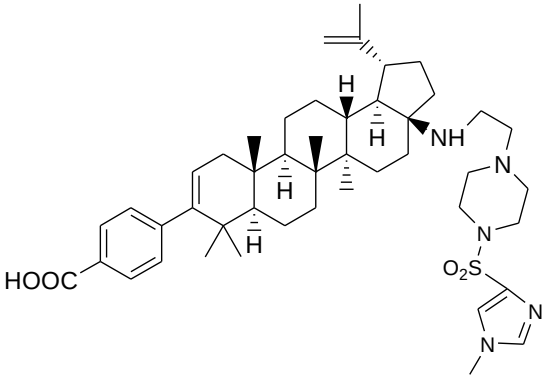
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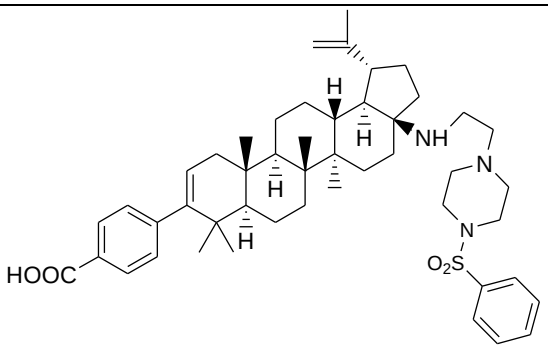
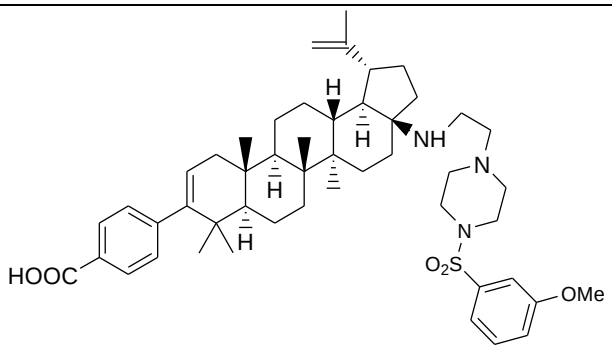
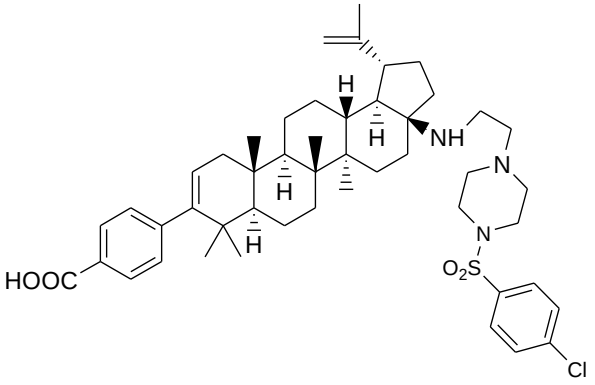
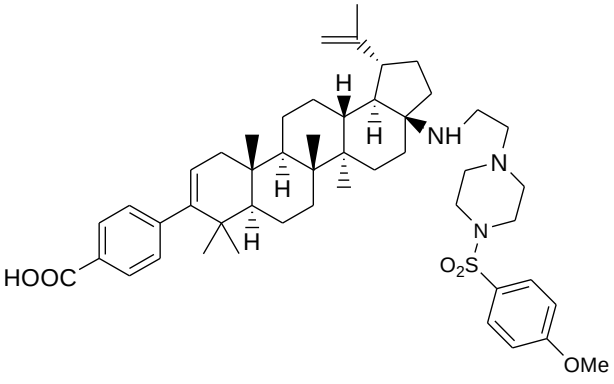
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B24		A
B25	+	A

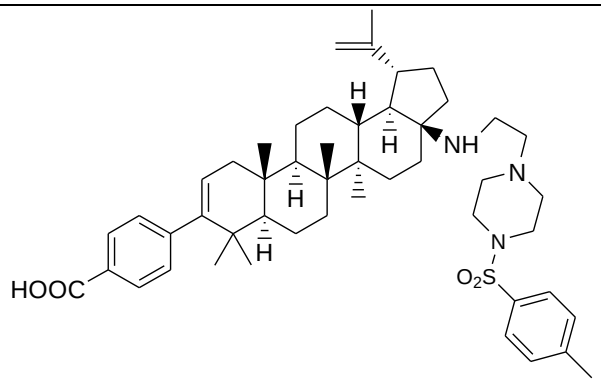
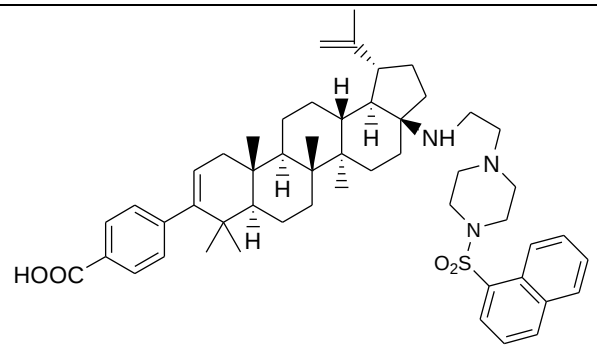
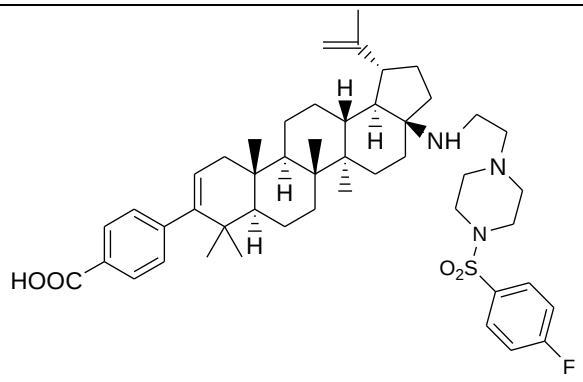
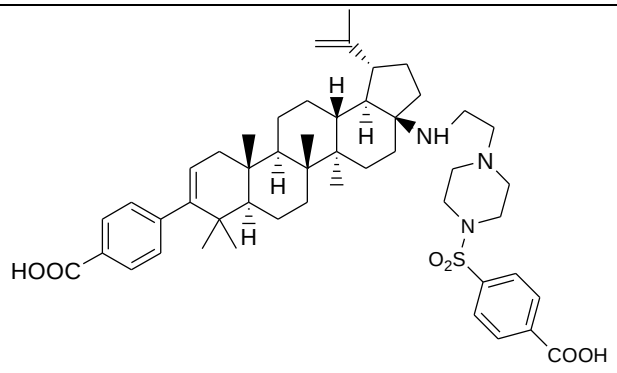
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B30		A

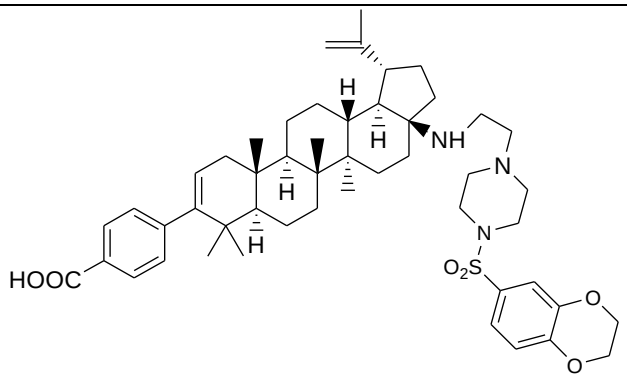
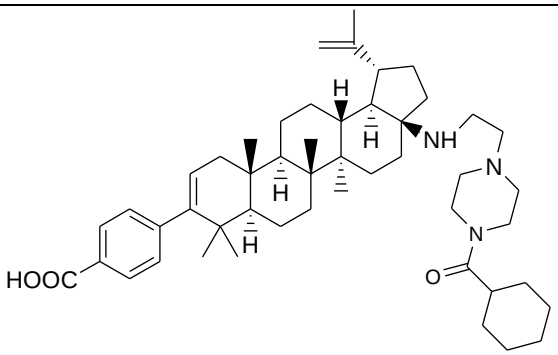
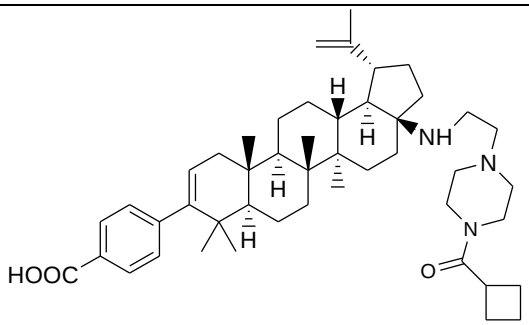
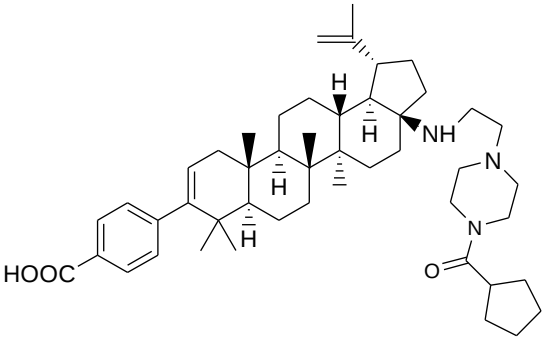
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B34		A

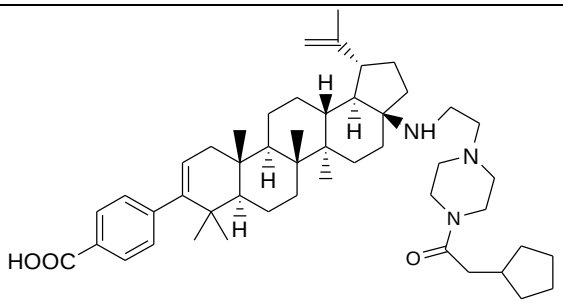
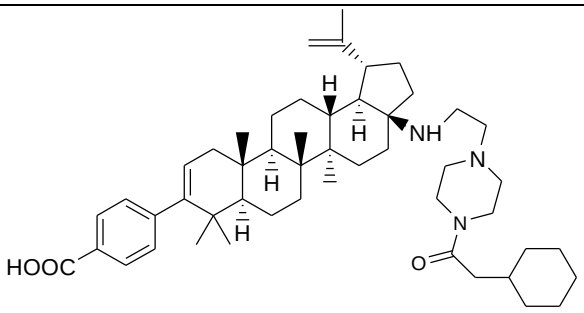
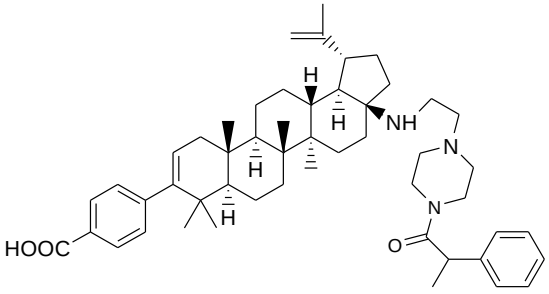
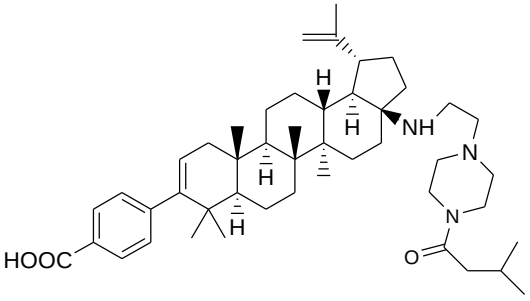
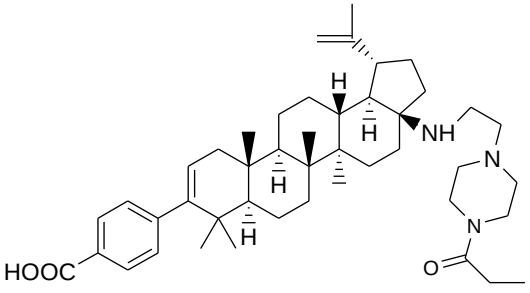
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B39		A

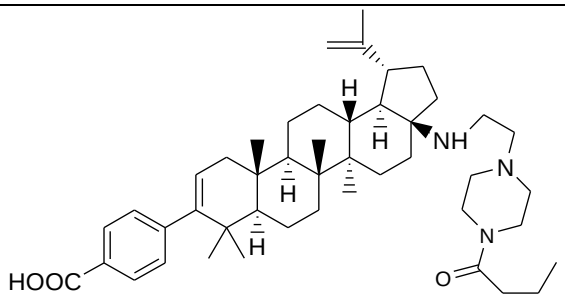
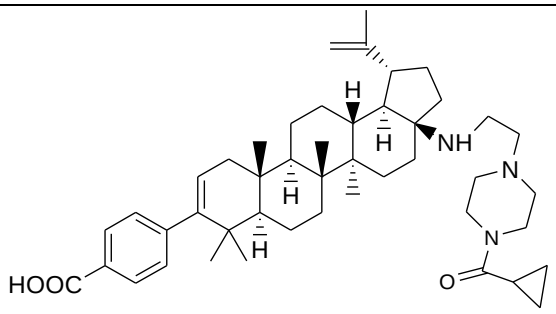
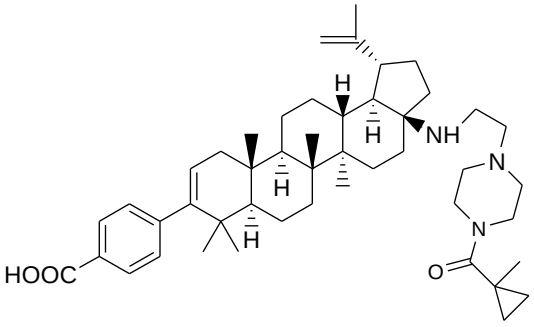
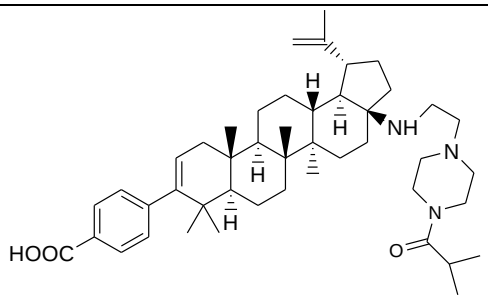
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B43		A

B44		A
B45		0.004
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B47		A

B48		A
B49		A
B50		A
B51		A

B52		A
B53		A
B54		A
B55		A

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B64		A

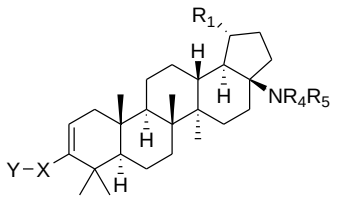
La descripción anterior es meramente ilustrativa y no debe interpretarse como que limita de modo alguno el alcance o los principios de la invención. De hecho, varias modificaciones de la invención, además de las que se muestran y describen en la presente serán evidentes para los expertos

en el arte, de acuerdo con los siguientes ejemplos y la descripción anterior. También se pretende que tales modificaciones se encuentren dentro del alcance de las reivindicaciones adjuntas.

REIVINDICACIONES

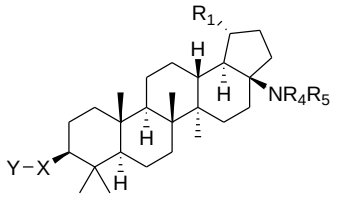
1. Un compuesto, que incluye sales de este farmacéuticamente aceptables, caracterizado porque se selecciona del grupo que consiste en:

un compuesto de la Fórmula I



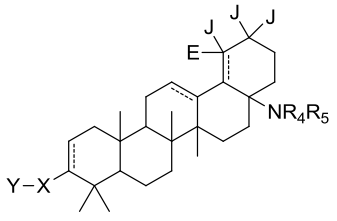
Fórmula I ;

un compuesto de la Fórmula II



Fórmula II ; y

un compuesto de la Fórmula III



Fórmula III ;

en donde R_1 es isopropenilo o isopropilo;

J y E son –H o $-CH_3$, y E está ausente cuando el enlace doble está presente;

X es un anillo de fenilo o heteroarilo sustituido con A, en donde A es, al menos, un elemento seleccionado del grupo de -H, -halo, -hidroxilo, -alquilo C_{1-6}, -alcoxi C_{1-6} y -$COOR_2$;

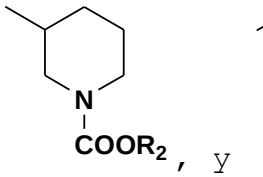
R_2 es -H, -alquilo C_{1-6}, alquilo C_{1-6} sustituido con -alquilo o alquilo C_{1-6} sustituido con -arilo;

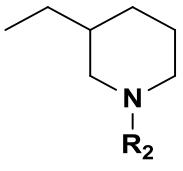
Y se selecciona del grupo de $-COOR_2$, $-C(O)NR_2SO_2R_3$, $C(O)NHSO_2NR_2R_2$, $-NR_2SO_2R_2$, $-SO_2NR_2R_2$, -cicloalquilo C_{3-6}-$COOR_2$, -alquenilo C_{2-6}-$COOR_2$, -alquinilo C_{2-6}-$COOR_2$, -alquilo C_{1-6}-$COOR_2$, $-NHC(O)(CH_2)_n$-$COOR_2$, $-SO_2NR_2C(O)R_2$, -tetrazol y $-CONHOH$,

en donde n= 1-6;

R_3 es -alquilo C_{1-6} o alquilo C_{1-6} sustituido con -alquilo;

R_4 se selecciona del grupo de -H, -alquilo C_{1-6}, -alquilo C_{1-6}-$C(OR_3)_2$-cicloalquilo C_{3-6}, -alquilo C_{1-6} sustituido, -alquilo C_{1-6}-cicloalquilo C_{3-6}, -alquilo C_{1-6}-Q_1, -alquilo C_{1-6}-cicloalquilo C_{3-6}-Q_1, arilo, heteroarilo, heteroarilo sustituido, $-COR_6$, $-COCOR_6$, $-SO_2R_7$, $-SO_2NR_2R_2$,



, y


;

en donde Q_1 se selecciona del grupo de heteroarilo, heteroarilo sustituido, halógeno, $-CF_3$, $-OR_2$, $-COOR_2$, $-NR_8R_9$, $-CONR_{10}R_{11}$ y $-SO_2R_7$;

R_5 se selecciona del grupo de -H, -alquilo C_{1-6}, -

cicloalquilo C_{3-6}, -alquilo C_{1-6} sustituido con alquilo, -alquilo C_{1-6}-NR_8R_9, $-COR_{10}$, $-COR_6$, $-COCOR_6$, $-SO_2R_7$ y $-SO_2NR_2R_2$;

siempre que solo uno de R_4 o R_5 se pueda seleccionar del grupo de $-COR_6$, $-COCOR_6$, $-SO_2R_7$ y $-SO_2NR_2R_2$;

o R_4 y R_5 se toman en forma conjunta con el N adyacente para formar



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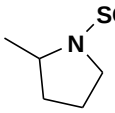
R_6 se selecciona del grupo de -H, -alquilo C_{1-6}, -alquilo C_{1-6} sustituido con alquilo, -cicloalquilo C_{3-6}, -cicloalquilo C_{3-6} sustituido con Q_2, -alquilo C_{1-6}-Q_2, -alquilo C_{1-6} sustituido con alquil-Q_2, -cicloalquilo C_{3-6}-Q_2, aril-Q_2, $-NR_{13}R_{14}$ y $-OR_{15}$;

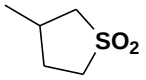
en donde Q_2 se selecciona del grupo de arilo, heteroarilo, heteroarilo sustituido, $-OR_2$, $-COOR_2$, $-NR_8R_9$, SO_2R_7, $-CONHSO_2R_3$ y $-CONHSO_2NR_2R_2$;

R_7 se selecciona del grupo de -alquilo C_{1-6}, -alquilo C_{1-6} sustituido, -cicloalquilo C_{3-6}, arilo y heteroarilo;

R_8 y R_9 se seleccionan independientemente del grupo de -H, -alquilo C_{1-6}, -alquilo C_{1-6} sustituido, arilo, heteroarilo, arilo sustituido, heteroarilo sustituido, -alquilo C_{1-6}-Q_2 y $-COOR_3$,

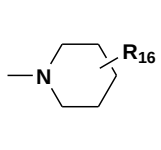
y R_8 y R_9 también se pueden seleccionar independientemente del siguiente grupo:

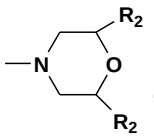


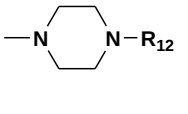
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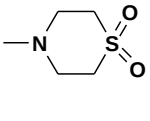
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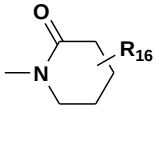
o R_8 y R_9 se toman en forma conjunta con el N adyacente para formar un ciclo seleccionado del siguiente grupo:

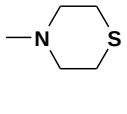


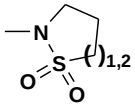
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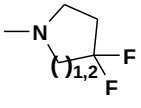
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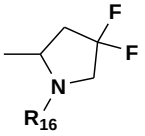
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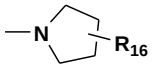
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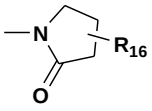
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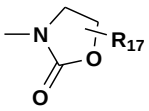
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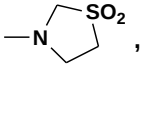
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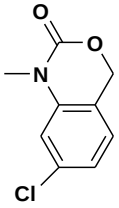
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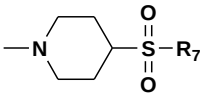
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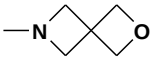
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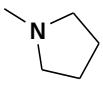
and
y


,

siempre que solo uno de R_8 o R_9 pueda ser $-COOR_3$;

R_{10} y R_{11} se seleccionan independientemente del grupo de -H, -alquilo C_{1-6}, -alquilo C_{1-6} sustituido y -cicloalquilo C_{3-6},

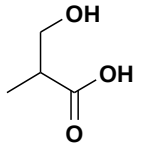
o R_{10} y R_{11} se toman en forma conjunta con el N adyacente para formar un ciclo, tal como



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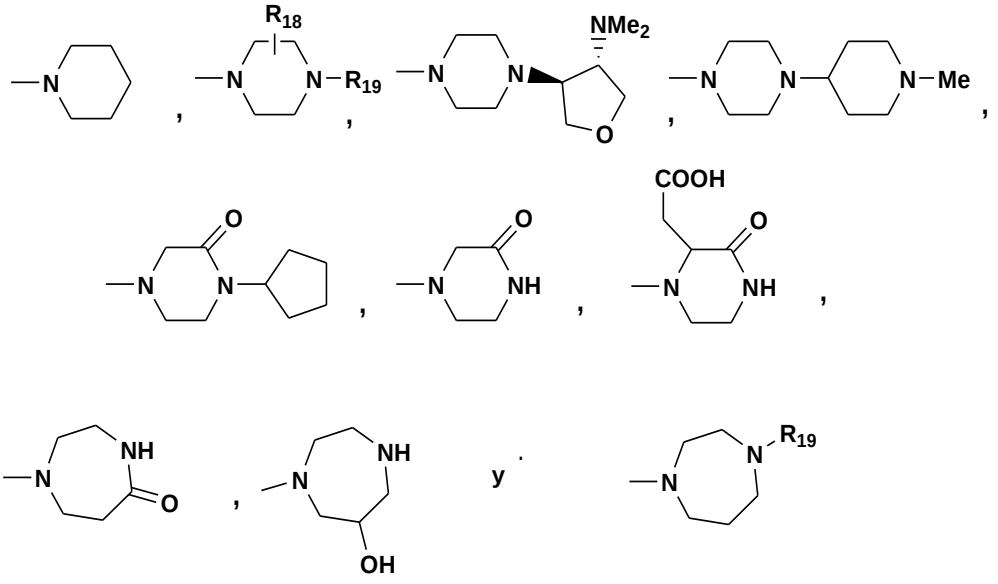
R_{12} se selecciona del grupo de -alquilo C1-6, $-NR_2R_2$, -alquilo C_{1-6}-OH, -alquilo C_{1-6}, -alquilo C_{1-6} sustituido, -cicloalquilo C_{3-6}, $-COR_7$, $-COONR_{22}R_{23}$, $-SOR_7$ y $-SONR_{24}R_{25}$;

R_{13} y R_{14} se seleccionan independientemente del grupo de -H, -alquilo C_{1-6}, -cicloalquilo C_{3-6}, -alquilo C_{1-6} sustituido, -alquilo C_{1-6}-Q_3, -alquilo C_{1-6}-cicloalquilo C_{3-6}-Q_3, alquilo C_{1-6} sustituido con Q_3 y



,

o R_{13} y R_{14} se toman en forma conjunta con el N adyacente para formar un ciclo seleccionado del siguiente grupo:



;

Q_3 se selecciona del grupo de heteroarilo, heteroarilo sustituido, -$NR_{20}R_{21}$, -$CONR_2R_2$, -$COOR_2$, -OR_2 y -SO_2R_3;

R_{15} se selecciona del grupo de -alquilo C_{1-6}, -cicloalquilo C_{3-6}, -alquilo C_{1-6} sustituido, -alquilo C_{1-6}-Q_3, -alquilo C_{1-6}-cicloalquilo C_{3-6}-Q_3 y -alquilo C_{1-6} sustituido con

Q_3;

R_{16} se selecciona del grupo de -H, -alquilo C_{1-6}, -NR_2R_2 y -$COOR_3$;

R_{17} se selecciona del grupo de -H, -alquilo C_{1-6}, -$COOR_3$ y arilo;

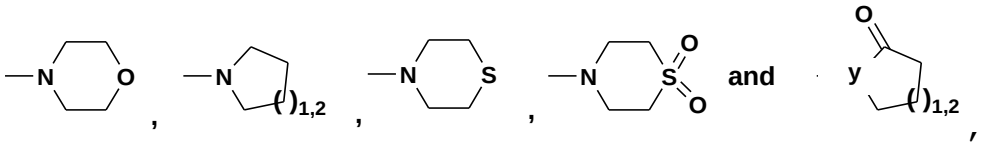
R_{18} se selecciona del grupo de -$COOR_2$ y -alquilo C_{1-6}-$COOR_2$;

R_{19} se selecciona del grupo de -H, -alquilo C_{1-6}, -alquilo C_{1-6}-Q_4, -COR_3, -$COOR_3$,

en donde Q_4 se selecciona del grupo de -NR_2R_2 y -OR_2;

R_{20} y R_{21} se seleccionan independientemente del grupo de -H, -alquilo C_{1-6}, -alquilo C_{1-6} sustituido, -alquilo C_{1-6} sustituido con OR_2 y -COR_3,

o R_{20} y R_{21} se toman en forma conjunta con el N adyacente para formar un ciclo seleccionado del siguiente grupo:

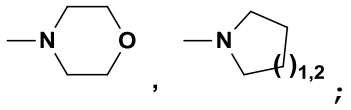


siempre que solo uno de R_{20} o R_{21} pueda ser -COR_3;

R_{22} y R_{23} se seleccionan independientemente del grupo de H, -alquilo C_{1-6}, -alquilo C_{1-6} sustituido y -cicloalquilo C_{1-6},

o R_{22} y R_{23} se toman en forma conjunta con el N

adyacente para formar un ciclo seleccionado del siguiente grupo:



R_{24} y R_{25} se seleccionan independientemente del grupo de H, -alquilo C_{1-6}, -alquilo C_{1-6} sustituido, -alquilo C_{1-6}-Q_5, -cicloalquilo C_{1-6}, arilo, arilo sustituido, heteroarilo y heteroarilo sustituido,

y Q_5 se selecciona del grupo de halógeno y SO_2R_3.

2. El compuesto de conformidad con la reivindicación 1, caracterizado porque tal compuesto tiene la Fórmula I.

3. El compuesto de conformidad con la reivindicación 1, caracterizado porque tal compuesto tiene la Fórmula II.

4. El compuesto de conformidad con la reivindicación 1, caracterizado porque tal compuesto tiene la Fórmula III.

5. El compuesto de conformidad con la reivindicación 2, caracterizado porque R_1 es isopropenilo.

6. El compuesto de conformidad con la reivindicación 5, caracterizado porque X es fenilo.

7. El compuesto de conformidad con la reivindicación 6, caracterizado porque Y es $-COOR_2$.

8. El compuesto de conformidad con la

reivindicación 7, caracterizado porque Y es –COOH.

9. El compuesto de conformidad con la reivindicación 6, caracterizado porque A es –H.

10. El compuesto de conformidad con la reivindicación 6, caracterizado porque R_4 se selecciona del grupo de –H, -alquilo C_{1-6}, -alquilo C_{1-6}-Q_1 y –COR_6.

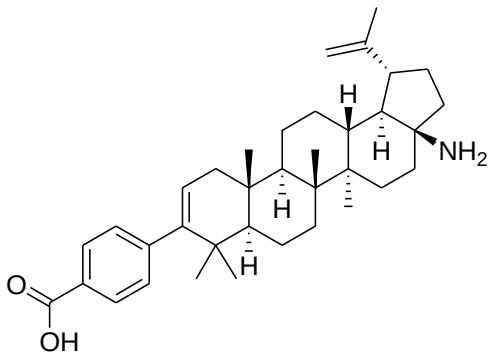
11. El compuesto de conformidad con la reivindicación 10, caracterizado porque R_5 es –H.

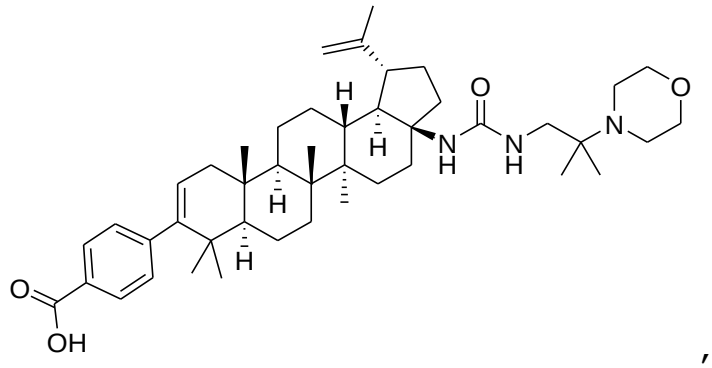
12. El compuesto de conformidad con la reivindicación 10, caracterizado porque R_4 –alquilo C_{1-6}-Q_1.

13. El compuesto de conformidad con la reivindicación 12, caracterizado porque Q_1 es –NR_8R_9.

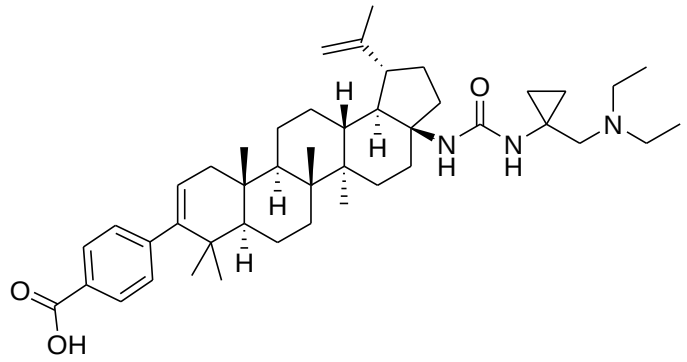
14. El compuesto de conformidad con la reivindicación 10, caracterizado porque R_4 es –COR_6.

15. Un compuesto, que incluye sales de este farmacéuticamente aceptables, caracterizado porque se selecciona del grupo que consiste en:

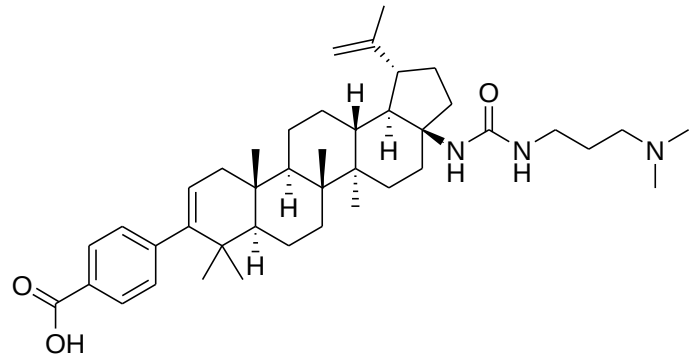




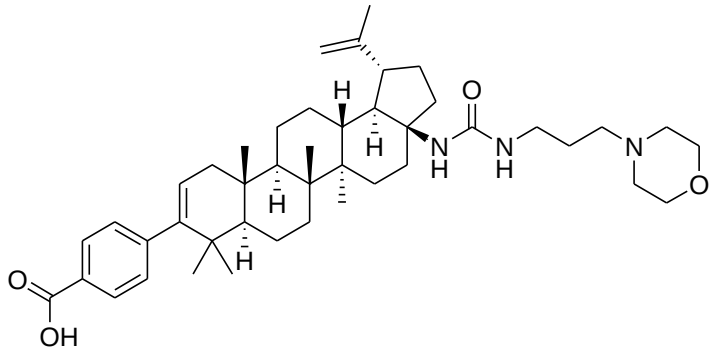
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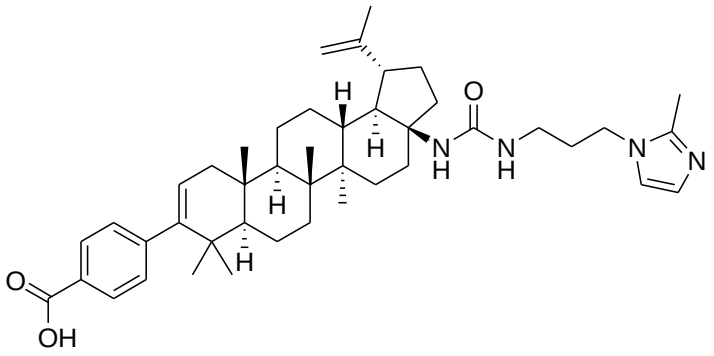
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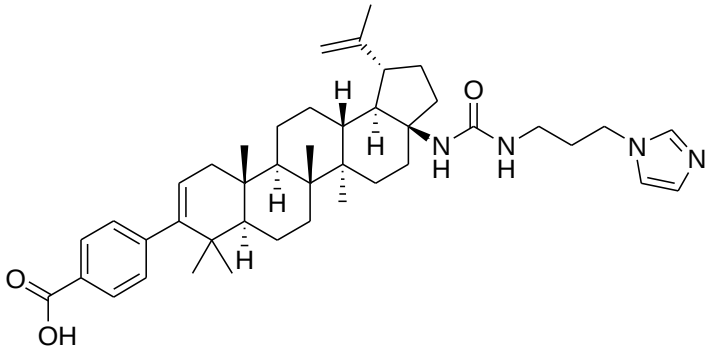
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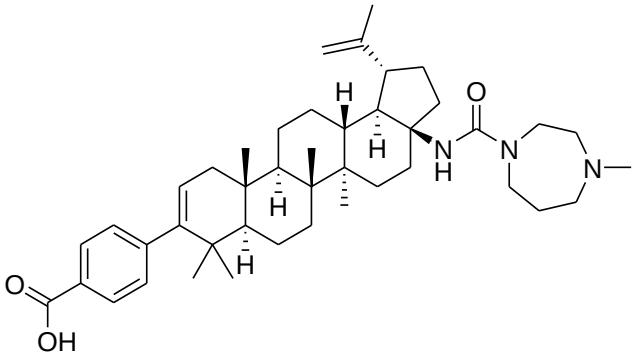
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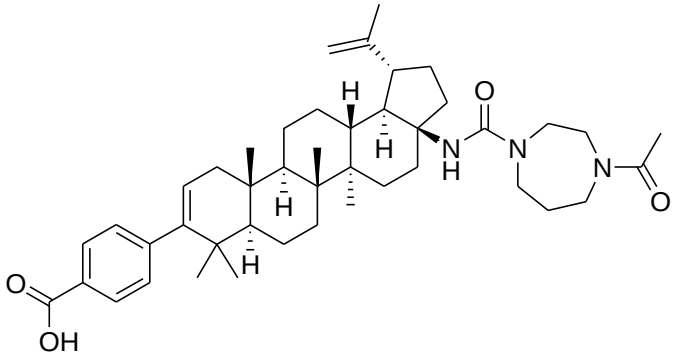
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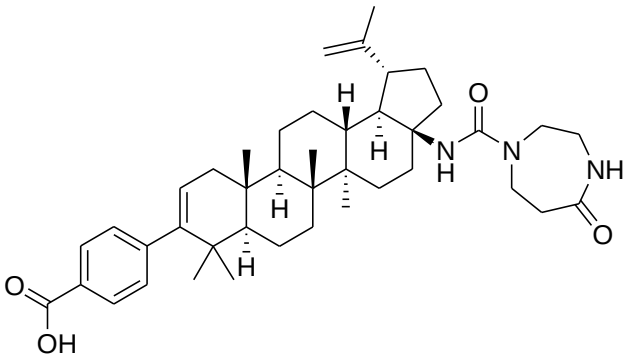
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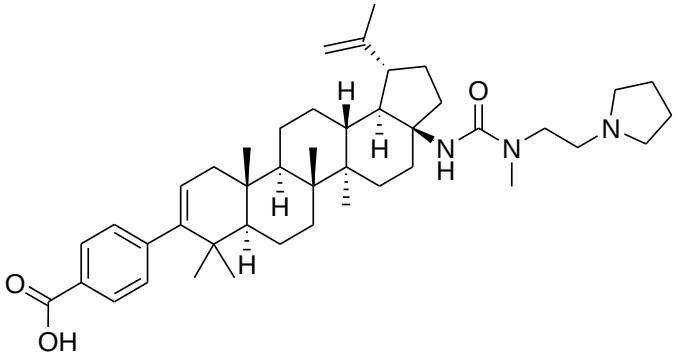
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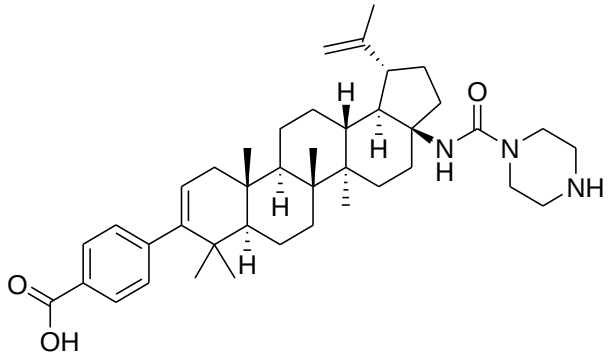
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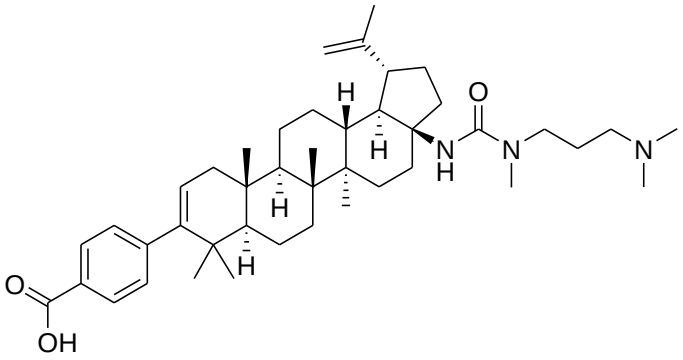
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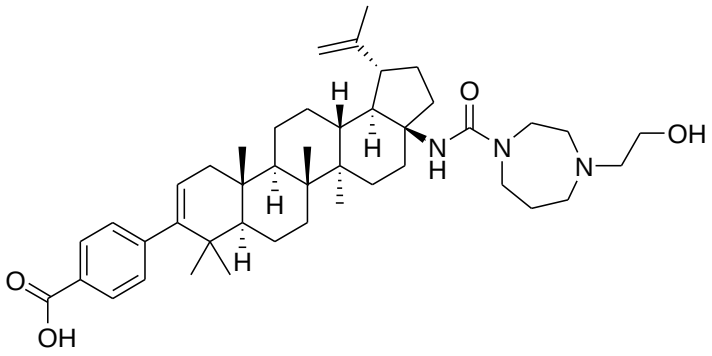
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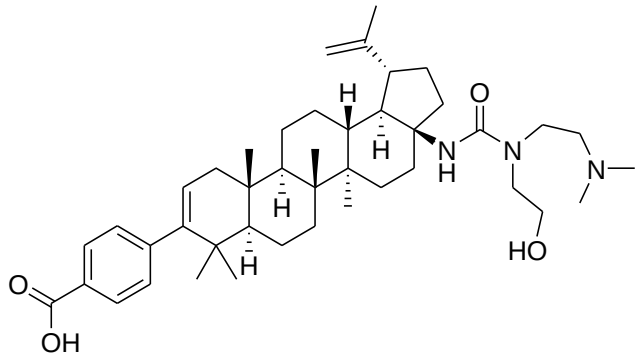
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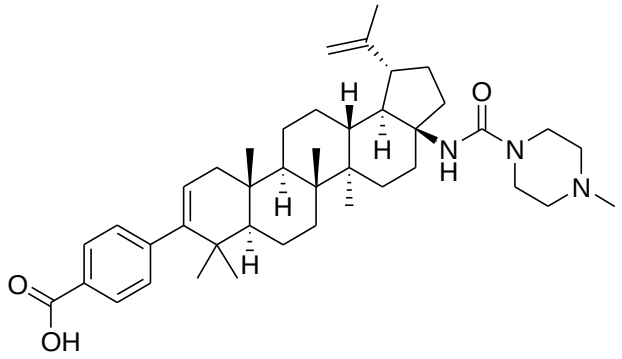
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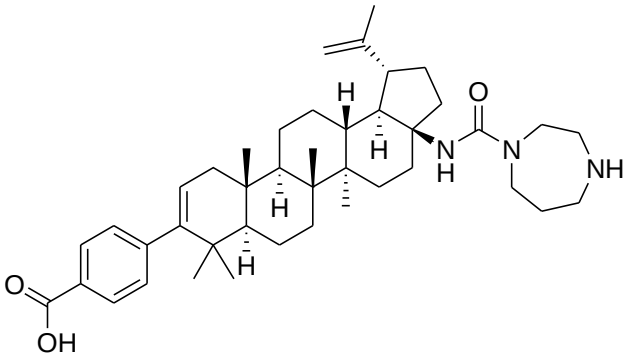
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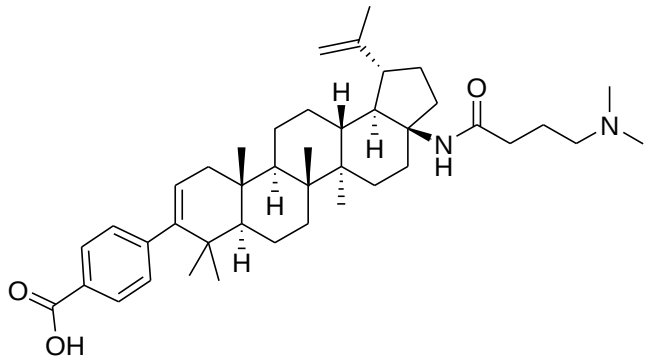
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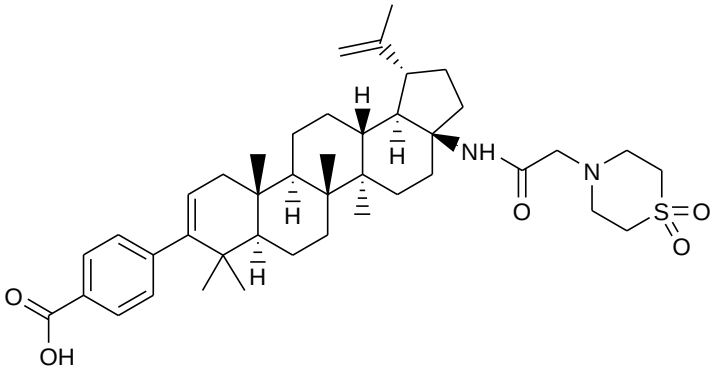
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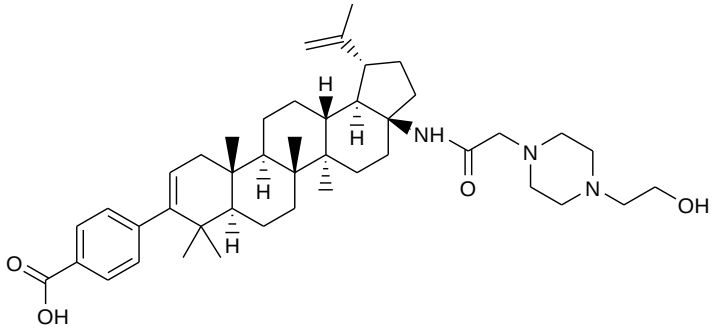


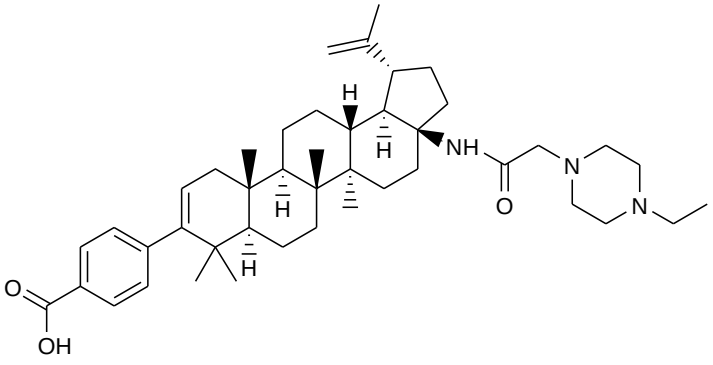
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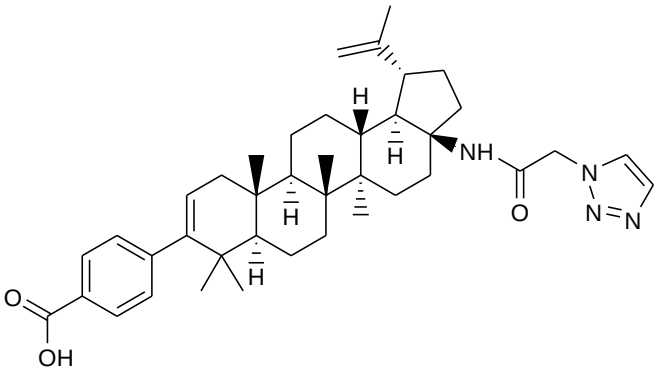
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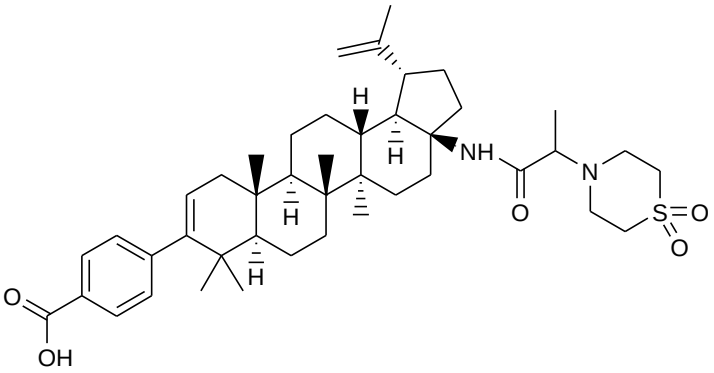




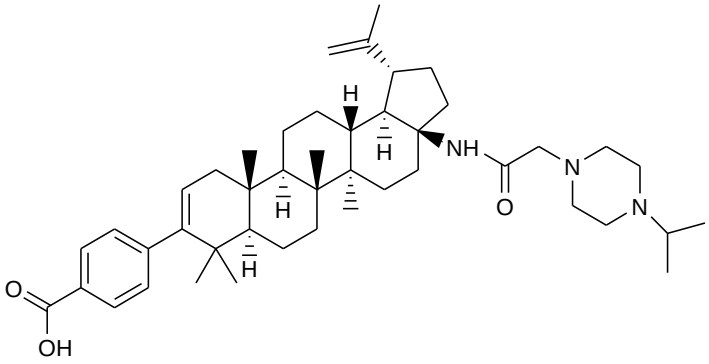


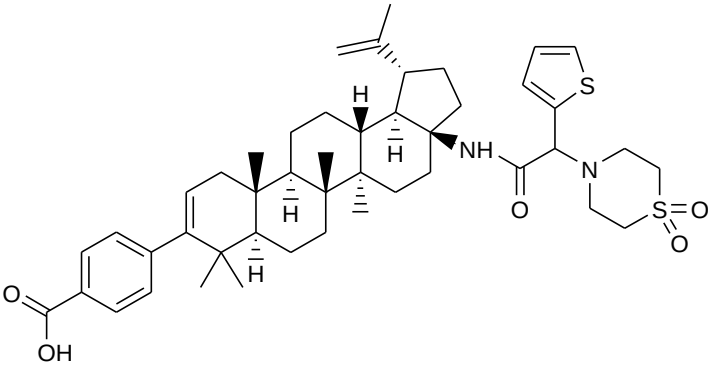
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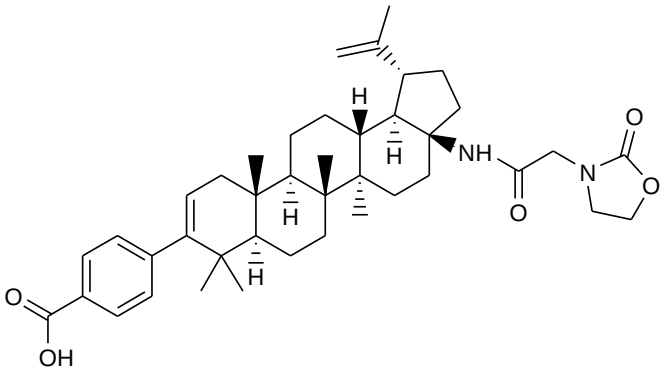


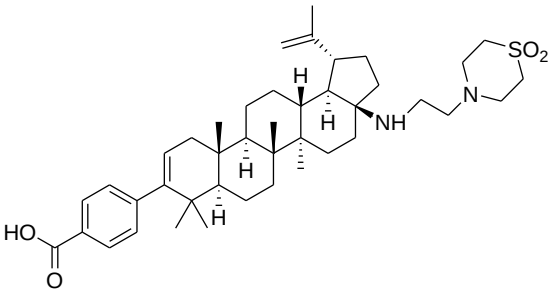


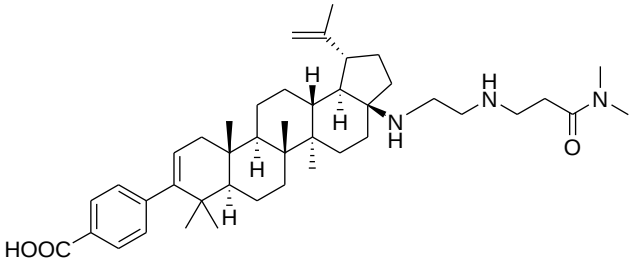
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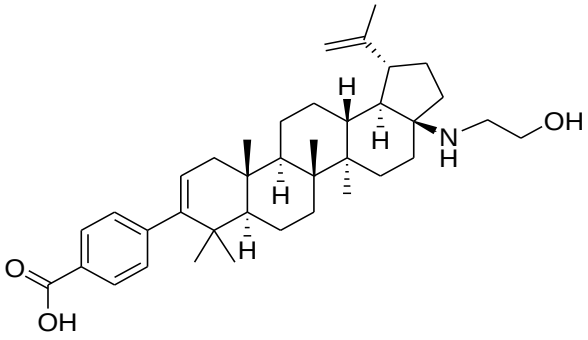


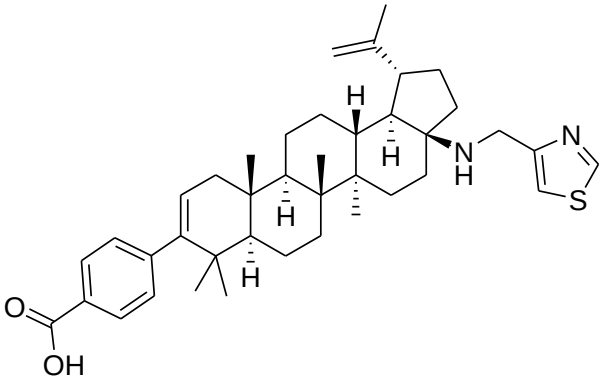


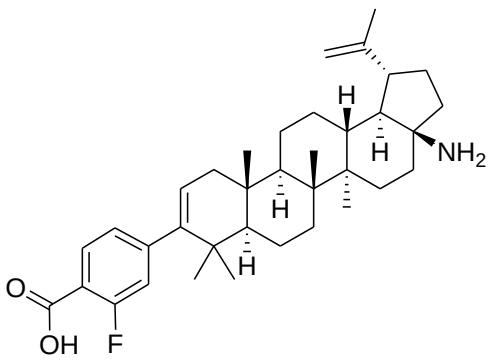


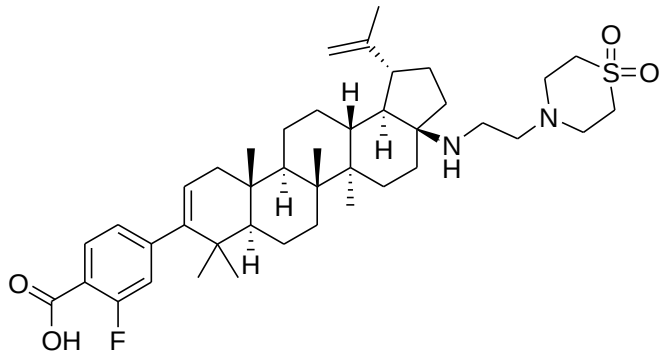




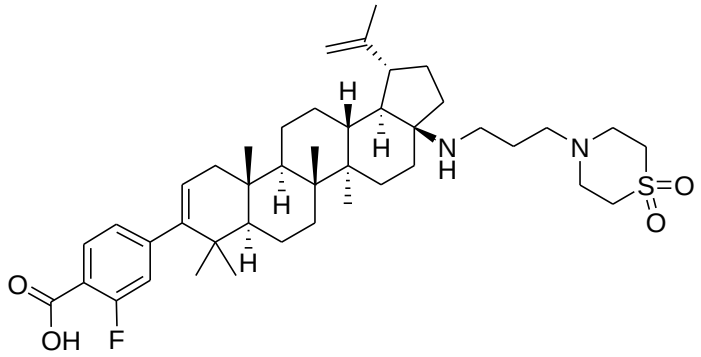






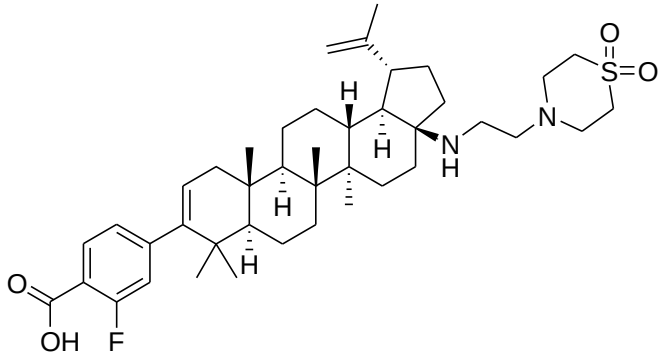


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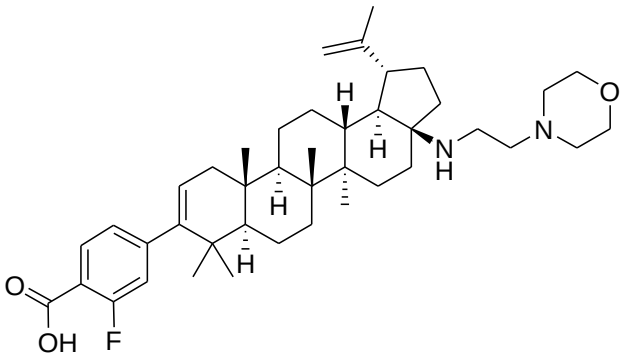


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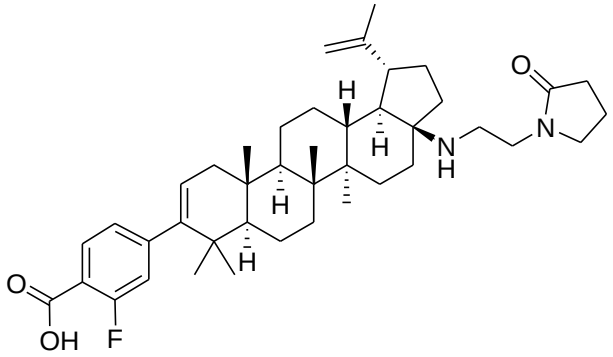
16. Un compuesto, que incluye sales de este farmacéuticamente aceptables, caracterizado porque se selecciona del grupo que consiste en:



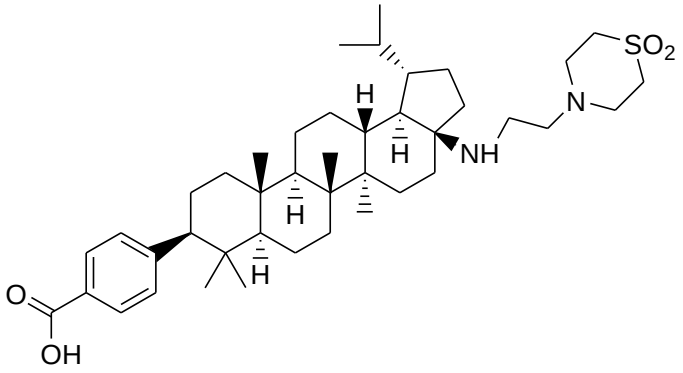
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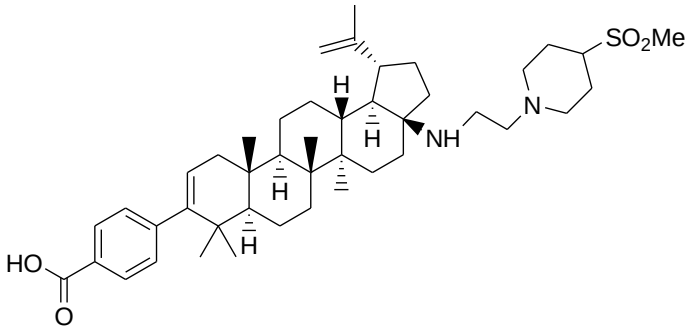
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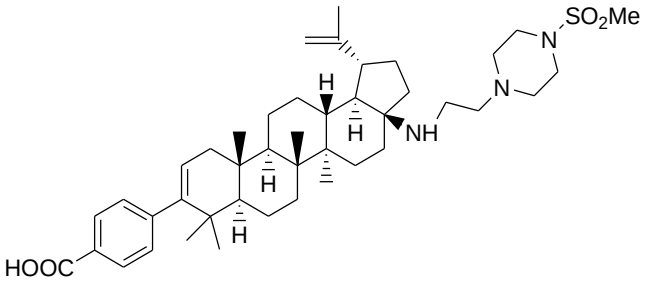
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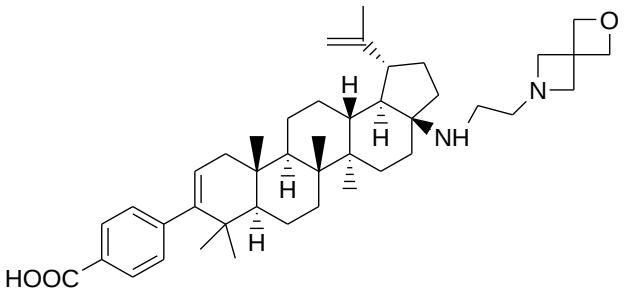
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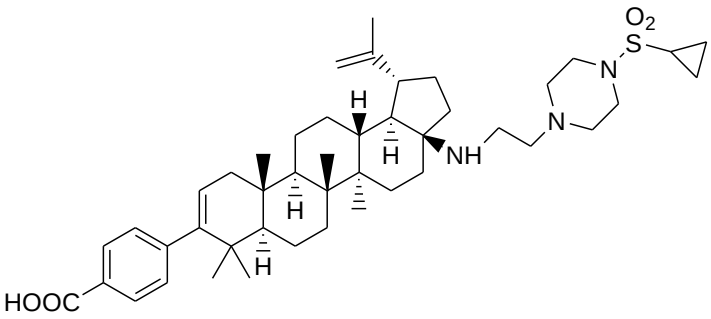


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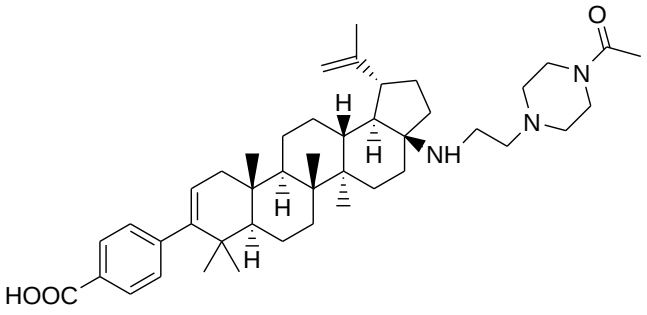

SO2Me
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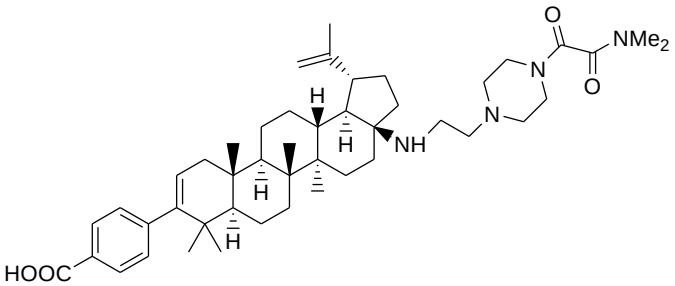

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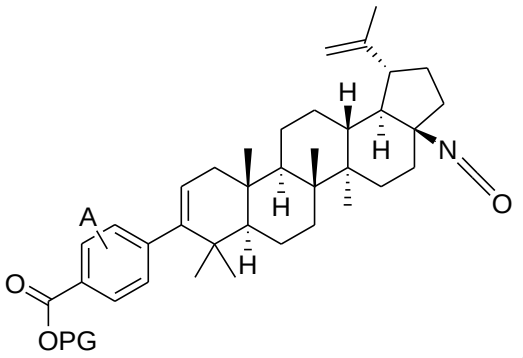
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17. Una composición farmacéutica caracterizada porque comprende una cantidad eficaz antiviral de uno o más de los compuestos de conformidad con la reivindicación 1, junto con uno o más portadores, excipientes o diluyentes farmacéuticamente aceptables.

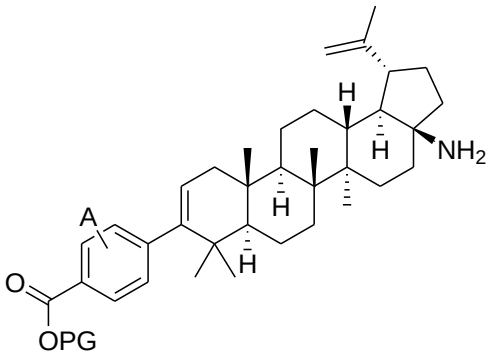
18. La composición farmacéutica de conformidad con la reivindicación 17, útil para tratar la infección por VIH, caracterizada porque también comprende una cantidad eficaz antiviral de un agente para el tratamiento del SIDA seleccionado del grupo que consiste en: (a) un agente antiviral del SIDA; (b) un agente antiinfeccioso; (c) un inmunomodulador; y (d) otro inhibidor de la entrada del VIH.

19. Uso de un compuesto de conformidad con la reivindicación 1 y uno o más portadores, excipientes o diluyentes farmacéuticamente aceptables para preparar un medicamento para el tratamiento de un mamífero infectado con el virus VIH.

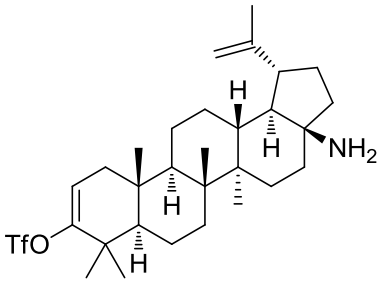
20. Un compuesto intermediario caracterizado porque se selecciona del siguiente grupo:



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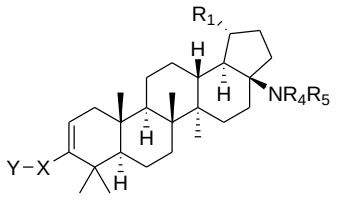
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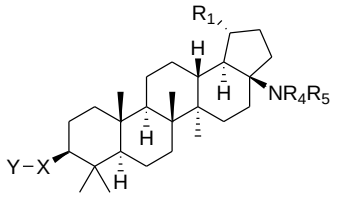
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RESUMEN DE LA INVENCIÓN

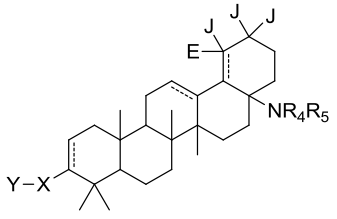
La presente invención se refiere a compuestos que tienen propiedades farmacológicas y que afectan el aspecto biológico, sus composiciones farmacéuticas y métodos de uso. En particular, los triterpenoides C-17 y C-3 modificados que tienen una actividad antiviral única se proporcionan como inhibidores de la maduración del VIH, como se representa mediante los compuestos de las Fórmulas I, II y III:



Fórmula I ;



Fórmula II ; y



Fórmula III .

Estos compuestos son útiles para el tratamiento del VIH y del SIDA.