SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 14-124179- -00000-0000

Fecha: 2014-06-09 16:47:39 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 8

Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

SOLICITUD
PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** _____

54. **TÍTULO** INHIBIDORES DE ACC Y USOS DE LOS MISMOS

51. **CLASIFICACIÓN INTERNACIONAL** _____

71. **SOLICITANTE** NIMBUS APOLLO, INC.

DOMICILIO CAMBRIDGE, ESTADOS UNIDOS.

74. **APODERADO** ALVARO CORREA.

22. **BOGOTÁ, D.C.,** 9 DE JUNIO DE 2014

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO — radicación
No. 14-124179- -00000-0000
Fecha: 2014-06-09 16:47:39 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 8

DIRECCIÓN DE NUEVAS CREACIONES
SOLICITUD FASE NACIONAL -PCT

1 TIPO DE SOLICITUD

☒ Patente de invención ☐ Patente de Modelo de Utilidad
☒ Capítulo I ☐ Capitulo II

2 DATOS SOLICITUD INTERNACIONAL PCT (86)

Solicitud Internacional No.	PCT/US2012/064528	**Fecha**	09/11/2012
Publicación Internacional No.	WO2013/071169	**Fecha**	16/05/2013

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

INHIBIDORES DE ACC Y USOS DE LOS MISMOS

4 CLASIFICACIÓN INTERNACIONAL (CIP)

A61K 31/519 (2006.01); A61K 31/38 (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. NIMBUS APOLLO, INC.			

6 DATOS DEL SOLICITANTE

DIRECCIÓN	25 First Street, Suite 404 Cambridge, MA 02141	No. TELÉFONO	6341500
CIUDAD	Cambridge	CORREO ELECTRÓNICO	Alvaro.correa@bakermckenzie.com
DEPARTAMENTO/ESTADO	Massachusetts	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. HARRIMAN,	Geraldine, C.	Estados Unidos de América
2. MASSE,	Craig, E.	Estados Unidos de América
3. HARWOOD,	James;	Estados Unidos de América
4. BHAT,	Sathesh;	Estados Unidos de América
5. GREENWOOD,	Jeremy, Robert;	Estados Unidos de América

DIRECCIÓN DE CORREO ELECTRÓNICO:

8 DATOS INVENTOR (ES)

PAÍS RESIDENCIA	DEPARTAMENTO/ESTADO	CIUDAD	DIRECCIÓN
1. Estados Unidos de América	Rhode Island	Charlestown	50 South Arlonda Road Charlestown, RI 02813
2. Estados unidos de América	Massachusetts	Cambridge	122 Hamilton Street Cambridge, MA 02139
3. Estados Unidos de América	Connecticut	Ledyard	10 Eska Drive Ledyard, CT 06339
4. Estados Unidos de América	Nueva York	West New York	55 Riverwalk Place, Apt. 943 West New York, NY 07093
5. Estados Unidos de América	Nueva York	Brooklyn	338 Prospect Place Brooklyn, NY 11238

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	Alvaro	C.C . 79.143.366	T.P . 20.281

DIRECCIÓN	Av. 82 No. 10-62 Piso 5	No. TELÉFONO	6341500
CIUDAD	Bogotá	CORREO ELECTRÓNICO	Alvaro.correa@bakermckenzie.com
PAÍS	Colombia	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	61/559,023	11/11/2011
2. Estados Unidos de América	US	61/615,092	23/03/2012
3. Estados Unidos de América	US	61/651,878	25/05/2012
4. Estados Unidos de América	US	61/675,513	25/07/2012

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° 14-0050034	Fecha 12-05-2014

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:
2. ☒ Reivindicaciones — N° Reivindicaciones: 20
3. ☒ Dibujos y/o figuras — N° folios:

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.

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 14 - 0050034

Bogotá D.C., Mayo 12 de 2014 - 16:37:13

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	587975964	08/05/2014	122.746.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCION	515.000.00	515.000.00
				$515.000.00

SON: **QUINIENTOSQUINCE MIL PESOS MONEDA CORRIENTE***

Responsable: _____
-**-

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 14-124179- -00000-0000

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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) N° de solicitud:

22) Fecha de solicitud:

(30) Prioridad

(31) *No.*	32) *Fecha*	(33) *País*
61/651,878	25/05/2011	US
61/615,092	23/03/2012	US
61/559,023	11/11/2011	US
61/675,513	25/07/2012	US

(51) Int Cl:

(71)Solicitante(s) NIMBUS APOLLO, INC.

(72) Inventor(es): HARRIMAN, Geraldine, C.
MASSE, Craig, E.
HARWOOD, James
BHAT, Sathesh
GREENWOOD, Jeremy, Robert

(74) Apoderado: ALVARO CORREA ORDOÑEZ

(85) Fecha limite inicio fase nacional: 11/06/2014

(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 09/11/2012
No. de solicitud PCT/US2012/064528

(87) Publicación internacional
Fecha: 16/05/2013
N° publicación: WO2013/071169

(54) Titulo: INHIBIDORES DE ACC Y USOS DE LOS MISMOS

Resumen: La presente invención proporciona compuestos, específicamente derivados de tienopirimidina útiles como inhibidores de acetil CoA carboxilasa (ACC), composiciones farmacéuticas de los mismos y métodos de uso de los mismos para tratar trastornos mediados por ACC tales como obesidad, dislipidemia, hiperlipidemia, infecciones micóticas, parasitarias o bacterianas en un sujeto. La invención proporciona a demás un método para inhibir ACC en una planta que comprende poner en contacto a la planta con el compuesto inhibidor.

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)
NIMBUS APOLLO, INC.

(72) Inventor(es)
HARRIMAN, Geraldine, C.; MASSE, Craig, E.; HARWOOD, James.; BHAT, Sathesh.; GREENWOOD, Jeremy, Robert.;

(74) Apoderado: ALVARO CORREA ORDOÑEZ

(30) Prioridad	(31) *No. Prioridad*	32) *Fecha*	(33) *País*
	61/651,878	25/05/2012	US
	61/615,092	23/03/2012	US
	61/559,023	11/11/2011	US
	61/675,513	25/07/2012	US

(85) Fecha inicio fase nacional: 11/06/2014
(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 09/11/2012
No. de solicitud PCT/US2012/064528

(87) Publicación internacional
Fecha: 16/05/2013
N° publicación: WO2013/071169

(54) Titulo: INHIBIDORES DE ACC Y USOS DE LOS MISMOS

Industria y Comercio
SUPERINTENDENCIA

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

PATENTE DE INVENCIÓN ___ PCT _X_ MODELO DE UTILIDAD ___ DISEÑO INDUSTRIAL ___

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

(71)Solicitante(s)
NIMBUS APOLLO, INC.

(72) Inventor(es)
HARRIMAN, Geraldine, C.; MASSE, Craig, E.; HARWOOD, James.; BHAT, Sathesh.; GREENWOOD, Jeremy, Robert.;

(74) Apoderado: ALVARO CORREA ORDOÑEZ

(30) Prioridad

(31) *No. Prioridad*	(32) *Fecha*	(33) *País*
61/651,878	25/05/2012	US
61/615,092	23/03/2012	US
61/559,023	11/11/2011	US
61/675,513	25/07/2012	US

(85) Fecha límite inicio fase nacional: 11/06/2014
(86) Datos relativos a la presentación de la solic. PCT
Fecha de presentación de la solicitud: 09/11/2012
No. de solicitud PCT/US2012/064528

(87) Publicación internacional:
Fecha: 16/05/2013
No. Publicación : WO2013/071169

(54) Titulo: INHIBIDORES DE ACC Y USOS DE LOS MISMOS

(57) Resumen: La presente invención proporciona compuestos, específicamente derivados de tienopirimidina útiles como inhibidores de acetil CoA carboxilasa (ACC), composiciones farmacéuticas de los mismos y métodos de uso de los mismos para tratar trastornos mediados por ACC tales como obesidad, dislipidemia, hiperlipidemia, infecciones micóticas, parasitarias o bacterianas en un sujeto. La invención proporciona además un método para inhibir ACC en una planta que comprende poner en contacto a la planta con el compuesto inhibidor.

CONTINUA AL RESPALDO ...

FC

Industria y Comercio
SUPERINTENDENCIA

PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA
RELACIÓN DE ANEXOS

Dependencia:	Fecha: AAAA / MM / DD	Recorrido:
2020	14 / 6 / 9	4

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

Radicador: | Planilla:

ID	No. Radicación	Consecutivo	Item
1	14-124179	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 1
8	Disquete
9	DVD
10	Folleto
11	Foto
12	Periódico
13	Plano
14	Publicación Periódica
15	USB
16	Otro

Observaciones:
El cd anexo contiene un total de 3 Archivos: 3 en formato PDF, los cuales fueron procesados en el folio 8

Claudia G

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 May 2013 (16.05.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/071169 A1

(51) **International Patent Classification**:
A61K 31/519 (2006.01) *A61K 31/38* (2006.01)

(21) **International Application Number**:
PCT/US2012/064528

(22) **International Filing Date**:
9 November 2012 (09.11.2012)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:

61/559,023	11 November 2011 (11.11.2011)	US
61/615,092	23 March 2012 (23.03.2012)	US
61/651,878	25 May 2012 (25.05.2012)	US
61/675,513	25 July 2012 (25.07.2012)	US

(71) **Applicant**: **NIMBUS APOLLO, INC.** [US/US]; 25 First Street, Suite 404, Cambridge, MA 02141 (US).

(72) **Inventors**: **HARRIMAN, Geraldine, C.**; 50 South Arlonda Road, Charlestown, RI 02813 (US). **MASSE, Craig, E.**; 122 Hamilton Street, Cambridge, MA 02139 (US). **HARWOOD, James**; 10 Eska Drive, Ledyard, CT 06339 (US). **BHAT, Sathesh**; 55 Riverwalk Place, Apt. 943, West New York, NY 07093 (US). **GREENWOOD, Jeremy, Robert**; 338 Prospect Place, Brooklyn, NY 11238 (US).

(74) **Agents**: **ROBIDOUX, Andrea, L.C.** et al.; Choate, Hall & Stewart LLP, Two Intetnational Place, Boston, MA 02110 (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, BN, 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, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Published:

— *with international search report (Art. 21(3))*

WO 2013/071169 A1

(54) **Title**: ACC INHIBITORS AND USES THEREOF

(57) **Abstract**: The present invention provides compounds, specifically thienopyrimidine derivatives, useful as inhibitors of Acetyl CoA Carboxylase (ACC), pharmaceutical compositions thereof, and methods of using the same for treating ACC-mediated disorders such as obesity, dyslipidemia, hyperiipidemia, fungal, parasitic or bacterial infections in a subject. The invention further provides a method of inhibiting ACC in a plant comprising contacting the plant with the inhibitor compound.

ACC INHIBITORS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present invention claims priority to United States provisional patent application serial number 61/559,023, filed November 11, 2011, United States provisional application serial number 61/615,092, filed March 23, 2012, United States provisional patent application serial number 61/651,878, filed May 25, 2012, and United States provisional patent application serial number 61/675,513, filed July 25, 2012, the entirety of each of which is hereby incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] Obesity is a health crisis of epic proportions. The health burden of obesity, measured by quality-adjusted life-years lost per adult, has surpassed that of smoking to become the most serious, preventable cause of death. In the US, about 34% of adults have obesity, up from 31% in 1999 and about 15% in the years 1960 through 1980. Obesity increases the rate of mortality from all causes for both men and women at all ages and in all racial and ethnic groups. Obesity also leads to social stigmatization and discrimination, which decreases quality of life dramatically. The chronic diseases that result from obesity cost the US economy more than $150 billion in weight-related medical bills each year. Furthermore, about half of the obese population, and 25% of the general population, have metabolic syndrome, a condition associated with abdominal obesity, hypertension, increased plasma triglycerides, decreased HDL cholesterol, and insulin resistance, which increases the risk for type-2 diabetes (T2DM), stroke and coronary heart disease. [Harwood, *Expert Opin. Ther. Targets* 9: 267, 2005].

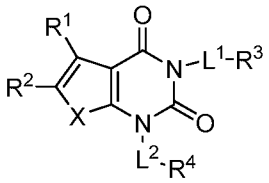
[0003] Diet and exercise, even when used in conjunction with the current pharmacotherapy, do not provide sustainable weight loss needed for long-term health benefit. Currently, only a few anti-obesity drugs are approved in the US, the fat absorption inhibitor orlistat (Xenical®), the 5-HT_{2C} antagonist lorcaserin (Belviq®), and the combination therapy phentermine/topiramate (Qsymia®). Unfortunately, poor efficacy and unappealing gastrointestinal side effects limit the use of orlistat. Surgery can be effective but is limited to patients with extremely high body-bass indices (BMI) and the low throughput of surgery limits the impact of this modality to about 200k patients per year. The majority of obesity drugs in clinical development are designed to reduce caloric intake through central action in

the CNS (e.g., anorectics and satiety agents). However, the FDA has taken an unfavorable position against CNS-active agents, due to their modest efficacy and observed/potential side-effect profiles.

[0004] The continuing and increasing problem of obesity, and the current lack of safe and effective drugs for treating it, highlight the overwhelming need for new drugs to treat this condition and its underlying causes.

SUMMARY OF THE INVENTION

[0005] It has now been found that compounds of this invention, and pharmaceutically acceptable compositions thereof, are effective as inhibitors of Acetyl-CoA carboxylase (ACC). Such compounds have the general formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

[0006] Compounds of the present invention, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with regulation of the production or oxidation of fatty acids. Such diseases, disorders, or conditions include those described herein.

[0007] Compounds provided by this invention are also useful for the study of ACC enzymes in biological and pathological phenomena; the study of intracellular signal transduction pathways occurring in lipogenic tissues; and the comparative evaluation of new ACC inhibitors or other regulators of fatty acid levels *in vitro* or *in vivo*.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts enzyme inhibition curves for compound I-158 against ACC1 and ACC2.

Figure 2 depicts the results of a thermal shift assay of compound I-97.

Figure 3 depicts the results of a thermal shift assay of compounds I-1, I-158, I-174, and Soraphen A.

Figure 4 depicts results of a [^{14}C] Acetate Incorporation HepG2 Cellular Assay for compounds I-158, I-174 and CP640186.

Figure 5 depicts results of a LnCAP cancer cell viability assay for I-158 and Soraphen A.

Figure 6 depicts enzyme inhibition curves for compound I-181 against ACC1 and ACC2 in vitro.

Figure 7 depicts inhibition of fatty acid synthesis in Hep-G2 cells by compound I-181, measured by [^{14}C]-acetate incorporation.

Figure 8 depicts inhibition of fatty acid synthesis in rats by compound I-181, showing an ED_{50} of less than 0.3 mg/kg.

Figure 9 depicts results of a respiratory quotient (RQ) study measuring the ratio of CO_2 production to O_2 consumption in rats, using compound I-181 at doses of 30 and 100 mg/kg bodyweight.

Figure 10 depicts results of a respiratory quotient (RQ) study measuring the ratio of CO_2 production to O_2 consumption in rats, using compound I-181 at doses of 3, 10, and 30 mg/kg bodyweight.

Figure 11 depicts results of a high fat diet-induced obesity (DIO) weight gain experiment, wherein rats were treated with 3, 10, or 30 mg/Kg of I-181.

Figure 12 depicts results of an insulin level reduction experiment, wherein rats on high fat diet-induced obesity (DIO) diet were treated with 3, 10, or 30 mg/Kg of I-181.

Figure 13 depicts results of a hepatic cholesterol and triglyceride measurement experiment, wherein rats on a high fat diet-induced obesity (DIO) diet were treated with 3, 10, or 30 mg/Kg of I-181.

Figure 14 depicts results of an experiment measuring cell death induction in wild type and p53 mutant hepatocellular tumor lines (HepG2 and HepB3) following administration of compound I-246.

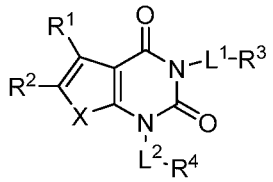
Figure 15 depicts results of an experiment measuring cell death in an androgen-sensitive human prostate adenocarcinoma (LNCaP) tumor line following administration of compound I-159 or Soraphen A.

Figure 16 depicts results of an experiment measuring fatty acid (FA) synthesis in rats following administration of compound I-278. These results show a dose-dependent decrease in FA synthesis.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

1. General Description of Compounds of the Invention:

[0008] In certain embodiments, the present invention provides inhibitors of ACC. In some embodiments, such compounds include those of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

X is –O-, -S-, or –NR-;

R^1 is hydrogen or C_{1-4} aliphatic, optionally substituted with one or more halogen, -OR, -SR, -$N(R)_2$, -N(R)C(O)R, -$C(O)N(R)_2$, -N(R)C(O)$N(R)_2$, -N(R)C(O)OR, -$OC(O)N(R)_2$, -N(R)SO_2R, -$SO_2RN(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -C(O)OR, -S(O)R, or -SO_2R;

R^2 is halogen, -R, -OR, -SR, -$N(R)_2$, -N(R)C(O)R, -$C(O)N(R)_2$, -N(R)C(O)$N(R)_2$, -N(R)C(O)OR, -$OC(O)N(R)_2$, -N(R)SO_2R, -$SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or -SO_2R or Hy, where Hy is selected from 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or

R^1 and R^2 are taken together to form an optionally substituted 4-7 membered partially unsaturated carbocyclo-, or heterocyclo-, benzo-, or 5-6 membered heteroarylo- fused ring;

each R is independently hydrogen, deuterium, or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring; a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each of L^1 and L^2 is independently a covalent bond or an optionally substituted 1-6 membered straight or branched bivalent hydrocarbon chain;

R^3 is hydrogen, halogen, -CN, -OR, -SR, -$N(R)_2$, -N(R)C(O)R, -$C(O)RN(R)_2$, -C(O)N(R)$S(O)_2$R, -N(R)C(O)$N(R)_2$, -N(R)C(O)OR, -$OC(O)N(R)_2$, -N(R)SO_2R, -$SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, -SO_2R, or an optionally substituted ring

selected from phenyl or 5-6 membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^4 is hydrogen or an optionally substituted ring selected from a 3-8 membered monocyclic saturated or partially unsaturated carbocyclic ring, a 4-8 membered monocyclic saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, phenyl, an 8-10 membered bicyclic aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

2. Compounds and Definitions:

[0009] Compounds of this invention include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0010] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle," "cycloaliphatic" or "cycloalkyl"), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-6 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-3 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1-2 aliphatic carbon atoms. In some embodiments, "cycloaliphatic" (or "carbocycle" or "cycloalkyl") refers to a monocyclic C_3-C_6 hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. Suitable

aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0011] The term "lower alkyl" refers to a C_{1-4} straight or branched alkyl group. Exemplary lower alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and tert-butyl.

[0012] The term "lower haloalkyl" refers to a C_{1-4} straight or branched alkyl group that is substituted with one or more halogen atoms.

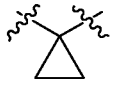
[0013] The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)).

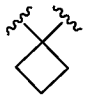
[0014] The term "unsaturated," as used herein, means that a moiety has one or more units of unsaturation.

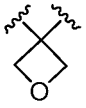
[0015] As used herein, the term "bivalent C_{1-8} (or C_{1-6}) saturated or unsaturated, straight or branched, hydrocarbon chain", refers to bivalent alkylene, alkenylene, and alkynylene chains that are straight or branched as defined herein.

[0016] The term "alkylene" refers to a bivalent alkyl group. An "alkylene chain" is a polymethylene group, i.e., $-(CH_2)_n-$, wherein n is a positive integer, preferably from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. A substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0017] The term "alkenylene" refers to a bivalent alkenyl group. A substituted alkenylene chain is a polymethylene group containing at least one double bond in which one or more hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0018] As used herein, the term "cyclopropylenyl" refers to a bivalent cyclopropyl group of the following structure:  .

[0019] As used herein, the term "cyclobutylenyl" refers to a bivalent cyclobutyl group of the following structure:  .

[0020] As used herein, the term "oxetanyl" refers to a bivalent oxetanyl group of the following structure:  .

[0021] The term "halogen" means F, Cl, Br, or I.

[0022] The term "aryl" used alone or as part of a larger moiety as in "aralkyl," "aralkoxy," or "aryloxyalkyl," refers to monocyclic or bicyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term "aryl" may be used interchangeably with the term "aryl ring."

[0023] The term "aryl" used alone or as part of a larger moiety as in "aralkyl," "aralkoxy," or "aryloxyalkyl," refers to monocyclic and bicyclic ring systems having a total of five to 10 ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains three to seven ring members. The term "aryl" may be used interchangeably with the term "aryl ring". In certain embodiments of the present invention, "aryl" refers to an aromatic ring system which includes, but not limited to, phenyl, biphenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. Also included within the scope of the term "aryl," as it is used herein, is a group in which an aromatic ring is fused to one or more non–aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like.

[0024] The terms "heteroaryl" and "heteroar–," used alone or as part of a larger moiety, e.g., "heteroaralkyl," or "heteroaralkoxy," refer to groups having 5 to 10 ring atoms, preferably 5, 6, or 9 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. The term "heteroatom" refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl. The terms "heteroaryl" and "heteroar–", as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the

heteroaromatic ring. Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4*H*–quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and pyrido[2,3–b]–1,4–oxazin–3(4H)–one. A heteroaryl group may be mono– or bicyclic. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring," "heteroaryl group," or "heteroaromatic," any of which terms include rings that are optionally substituted. The term "heteroaralkyl" refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[0025] As used herein, the terms "heterocycle," "heterocyclyl," "heterocyclic radical," and "heterocyclic ring" are used interchangeably and refer to a stable 5– to 7–membered monocyclic or 7–10–membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term "nitrogen" includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0–3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4–dihydro–2*H*–pyrrolyl), NH (as in pyrrolidinyl), or $^{+}$NR (as in *N*–substituted pyrrolidinyl).

[0026] A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothiophenyl pyrrolidinyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl. The terms "heterocycle," "heterocyclyl," "heterocyclyl ring," "heterocyclic group," "heterocyclic moiety," and "heterocyclic radical," are used interchangeably herein, and also include groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3*H*–indolyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl, where the radical or point of attachment is on the heterocyclyl ring. A heterocyclyl group may be mono– or bicyclic. The term "heterocyclylalkyl" refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted.

[0027] As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

[0028] As described herein, compounds of the invention may contain "optionally substituted" moieties. In general, the term "substituted," whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0029] Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group are independently halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$, $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R°; $-CH=CHPh$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}$-pyridyl which may be substituted with R°; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR-$, $SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$, $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-P(O)_2R^\circ$; $-P(O)R^\circ_2$; $-OP(O)R^\circ_2$; $-OP(O)(OR^\circ)_2$; SiR°_3; $-(C_{1-4}$ straight or branched alkylene$)O-N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene$)C(O)O-N(R^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2$-(5-6 membered heteroaryl ring), or a 5–6–

membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[0030] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $–(CH_2)_{0–2}R^•$, –(haloR•), $–(CH_2)_{0–2}OH$, $–(CH_2)_{0–2}OR^•$, $–(CH_2)_{0–2}CH(OR^•)_2$; -O(haloR•), –CN, $–N_3$, $–(CH_2)_{0–2}C(O)R^•$, $–(CH_2)_{0–2}C(O)OH$, $–(CH_2)_{0–2}C(O)OR^•$, $–(CH_2)_{0–2}SR^•$, $–(CH_2)_{0–2}SH$, $–(CH_2)_{0–2}NH_2$, $–(CH_2)_{0–2}NHR^•$, $–(CH_2)_{0–2}NR^•_2$, $–NO_2$, $–SiR^•_3$, $–OSiR^•_3$, -C(O)SR•, –($C_{1–4}$ straight or branched alkylene)C(O)OR•, or –SSR• wherein each R• is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently selected from $C_{1–4}$ aliphatic, $–CH_2Ph$, $–O(CH_2)_{0–1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

[0031] Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: =O, =S, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $–O(C(R^*_2))_{2–3}O–$, or $–S(C(R^*_2))_{2–3}S–$, wherein each independent occurrence of R^* is selected from hydrogen, $C_{1–6}$ aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: $–O(CR^*_2)_{2–3}O–$, wherein each independent occurrence of R^* is selected from hydrogen, $C_{1–6}$ aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0032] Suitable substituents on the aliphatic group of R^* include halogen, –R•, -(haloR•), -OH, –OR•, –O(haloR•), –CN, –C(O)OH, –C(O)OR•, $–NH_2$, –NHR•, $–NR^•_2$, or $–NO_2$, wherein each R• is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently $C_{1–4}$ aliphatic, $–CH_2Ph$, $–O(CH_2)_{0–1}Ph$, or a

5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0033] Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include $–R^{\dagger}$, $–NR^{\dagger}_2$, $–C(O)R^{\dagger}$, $–C(O)OR^{\dagger}$, $–C(O)C(O)R^{\dagger}$, $–C(O)CH_2C(O)R^{\dagger}$, $-S(O)_2R^{\dagger}$, $-S(O)_2NR^{\dagger}_2$, $–C(S)NR^{\dagger}_2$, $–C(NH)NR^{\dagger}_2$, or $–N(R^{\dagger})S(O)_2R^{\dagger}$; wherein each $R^{\dagger}$ is independently hydrogen, $C_{1–6}$ aliphatic which may be substituted as defined below, unsubstituted –OPh, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $R^{\dagger}$, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0034] Suitable substituents on the aliphatic group of $R^{\dagger}$ are independently halogen, $–R^{\bullet}$, -(halo$R^{\bullet}$), –OH, $–OR^{\bullet}$, –O(halo$R^{\bullet}$), –CN, –C(O)OH, $–C(O)OR^{\bullet}$, $–NH_2$, $–NHR^{\bullet}$, $–NR^{\bullet}_2$, or $-NO_2$, wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently $C_{1–4}$ aliphatic, $–CH_2Ph$, $–O(CH_2)_{0–1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0035] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1–19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate,

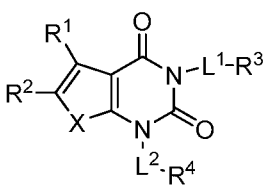
hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like.

[0036] Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[0037] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention. In certain embodiments, a warhead moiety, R^1, of a provided compound comprises one or more deuterium atoms.

3. Description of Exemplary Embodiments:

[0038] In certain embodiments, the present invention provides inhibitors of ACC. In some embodiments, such compounds include those of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

X is –O-, -S-, or –NR-;

R^1 is hydrogen or C_{1-4} aliphatic, optionally substituted with one or more halogen, -OR, -SR, -$N(R)_2$, -N(R)C(O)R, -$C(O)N(R)_2$, -N(R)C(O)$N(R)_2$, -N(R)C(O)OR, -$OC(O)N(R)_2$, -$N(R)SO_2R$, -$SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or -SO_2R;

R^2 is halogen, -R, -OR, -SR, -$N(R)_2$, -N(R)C(O)R, -$C(O)N(R)_2$, -N(R)C(O)$N(R)_2$, -N(R)C(O)OR, -$OC(O)N(R)_2$, -$N(R)SO_2R$, -$SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or -SO_2R, or Hy, where Hy is selected from 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or R^1 and R^2 are taken together to form an optionally substituted 4-7 membered partially unsaturated carbocyclo-, or heterocyclo-, benzo-, or 5-6 membered heteroarylo- fused ring;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring; a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each of L^1 and L^2 is independently a covalent bond or an optionally substituted 1-6 membered straight or branched bivalent hydrocarbon chain; or a cyclopropylenyl, cyclobutylenyl, or oxetanyl group;

R^3 is hydrogen, halogen, -CN,-OR, -SR, -$N(R)_2$, -N(R)C(O)R, -$C(O)N(R)_2$, -$C(O)N(R)S(O)_2R$, -N(R)C(O)$N(R)_2$, -N(R)C(O)OR, -$OC(O)N(R)_2$, -$N(R)SO_2R$, -$SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, -SO_2R, -$B(OH)_2$, or an optionally substituted ring selected from phenyl or 5-6 membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

R^4 is hydrogen or an optionally substituted ring selected from a 3-8 membered monocyclic saturated or partially unsaturated carbocyclic ring, a 4-8 membered monocyclic saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, phenyl, an 8-10 membered bicyclic aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0039] In certain embodiments, if L^2 is a covalent bond, then R^4 is not hydrogen. In certain embodiments, the group $-L^2-R^4$ is not alkyl when R^2 is unsubstituted alkyl. In certain embodiments, the group $-L^1-R^3$ taken together is not unsubstituted alkyl. In certain embodiments, R^1 is not the group $-CH_2C(O)N(R)V$, where V is an aryl or heteroaryl ring, when $-L^1-R^3$ taken together is unsubstituted alkyl.

[0040] As defined generally above, X is –O-, -S-, or –NR-. In certain embodiments, X is –O-. In certain embodiments, X is –S-. In some embodiments, X is –NR-. In certain embodiments, X is –NH-.

[0041] As defined generally above, R^1 is hydrogen or C_{1-4} aliphatic, optionally substituted with one or more halogen, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or $-SO_2R$. In certain embodiments, R^1 is hydrogen. In some embodiments, R^1 is C_{1-4} aliphatic. In some embodiments, R^1 is methyl. In some embodiments, R^1 is trifluoromethyl.

[0042] As defined generally above, R^2 is halogen, -R, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or $-SO_2R$, or Hy, where Hy is selected from 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In certain embodiments, R^2 is halogen. In certain embodiments, R^2 is methyl. In certain embodiments, R^2 is trifluoromethyl. In certain embodiments, R^2 is fluorine. In certain embodiments, R^2 is chlorine. In certain embodiments, R^2 is bromine. In certain embodiments, R^2 is iodine. In certain embodiments, R^2 is -C(O)OR or $-C(O)N(R)_2$. In some embodiments, R^2 is Hy.

[0043] As defined generally above, Hy is selected from 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Hy is a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Hy is a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Hy is an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Hy is oxazolyl.

[0044] In some embodiments, R^1 and R^2 are taken together to form an optionally substituted 4-7 membered partially unsaturated carbocyclic ring. In some embodiments, R^1 and R^2 are taken together to form an optionally substituted 4-7 membered partially unsaturated carbocyclo-, or heterocyclo-, benzo-, or 5-6 membered heteroarylo- fused ring;

[0045] As defined generally above, R^3 is hydrogen, halogen, -CN, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-C(O)N(R)S(O)_2R$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, $-SO_2R$, $-B(OH)_2$ or an optionally substituted ring selected from phenyl or 5-6 membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In certain embodiments, R^3 is –CN, –OR, -C(O)OR, $-C(O)N(R)_2$, $-SO_2R$, or an optionally substituted ring selected from phenyl or a 5-6 membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, R^3 is –OR. In some embodiments, R^3 is –C(O)OR. In some embodiments, R^3 is phenyl or tetrazolyl.

[0046] As defined generally above, each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring; a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic

heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0047] In certain embodiments, each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, 3-8 membered unsaturated or partially unsaturated monocyclic carbocyclic ring. In some embodiments, each R is independently hydrogen or optionally substituted C_{1-6} aliphatic.

[0048] As defined generally above, each of L^1 and L^2 is independently a covalent bond or an optionally substituted 1-6 membered straight or branched bivalent hydrocarbon chain, or a cyclopropylenyl, cyclobutylenyl, or oxetanyl group. In certain embodiments, L^1 is a C_{1-3} straight or branched bivalent hydrocarbon chain. In some embodiments, L^1 is a straight or branched bivalent C_2 hydrocarbon chain. In some embodiments L^1 is a straight or branched bivalent C_3 hydrocarbon chain. In some embodiments, L^1 is a cyclopropylenyl, cyclobutylenyl, or oxetanyl group.

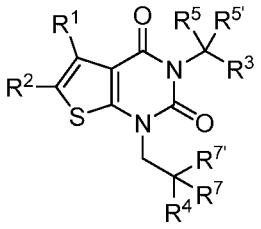
[0049] In some embodiments, L^2 is an optionally substituted C_{1-3} straight or branched hydrocarbon chain. In some embodiments L^2 is an optionally substituted C_2 straight hydrocarbon chain. In some embodiments L^2 is an optionally substituted C_3 straight or branched hydrocarbon chain.

[0050] As defined generally above, R^4 is hydrogen or an optionally substituted ring selected from a 3-8 membered monocyclic saturated or partially unsaturated carbocyclic ring, a 4-8 membered monocyclic saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, phenyl, an 8-10 membered bicyclic aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0051] In certain embodiments, R^4 is hydrogen. In some embodiments, R^4 is an optionally substituted 5-6 membered monocyclic saturated or partially unsaturated ring. In some embodiments R^4 is an optionally substituted 5-6 membered monocyclic saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, R^4 is optionally substituted phenyl. In some embodiments R^4 is an optionally substituted 10 membered bicyclic aryl ring. In some embodiments, R^4 is an optionally substituted 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, R^4 is an optionally substituted 8-10 membered bicyclic

heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0052] In certain embodiments, the present invention provides a compound of formula **II**:



II

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen or C_{1-4} aliphatic, optionally substituted with one or more halogen, -OR, -SR, -$N(R)_2$, -N(R)C(O)R, -C(O)$N(R)_2$, -N(R)C(O)$N(R)_2$, -N(R)C(O)OR, -OC(O)$N(R)_2$, -$N(R)SO_2R$, -$SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or -SO_2R;

R^2 is halogen, -R, -OR, -SR, -$N(R)_2$, -N(R)C(O)R, -C(O)$N(R)_2$, -N(R)C(O)$N(R)_2$, -N(R)C(O)OR, -OC(O)$N(R)_2$, -$N(R)SO_2R$, -$SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or -SO_2R, or Hy, where Hy is selected from 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or R^1 and R^2 are taken together to form an optionally substituted 4-7 membered partially unsaturated carbocyclo-, or heterocyclo-, benzo-, or 5-6 membered heteroarylo- fused ring;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring; a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^3 is hydrogen, halogen, -CN, -OR, -SR, -$N(R)_2$, -N(R)C(O)R, -C(O)$N(R)_2$, -N(R)C(O)$N(R)_2$, -N(R)C(O)OR, -OC(O)$N(R)_2$, -$N(R)SO_2R$, -$SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, -SO_2R, -$B(OH)_2$, or an optionally substituted ring selected

from phenyl or 5-6 membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^4 is an optionally substituted phenyl or naphthyl ring;

each of R^5 and $R^{5'}$ is independently -R, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or $-SO_2R$; or R^5 and $R^{5'}$ are taken together to form a cyclopropylenyl, cyclobutylenyl, or oxetanyl group; and

each of R^7 and $R^{7'}$ is independently hydrogen, -R, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or $-SO_2R$; or R^7 and $R^{7'}$ are taken together to form a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0053] As defined generally above, each of R^5 and $R^{5'}$ is independently -R, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or $-SO_2R$; or R^5 and $R^{5'}$ are taken together to form a cyclopropylenyl, cyclobutylenyl, or oxetanyl group.

[0054] In some embodiments, each of R^5 and $R^{5'}$ is –R, wherein –R is not hydrogen. In some embodiments, each of R^5 and $R^{5'}$ is methyl. In some embodiments, R^5 and $R^{5'}$ are taken together to form a cyclopropylenyl, cyclobutylenyl, or oxetanyl group. In some embodiments, R^5 and $R^{5'}$ are taken together to form a cyclobutylenyl group.

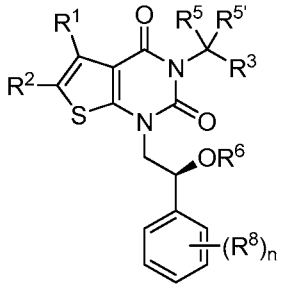
[0055] As defined generally above, each of R^7 and $R^{7'}$ is independently hydrogen, -R, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or $-SO_2R$; or R^7 and $R^{7'}$ are taken together to form a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0056] In certain embodiments, one of R^7 and $R^{7'}$ is hydrogen, and the other is –OR. In some embodiments one of R^7 and $R^{7'}$ is hydrogen, and the other is isopropoxy. In some embodiments R^7 and $R^{7'}$ are taken together to form a 3-6 membered saturated or partially unsaturated monocyclic carbocyclic ring. In some embodiments R^7 and $R^{7'}$ are taken together to form a 4-6 membered saturated or partially unsaturated monocyclic

heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, one of R^7 and $R^{7'}$ is hydrogen and the other is –OR, where R in this instance is a 4-7 membered saturated heterocyclic ring containing 1-2 heteroatoms independently selected from nitrogen, oxygen and sulfur. In some embodiments, one of R^7 and $R^{7'}$ is hydrogen and the other is –OR, where R in this instance is oxetane, tetrahydrofuran, or tetrahydropyran.

[0057] In certain embodiments, the present invention provides a compound of formula **II**, wherein each variable is as described in embodiments for formula **I**, *supra*, or described in embodiments herein, both singly and in combination..

[0058] In certain embodiments, the present invention provides a compound of formula **III**:



III

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen or C_{1-4} aliphatic, optionally substituted with one or more halogen, -OR, -SR, -$N(R)_2$, -N(R)C(O)R, -$C(O)N(R)_2$, -$N(R)C(O)N(R)_2$, -N(R)C(O)OR, -$OC(O)N(R)_2$, -$N(R)SO_2R$, -$SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or -SO_2R;

R^2 is halogen, -R, -OR, -SR, -$N(R)_2$, -N(R)C(O)R, -$C(O)N(R)_2$, -$N(R)C(O)N(R)_2$, -N(R)C(O)OR, -$OC(O)N(R)_2$, -$N(R)SO_2R$, -$SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or -SO_2R; or R^1 and R^2 are taken together to form an optionally substituted 4-7 membered partially unsaturated carbocyclo-, or heterocyclo-, benzo-, or 5-6 membered heteroarylo- fused ring;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring; a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen,

oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^3 is hydrogen, halogen, -CN, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, $-SO_2R$, $-B(OH)_2$, or an optionally substituted ring selected from phenyl or 5-6 membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each of R^5 and $R^{5'}$ is independently -R, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or $-SO_2R$; or R^5 and $R^{5'}$ are taken together to form a cyclopropylenyl, cyclobutylenyl, or oxetanyl group;

R^6 is -R, $-C(O)N(R)_2$, or -C(O)R;

each R^8 is independently selected from halogen, -R, -OR, -SR, $-N(R)_2$ or deuterium; and

n is 0-5.

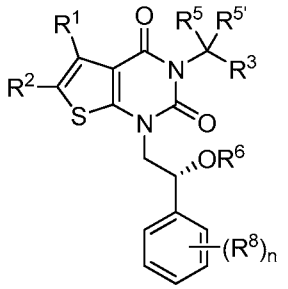
[0059] In certain embodiments, the present invention provides a compound of formula **III**, wherein each variable is as described in embodiments for formula **I** or **II**, *supra*.

[0060] In certain embodiments R^6 is hydrogen. In certain embodiments, R^6 is isopropyl.

[0061] As defined generally above, each In certain embodiments, each R^8 is independently selected from halogen, -R, -OR, -SR, $-N(R)_2$ or deuterium. In certain embodiments, each R^8 is halogen.

[0062] As defined generally above, n is 0-5. In certain embodiments, n is 0. In some embodiments, n is 1-2.

[0063] In certain embodiments, the present invention provides a compound of formula **IV**:



IV

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen or C_{1-4} aliphatic, optionally substituted with one or more halogen, -OR, -SR, -$N(R)_2$, -N(R)C(O)R, -$C(O)N(R)_2$, -N(R)C(O)$N(R)_2$, -N(R)C(O)OR, -$OC(O)N(R)_2$, -$N(R)SO_2R$, -$SO_2RN(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -C(O)OR, -S(O)R, or -SO_2R;

R^2 is halogen, -R, -OR, -SR, -$N(R)_2$, -N(R)C(O)R, -$C(O)N(R)_2$, -N(R)C(O)$N(R)_2$, -N(R)C(O)OR, -$OC(O)N(R)_2$, -$N(R)SO_2R$, -$SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or -SO_2R; or R^1 and R^2 are taken together to form an optionally substituted 4-7 membered partially unsaturated carbocyclo-, or heterocyclo-, benzo-, or 5-6 membered heteroarylo- fused ring;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring; a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^3 is hydrogen, halogen, -CN, -OR, -SR, -$N(R)_2$, -N(R)C(O)R, -$C(O)N(R)_2$, -N(R)C(O)$N(R)_2$, -N(R)C(O)OR, -$OC(O)N(R)_2$, -$N(R)SO_2R$, -$SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, -SO_2R, -$B(OH)_2$, or an optionally substituted ring selected from phenyl or 5-6 membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each of R^5 and $R^{5'}$ is independently -R, -OR, -SR, -$N(R)_2$, -N(R)C(O)R, -$C(O)N(R)_2$, -N(R)C(O)$N(R)_2$, -N(R)C(O)OR, -$OC(O)N(R)_2$, -$N(R)SO_2R$, -$SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or -SO_2R or R^5 and $R^{5'}$ are taken together to form a cyclopropylenyl, cyclobutylenyl, or oxetanyl group; and

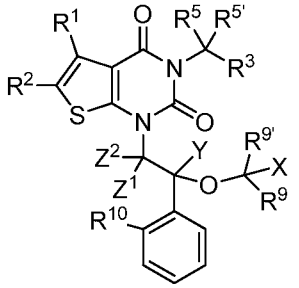
R^6 is -R, -$C(O)N(R)_2$, or -C(O)R;

each R^8 is independently selected from halogen, -R, -OR, -SR, -$N(R)_2$ or deuterium; and

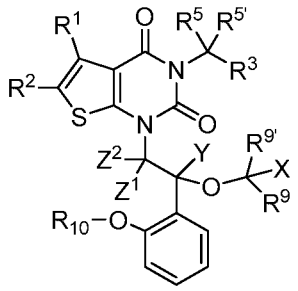
n is 0-5.

[0064] In certain embodiments, the present invention provides a compound of formula **IV**, wherein each variable is as described in embodiments for formula **I** or **II**, *supra.*

[0065] In certain embodiments, the present invention provides a compound of formula **V-i** or **V-ii**:



V-i



V-ii,

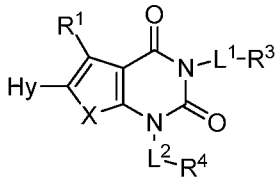
or a pharmaceutically acceptable salt thereof, wherein R^2, R^3, R^5, $R^{5'}$, are as described in embodiments for formula **I**, *supra*; and

each of R^1, R^9, and $R^{9'}$ is independently CH_3 or CD_3;

each of X, Y, Z^1, and Z^2 is independently H or D; and

R^{10} is CH_3, CD_3, CH_2CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, CF_2H, CH_2CD_3, CD_2CH_3, or CD_2CD_3.

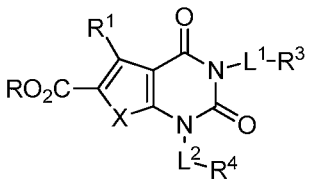
[0066] In certain embodiments, the present invention provides a compound of formula **I**, wherein R^2 is Hy, thereby forming a compound of formula **VI**:



VI

[0067] or a pharmaceutically acceptable salt thereof, wherein each of X, L^1, L^2, R^1, R^3, R^4, and Hy is defined above and described in embodiments herein, both singly and in combination.

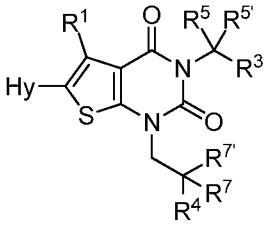
[0068] In certain embodiments, the present invention provides a compound of formula **I**, wherein R^2 is –C(O)OR, thereby forming a compound of formula **VII**:



VII

[0069] or a pharmaceutically acceptable salt thereof, wherein each of X, L^1, L^2, R, R^1, R^3, and R^4 is defined above and described in embodiments herein, both singly and in combination.

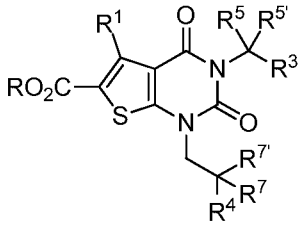
[0070] In certain embodiments, the present invention provides a compound of formula **II**, wherein R^2 is Hy, thereby forming a compound of formula **VIII**:



VIII

[0071] or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^3, R^4, R^5, $R^{5'}$, R^7, $R^{7'}$, and Hy is defined above and described in embodiments herein, both singly and in combination.

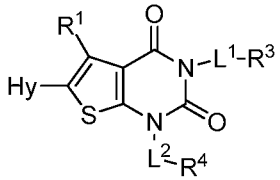
[0072] In certain embodiments, the present invention provides a compound of formula **II**, wherein R^2 is –C(O)OR, thereby forming a compound of formula **IX**:



IX

[0073] or a pharmaceutically acceptable salt thereof, wherein each of R, R^1, R^3, R^4, R^5, $R^{5'}$, R^7, and $R^{7'}$ is defined above and described in embodiments herein, both singly and in combination.

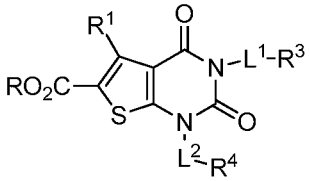
[0074] In certain embodiments, the present invention provides a compound of formula **VI**, wherein X is S, thereby forming a compound of formula **X**:



X

[0075] or a pharmaceutically acceptable salt thereof, wherein each of L^1, L^2, R^1, R^3, R^4, and Hy is defined above and described in embodiments herein, both singly and in combination.

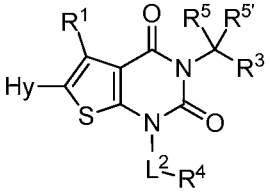
[0076] In certain embodiments, the present invention provides a compound of formula **VII**, wherein X is S, thereby forming a compound of formula **XI**:



XI

[0077] or a pharmaceutically acceptable salt thereof, wherein each of L^1, L^2, R, R^1, R^3, and R^4 is defined above and described in embodiments herein, both singly and in combination.

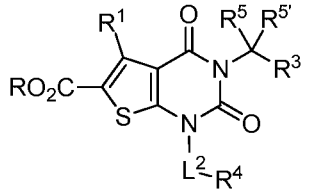
[0078] In certain embodiments, the present invention provides a compound of formula **X**, wherein L^1 is $-C(R^5)(R^{5'})-$, thereby forming a compound of formula **XII**:



XII

[0079] or a pharmaceutically acceptable salt thereof, wherein each of L^2, R^1, R^3, R^4, R^5, $R^{5'}$, and Hy is defined above and described in embodiments herein, both singly and in combination.

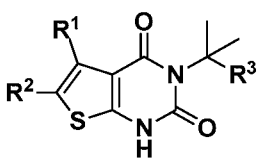
[0080] In certain embodiments, the present invention provides a compound of formula **XI**, wherein L^1 is $-C(R^5)(R^{5'})-$, thereby forming a compound of formula **XIII**:



XIII

[0081] or a pharmaceutically acceptable salt thereof, wherein each of L^2, R, R^1, R^3, R^4, R^5, $R^{5'}$, and R^4 is defined above and described in embodiments herein, both singly and in combination.

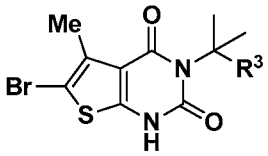
[0082] In certain embodiments, the present invention provides a compound of formula **XIV** of the formula:



XIV

[0083] or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, and R^3 is defined above and described in embodiments herein, both singly and in combination.

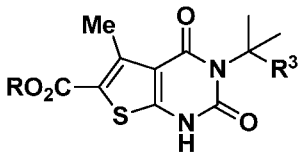
[0084] In certain embodiments, the present invention provides a compound of formula **XIV**, wherein R^1 is methyl, and R^2 is bromine, thereby forming a compound of formula **XV**:



XV

[0085] or a pharmaceutically acceptable salt thereof, wherein R^3 is defined above and described in embodiments herein, both singly and in combination.

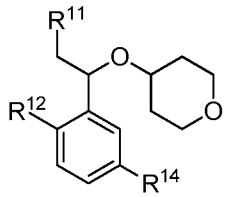
[0086] In certain embodiments, the present invention provides a compound of formula **XIV**, wherein R^1 is methyl, and R^2 is –C(O)OR, thereby forming a compound of formula **XVI**:



XVI

[0087] or a pharmaceutically acceptable salt thereof, wherein R^3 is defined above and described in embodiments herein, both singly and in combination.

[0088] In certain embodiments, the present invention provides a compound of formula **XVII** of the formula:



XVII

wherein:

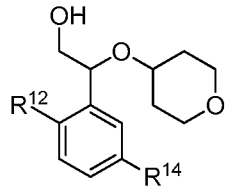
R^{11} is selected from the group consisting of -OH, halogen,and $-OS(O)_2R$

R^{12} is $-R^{13}$ or $-OR^{13}$

R^{13} is straight or branched C_{1-4} aliphatic; and

R^{14} is hydrogen or halogen.

[0089] In certain embodiments, the present invention provides a compound of formula **XVII**, wherein R^{11} is –OH, thereby forming a compound of formula **XVIII**:



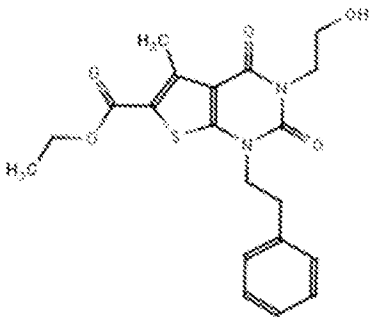
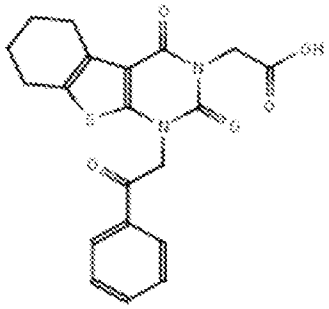
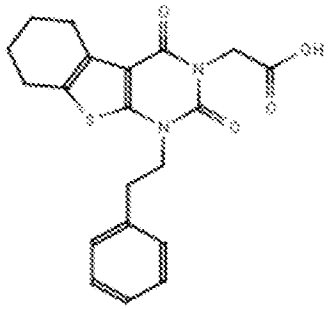
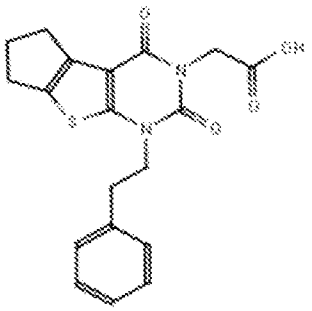
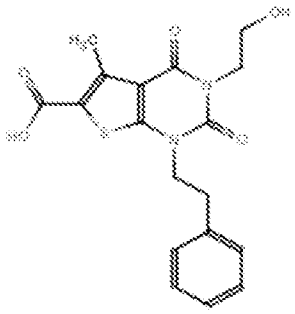
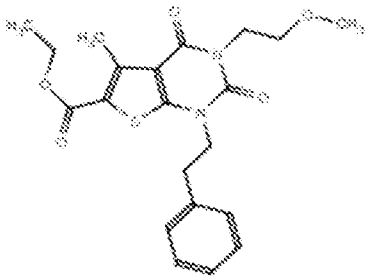
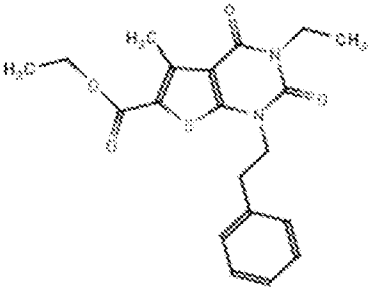
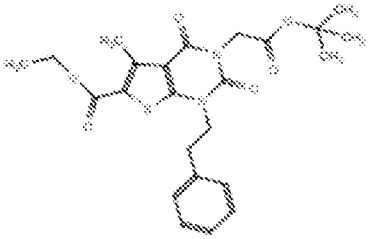
XVIII

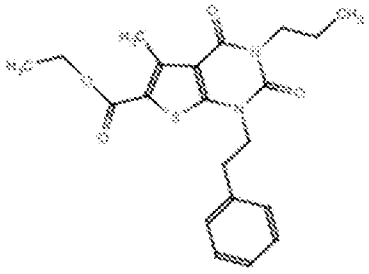
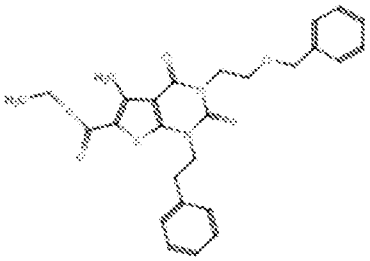
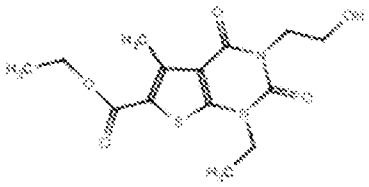
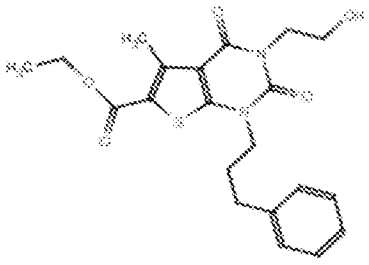
wherein each of R^{12}, R^{13}, and R^{14} is defined above for formula **XVII** and described in embodiments herein, both singly and in combination.

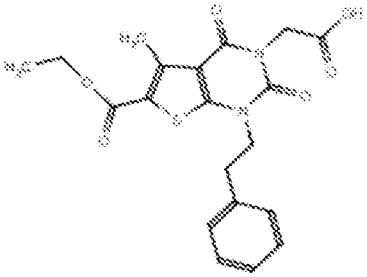
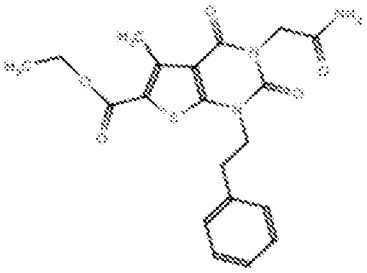
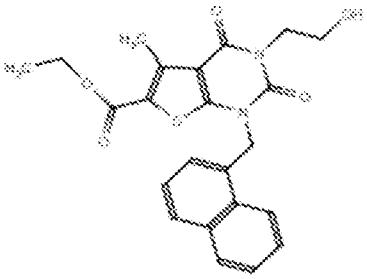
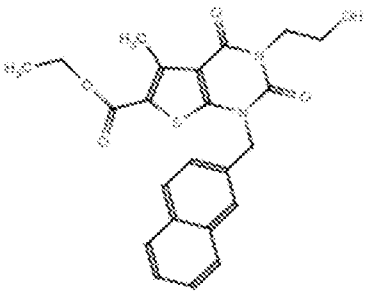
[0090] In certain embodiments, the present invention provides a compound of formula **XVIII** wherein R^{12} is selected from the group consisting of methyl, ethyl, methoxy and ethoxy.

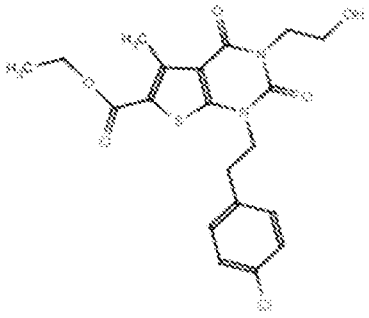
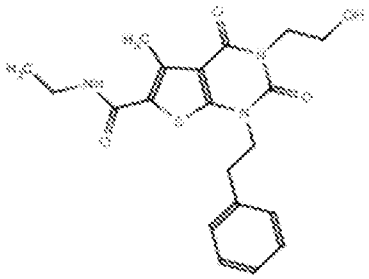
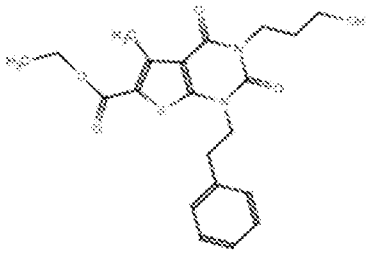
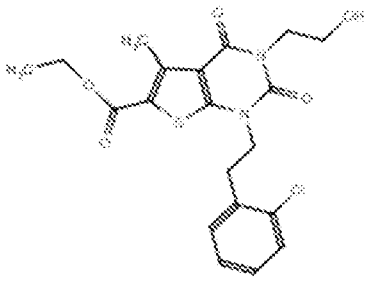
[0091] Exemplary compounds of formula **I** are set forth in Table 1, below:

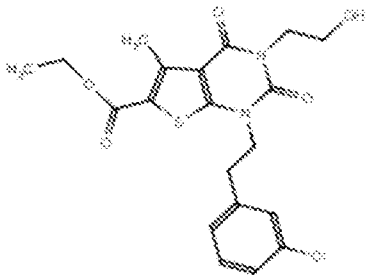
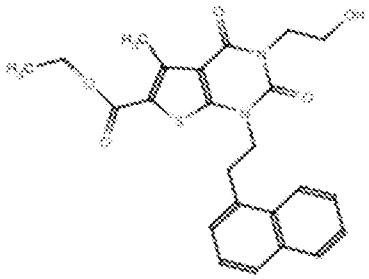
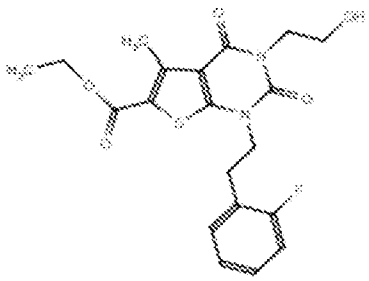
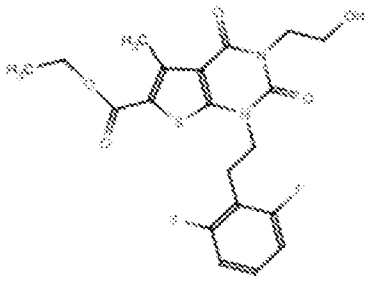
Table 1. Exemplary Compounds of Formula I

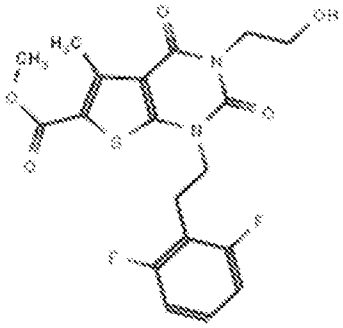
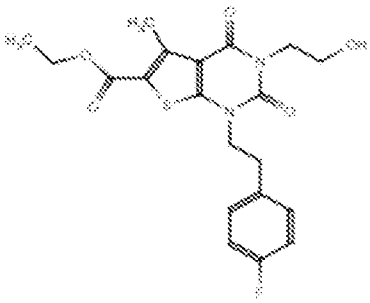
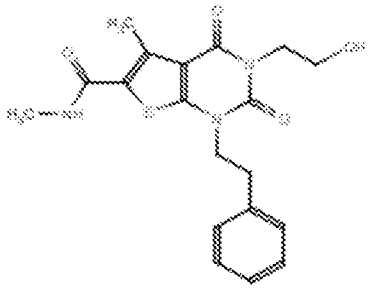
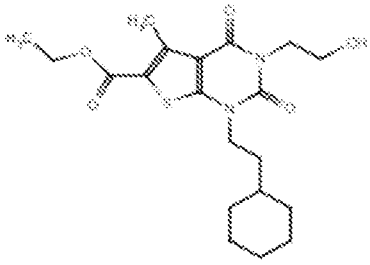
Cmpd #	Compound Structure	m/z
I-1		403 (M+1)
I-2		399 (M+1)
I-3		385 (M+1)
I-4		371 (M+1)
I-5		375 (M+1)
I-6		417 (M+1)
I-7		387 (M+1)
I-8		495 (M+Na)

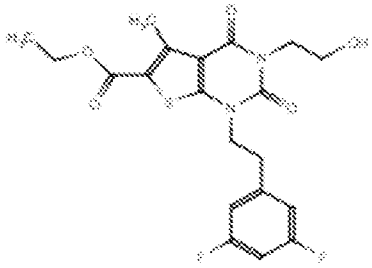
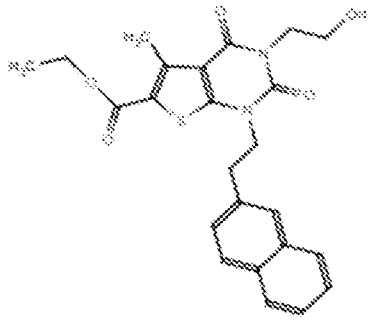
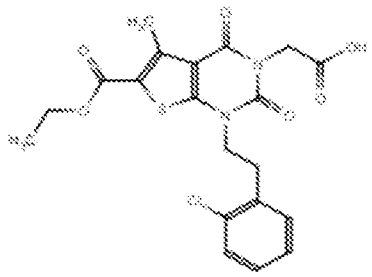
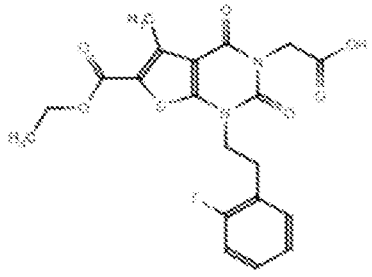
Cmpd #	Compound Structure	m/z
I-9		401 (M+1)
I-10		493 (M+1)
I-11		327 (M+1)
I-12		417 (M+1)

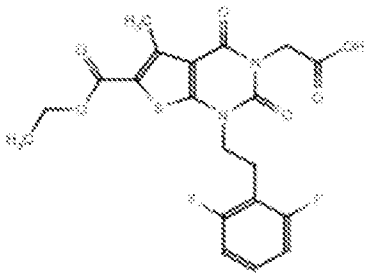
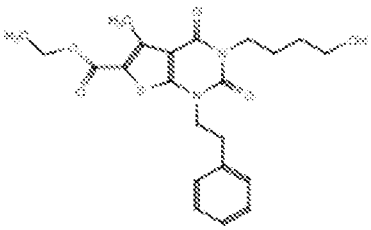
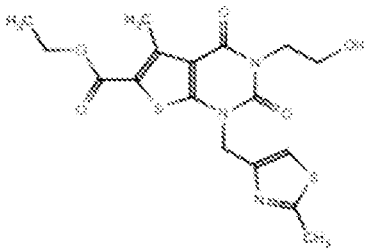
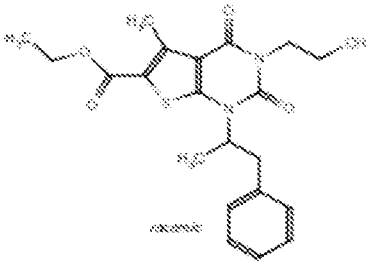
Cmpd #	Compound Structure	m/z
I-13		417 (M+1)
I-14		416 (M+1)
I-15		439 (M+1)
I-16		439 (M+1)

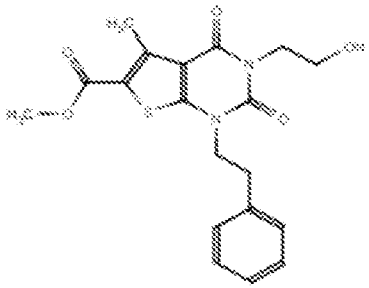
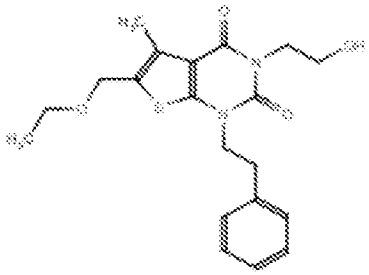
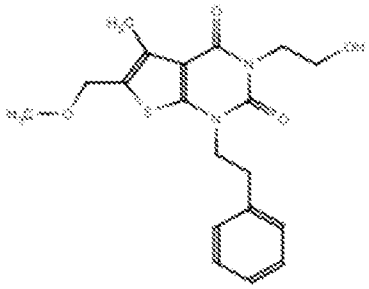
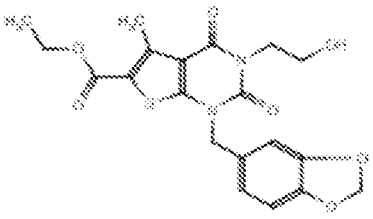
Cmpd #	Compound Structure	m/z
I-17		437 (M+1)
I-18		402 (M+1)
I-19		417 (M+1)
I-20		437 (M+1)

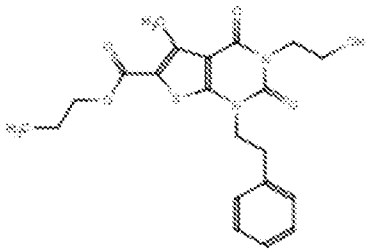
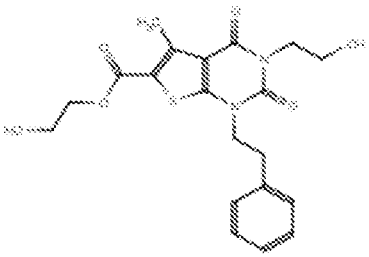
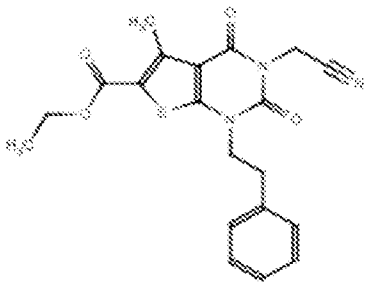
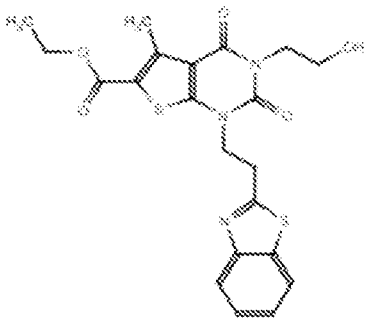
Cmpd #	Compound Structure	m/z
I-21		437 (M+1)
I-22		453 (M+1)
I-23		421 (M+1)
I-24		439 (M+1)

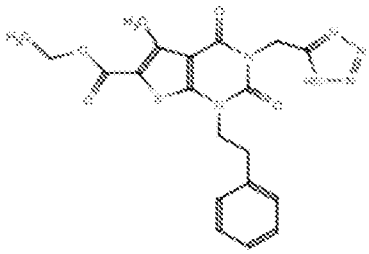
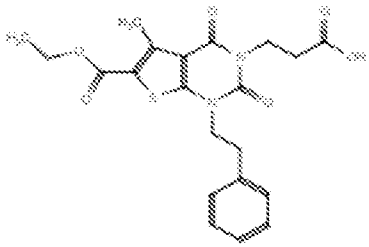
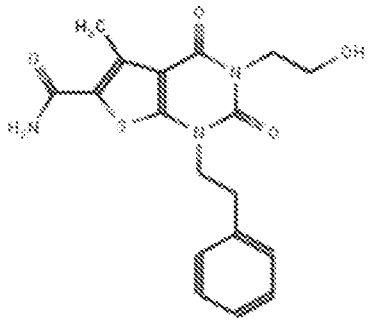
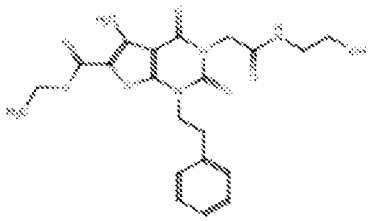
Cmpd #	Compound Structure	m/z
I-25		425 (M+1)
I-26		421 (M+1)
I-27		388 (M+1)
I-28		409 (M+1)

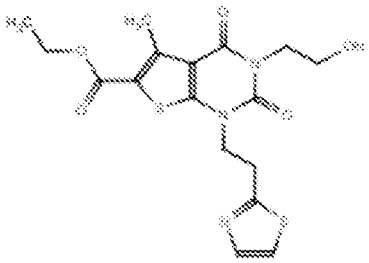
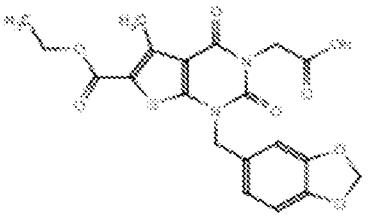
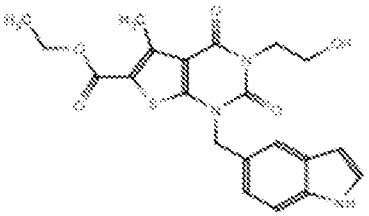
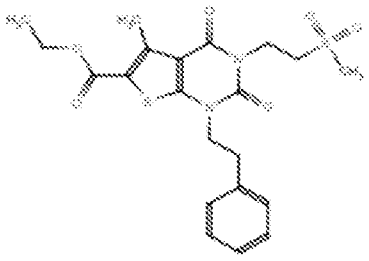
Cmpd #	Compound Structure	m/z
I-29		439 (M+1)
I-30		453 (M+1)
I-31		451 (M+1)
I-32		435 (M+1)

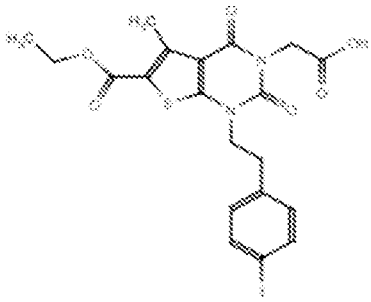
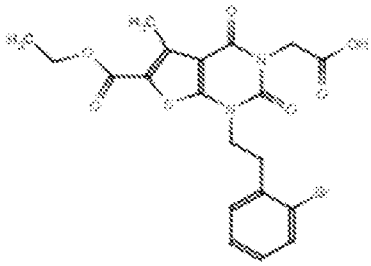
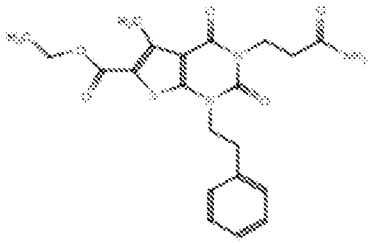
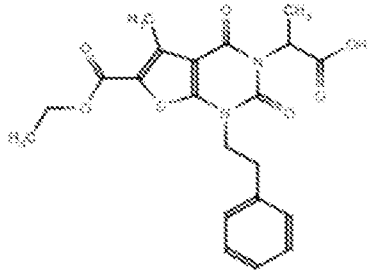
Cmpd #	Compound Structure	m/z
I-33		453 (M+1)
I-34		431 (M+1)
I-35		410 (M+1)
I-36		417 (M+1)

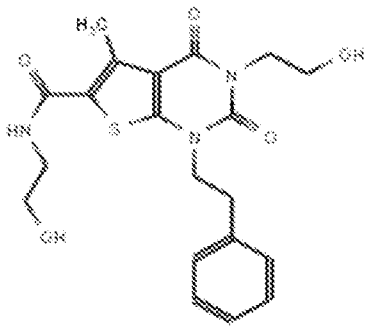
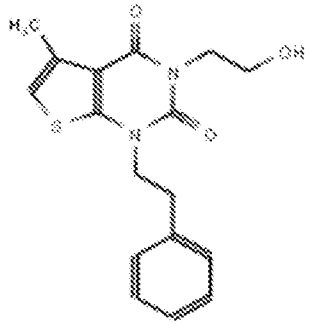
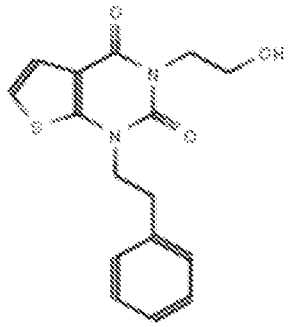
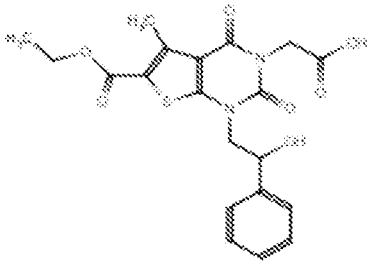
Cmpd #	Compound Structure	m/z
I-37		389 (M+1)
I-38		389 (M+1)
I-39		375 (M+1)
I-40		433 (M+1)

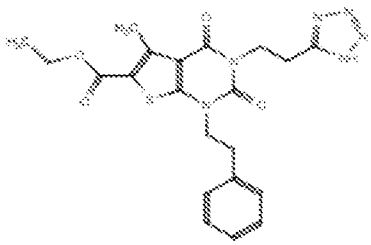
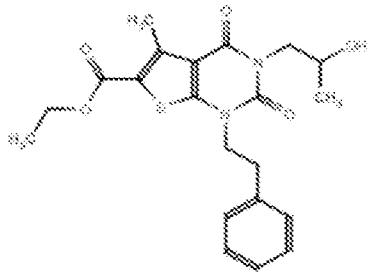
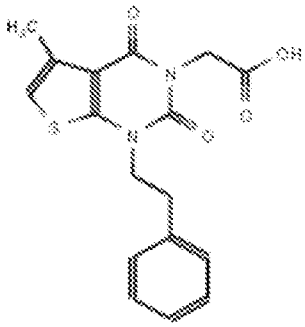
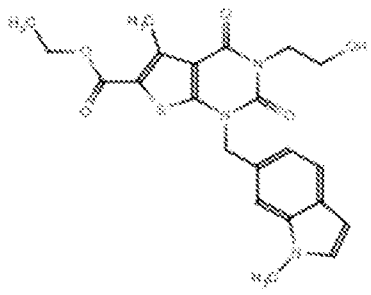
Cmpd #	Compound Structure	m/z
I-41		417 (M+1)
I-42		419 (M+1)
I-43		398 (M+1)
I-44		460 (M+1)

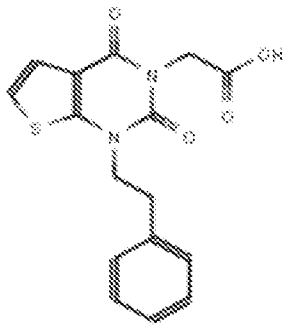
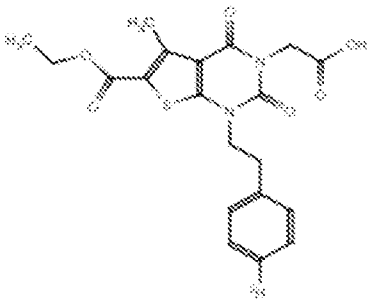
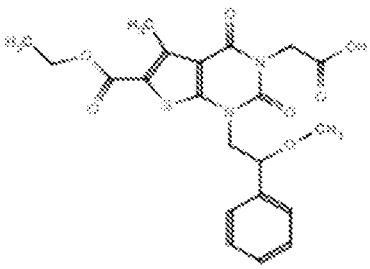
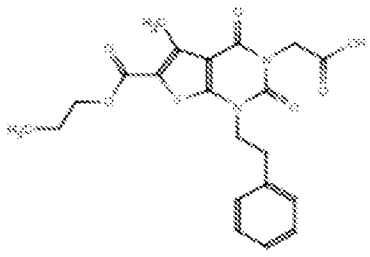
Cmpd #	Compound Structure	m/z
I-45		441 (M+1)
I-46		431 (M+1)
I-47		374 (M+1)
I-48		460 (M+1)

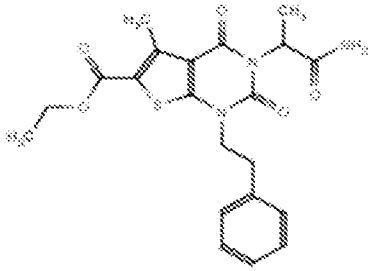
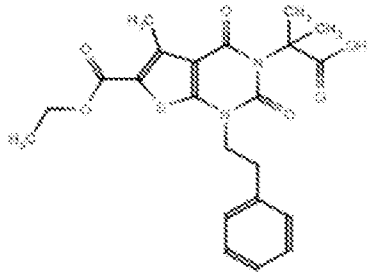
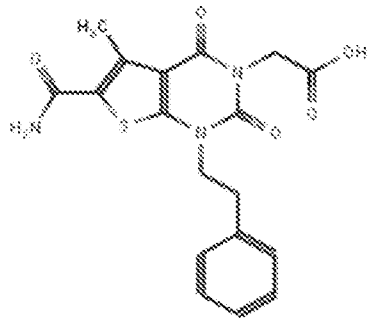
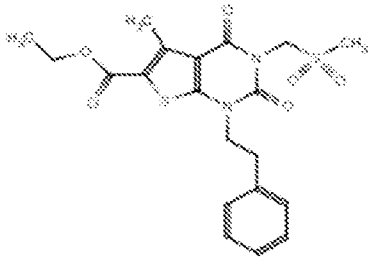
Cmpd #	Compound Structure	m/z
I-49		410 (M+1)
I-50		447 (M+1)
I-51		428 (M+1)
I-52		465 (M+1)

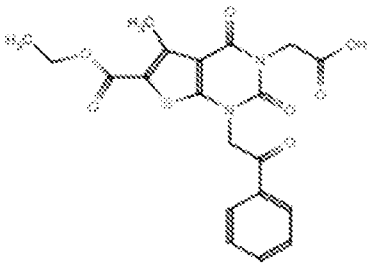
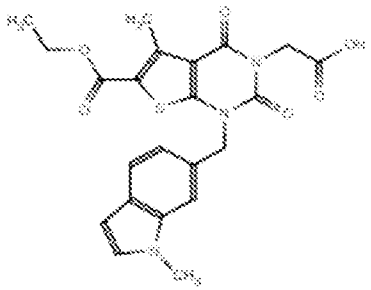
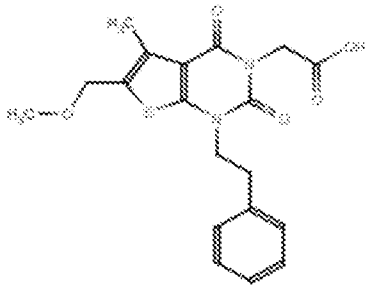
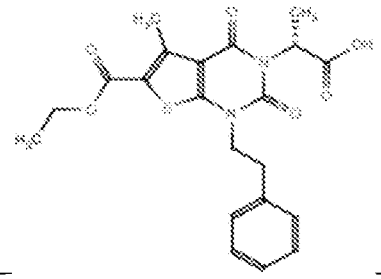
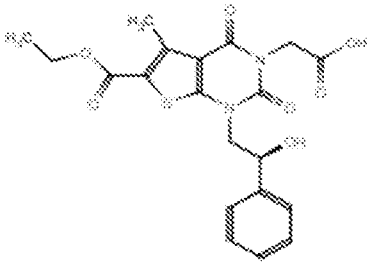
Cmpd #	Compound Structure	m/z
I-53		543 (M+1)
I-54		495 (M+1)
I-55		430 (M+1)
I-56		431 (M+1)

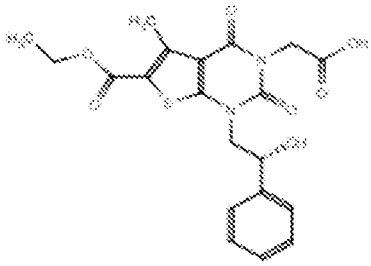
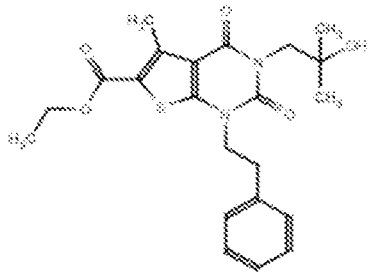
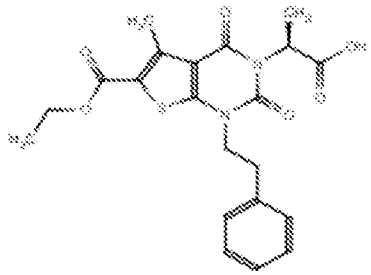
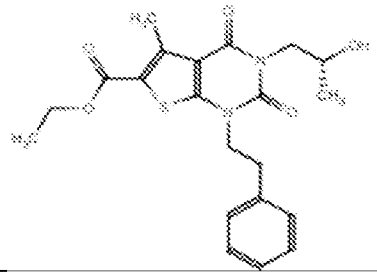
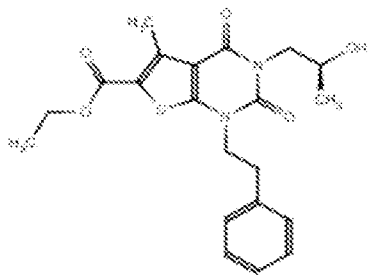
Cmpd #	Compound Structure	m/z
I-57		418 (M+1)
I-58		331 (M+1)
I-59		317 (M+1)
I-60		433 (M+1)

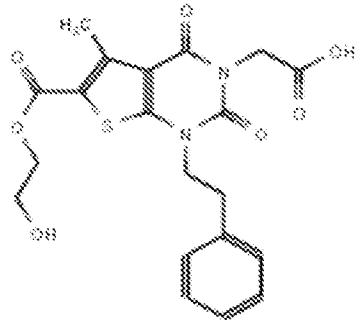
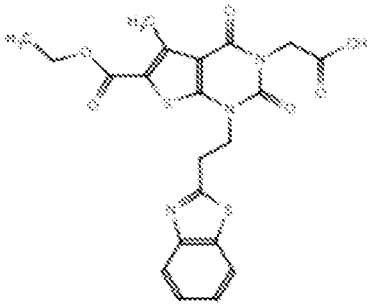
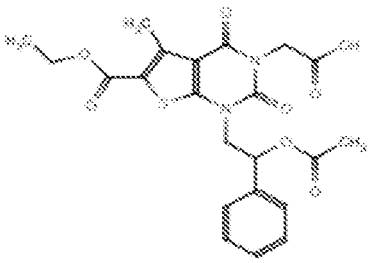
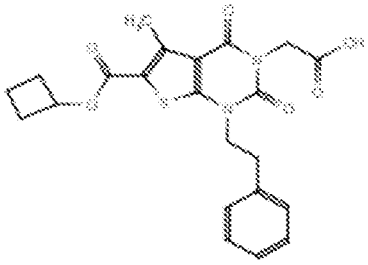
Cmpd #	Compound Structure	m/z
I-61		455 (M+1)
I-62		417 (M+1)
I-63		345 (M+1)
I-64		442 (M+1)

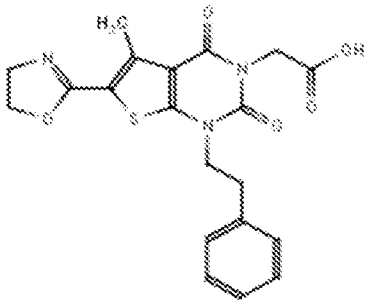
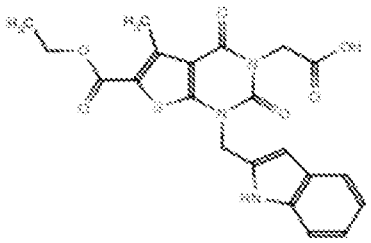
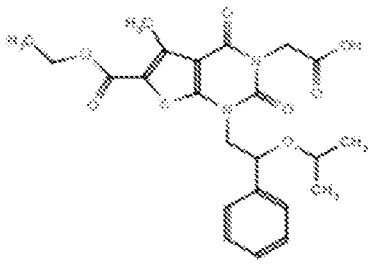
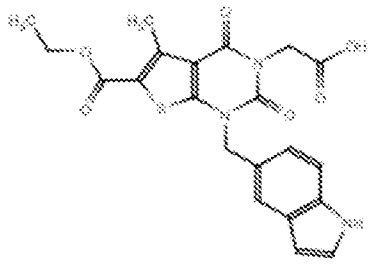
Cmpd #	Compound Structure	m/z
I-65		331 (M+1)
I-66		418 (M+1)
I-67		447 (M+1)
I-68		431 (M+1)

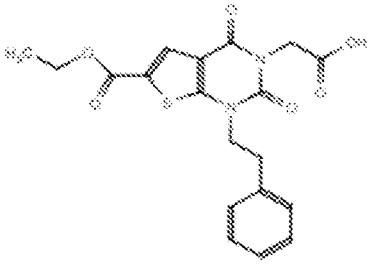
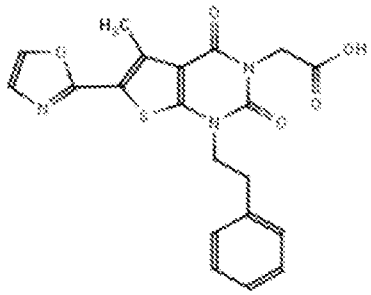
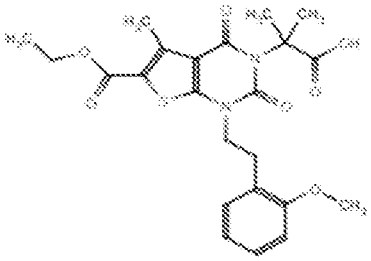
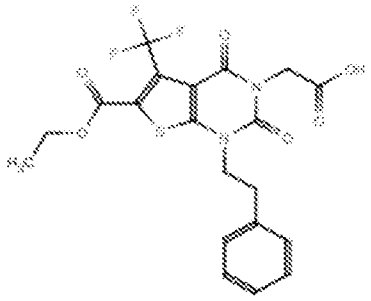
Cmpd #	Compound Structure	m/z
I-69		430 (M+1)
I-70		445 (M+1)
I-71		388 (M+1)
I-72		473 (M+Na)

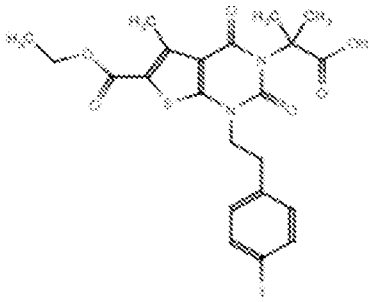
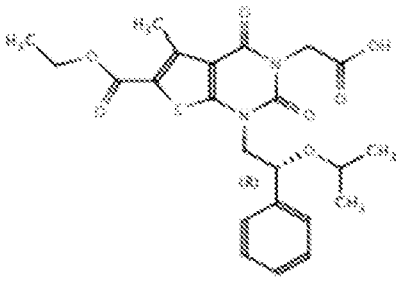
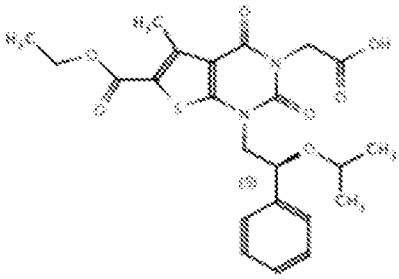
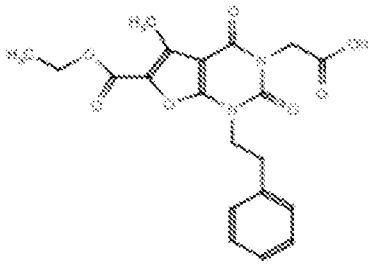
Cmpd #	Compound Structure	m/z
I-73		431 (M+1)
I-74		456 (M+1)
I-75		389 (M+1)
I-76		431 (M+1)
I-77		433 (M+1)

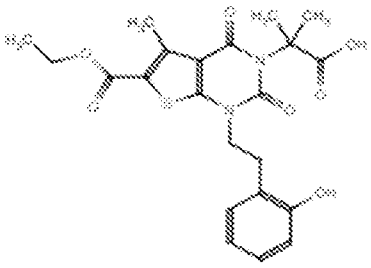
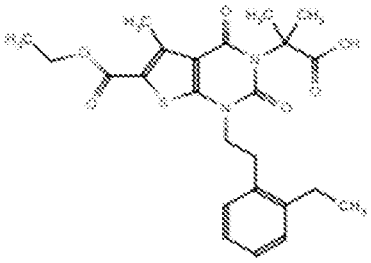
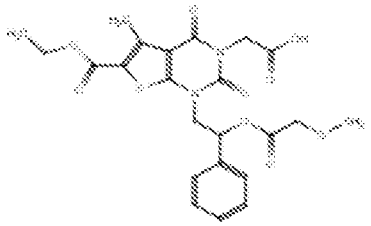
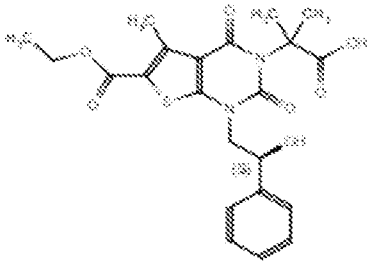
Cmpd #	Compound Structure	m/z
I-78		433 (M+1)
I-79		453 (M+Na)
I-80		431 (M+1)
I-81		417 (M+1)
I-82		417 (M+1)

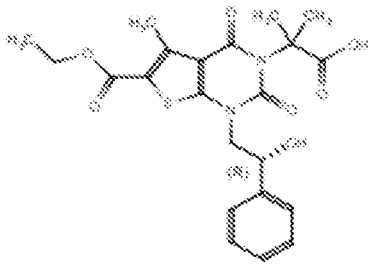
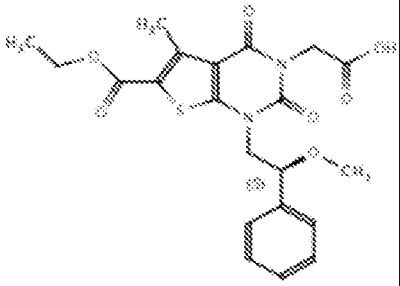
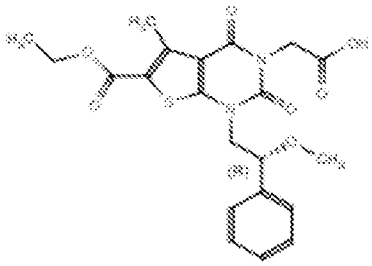
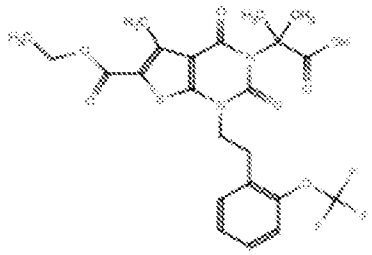
Cmpd #	Compound Structure	m/z
I-83		433 (M+1)
I-84		474 (M+1)
I-85		475 (M+1)
I-86		443 (M+1)

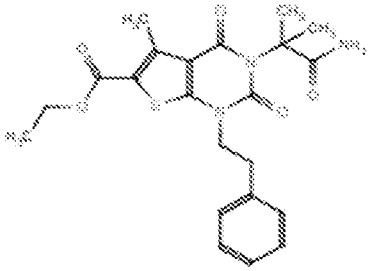
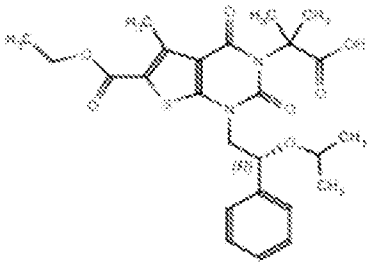
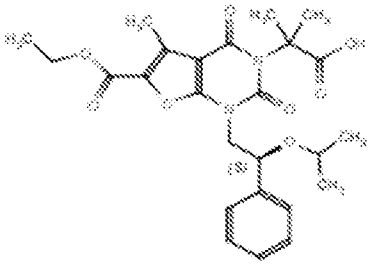
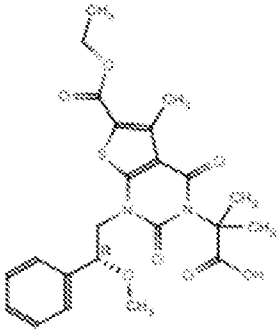
Cmpd #	Compound Structure	m/z
I-87		414 (M+1)
I-88		442 (M+1)
I-89		475 (M+1)
I-90		442 (M+1)

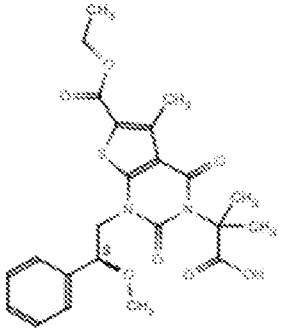
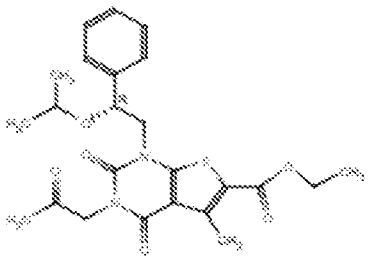
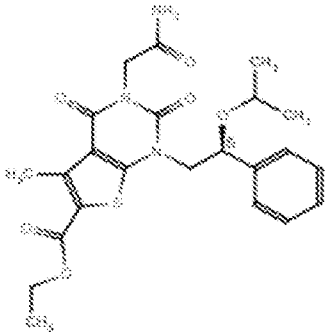
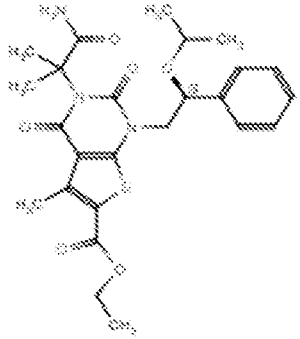
Cmpd #	Compound Structure	m/z
I-91		403 (M+1)
I-92		412 (M+1)
I-93		475 (M+1)
I-94		471 (M+1)

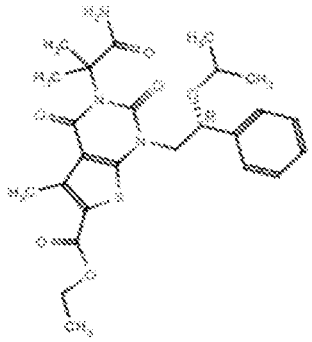
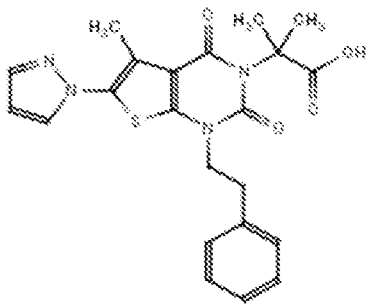
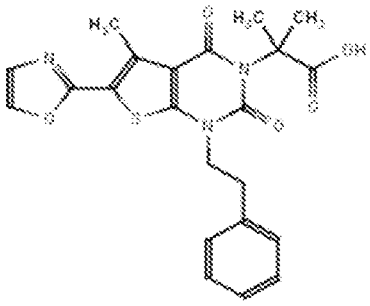
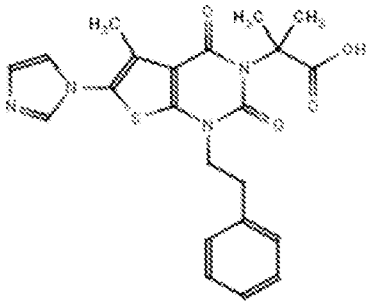
Cmpd #	Compound Structure	m/z
I-95		571 (M+1)
I-96		475 (M+1)
I-97		475 (M+1)
I-98		400 (M+1)

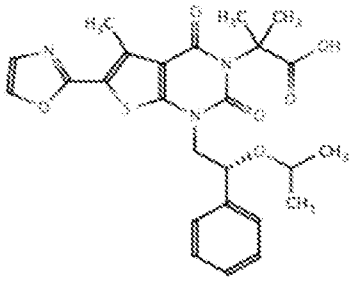
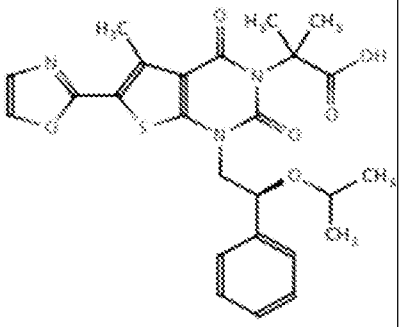
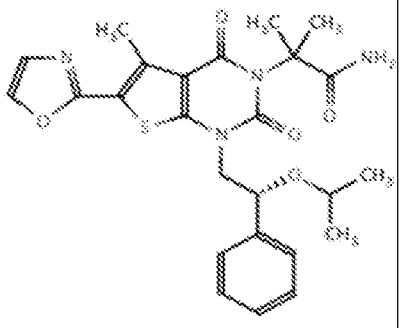
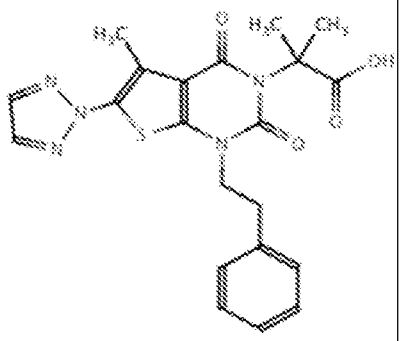
Cmpd #	Compound Structure	m/z
I-99		461 (M+1)
I-100		473 (M+1)
I-101		527(M +Na)
I-102		461 (M+1)

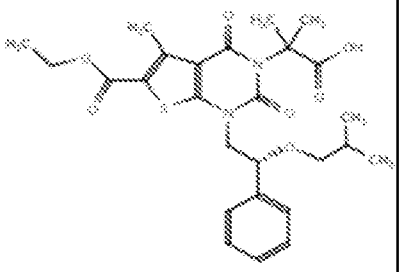
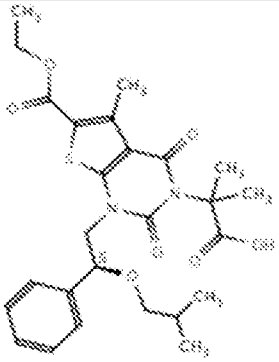
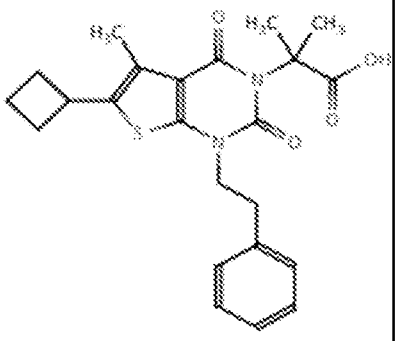
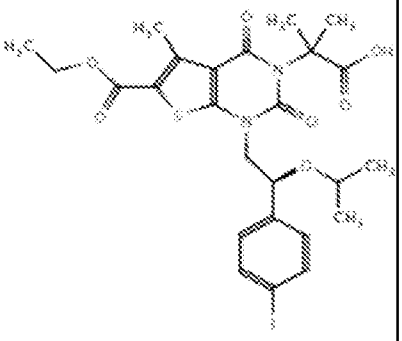
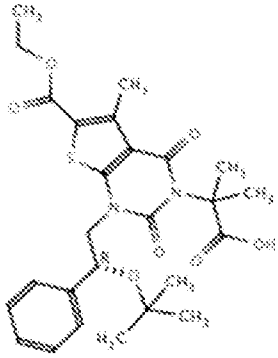
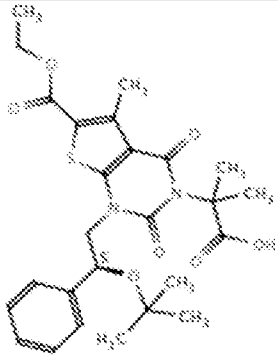
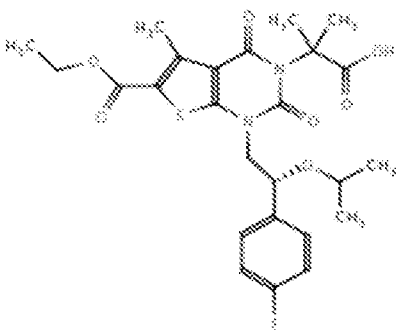
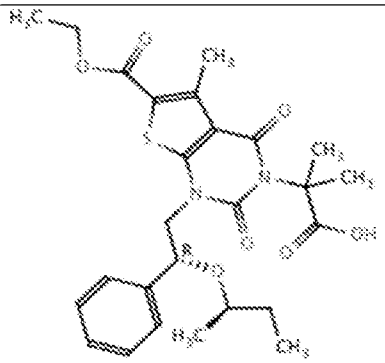
Cmpd #	Compound Structure	m/z
I-103		461 (M+1)
I-104		447 (M+1)
I-105		447 (M+1)
I-106		529 (M+1)

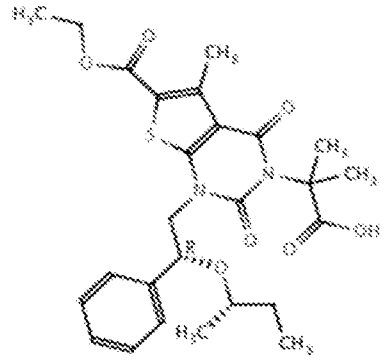
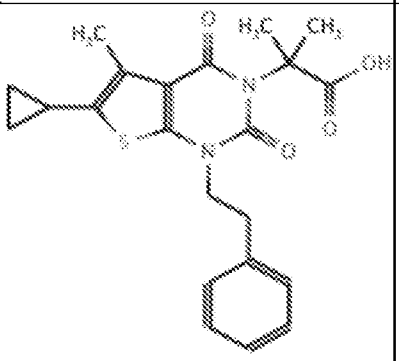
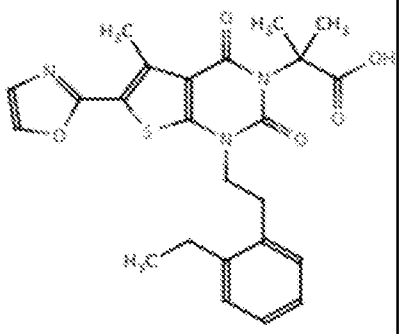
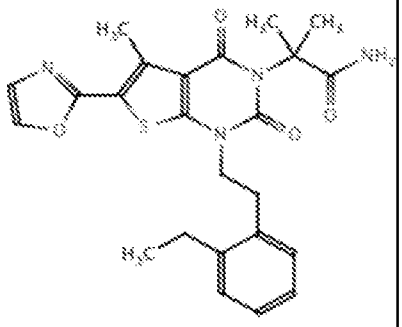
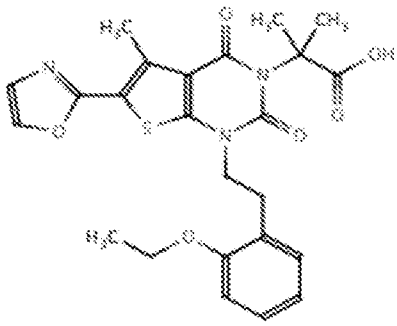
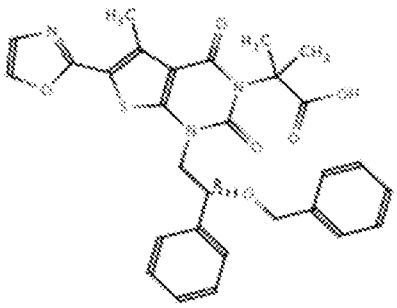
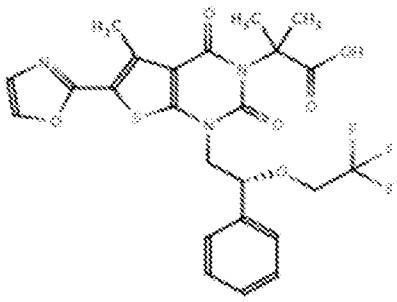
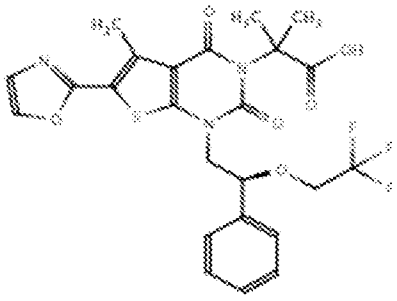
Cmpd #	Compound Structure	m/z
I-107		466 (M+Na)
I-108		503 (M+1)
I-109		503 (M+1)
I-110		475 (M+1)

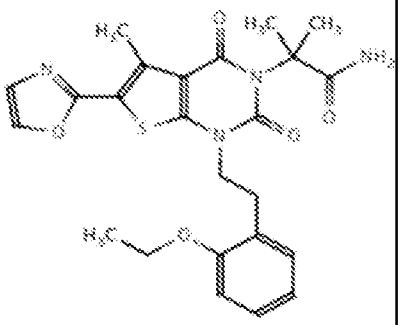
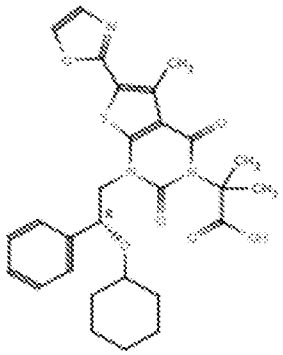
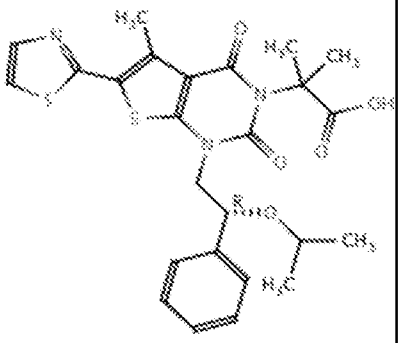
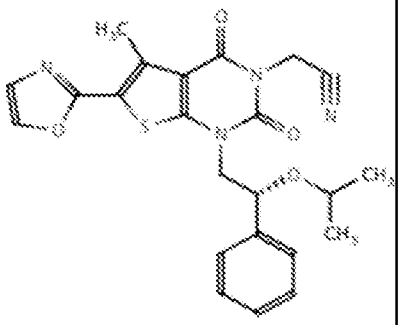
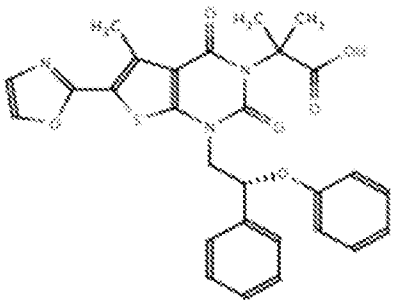
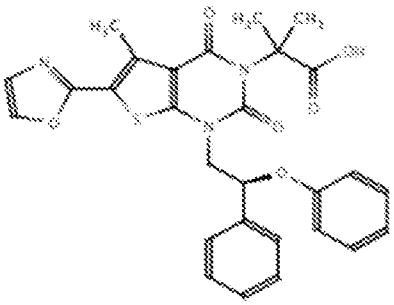
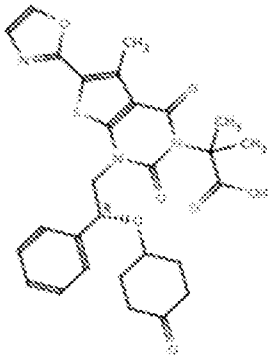
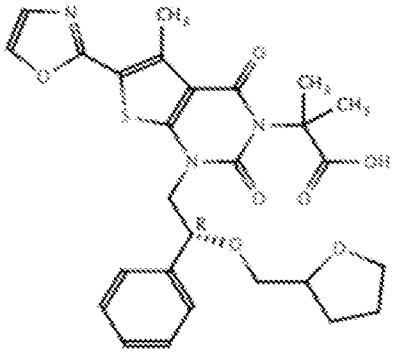
Cmpd #	Compound Structure	m/z
I-111		475 (M+1)
I-112		474 (M+1)
I-113		474 (M+1)
I-114		524 (M+Na)

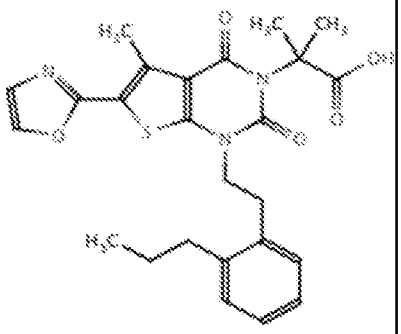
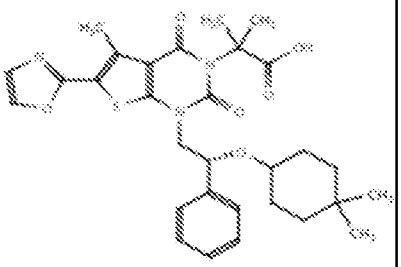
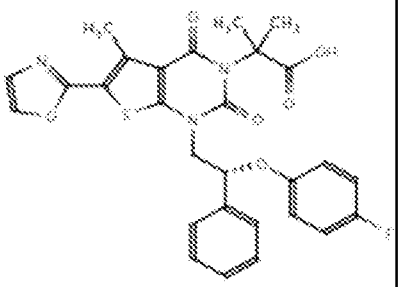
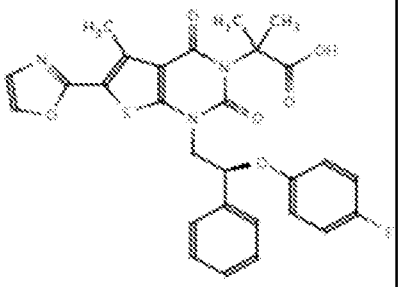
Cmpd #	Compound Structure	m/z
I-115		524 (M+Na)
I-116		439 (M+1)
I-117		440 (M+1)
I-118		439 (M+1)

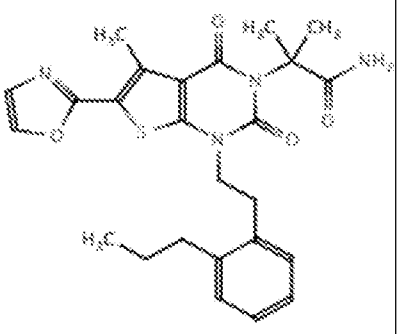
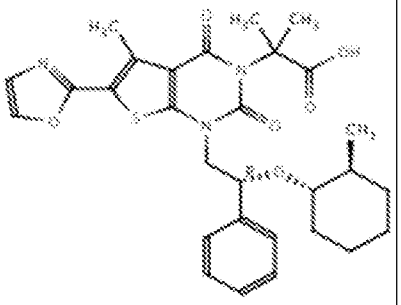
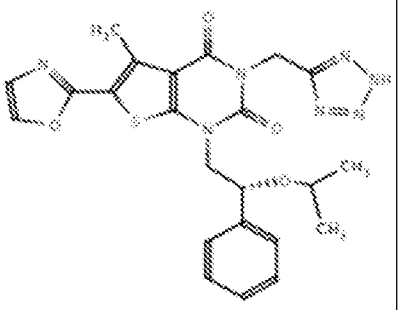
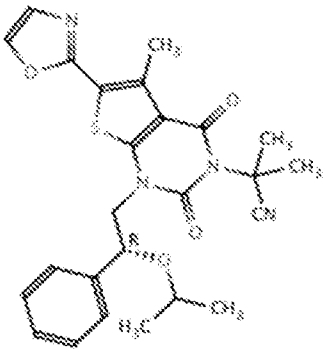
Cmpd #	Compound Structure	m/z
I-119		498 (M+1)
I-120		498 (M+1)
I-121		480 (M-NH2)
I-122		440 (M+1)

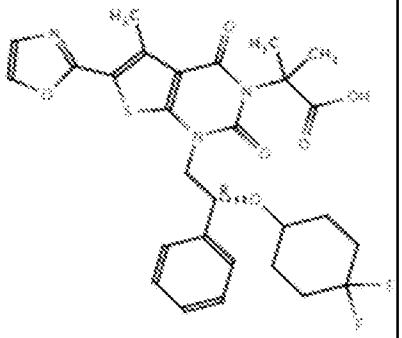
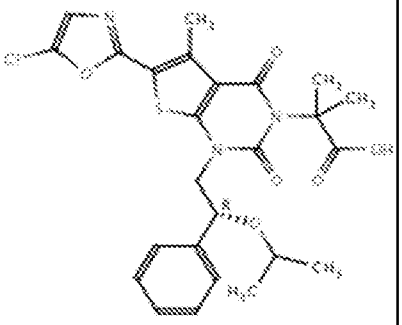
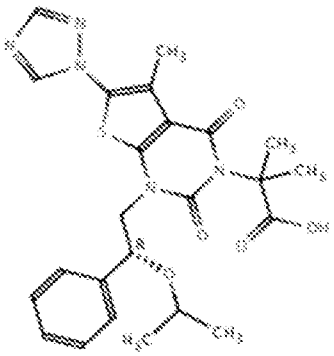
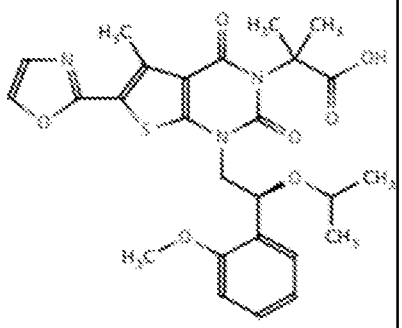
Cmpd #	Compound Structure	m/z
I-123		517 (M+1)
I-124		517 (M+1)
I-125		427 (M+1)
I-126		629 (M+1)
I-127		443 (M-C_4H_9O)
I-128		445 (M-C_4H_9O)
I-129		629 (M+1)
I-130		517 (M+1)

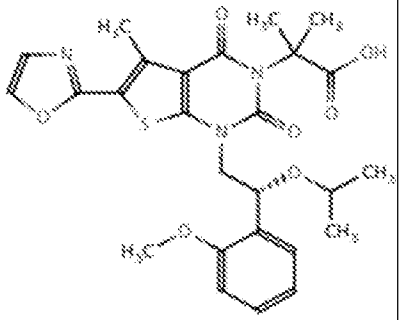
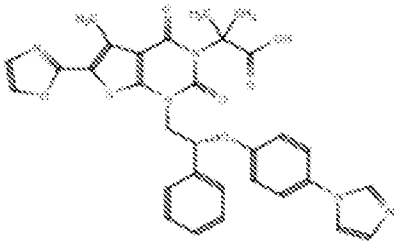
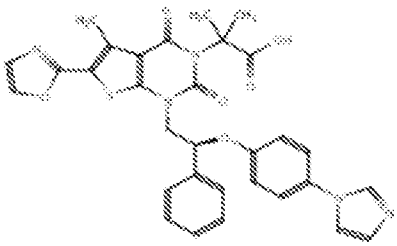
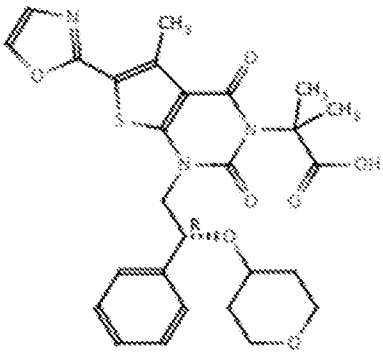
Cmpd #	Compound Structure	m/z
I-131		517 (M+1)
I-132		413 (M+1)
I-133		468 (M+1)
I-134		450 (M-NH2)
I-135		484 (M+1)
I-136		546 (M+1)
I-137		538 (M+1)
I-138		538 (M+1)

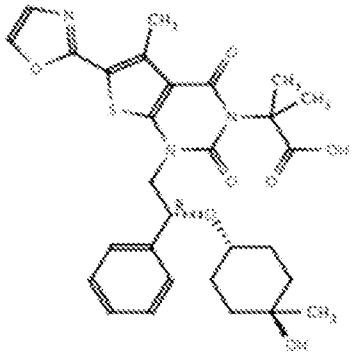
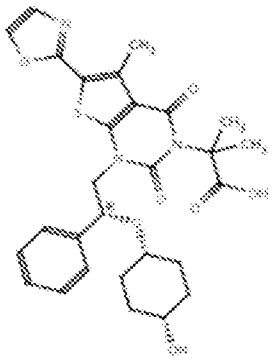
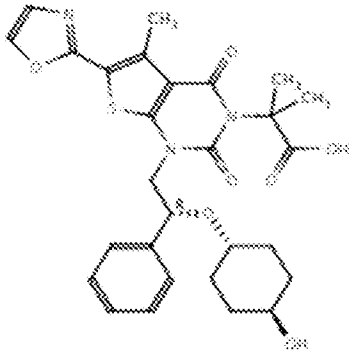
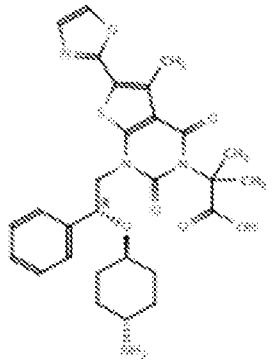
Cmpd #	Compound Structure	m/z
I-139		505 (M+Na)
I-140		538 (M+1)
I-141		514 (M+1)
I-142		451 (M+1)
I-143		532 (M+1)
I-144		532 (M+1)
I-145		552 (M+1)
I-146		562 (M+Na)

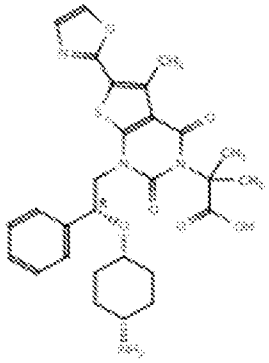
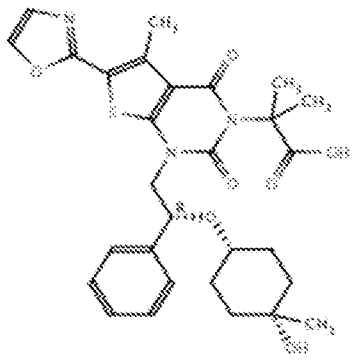
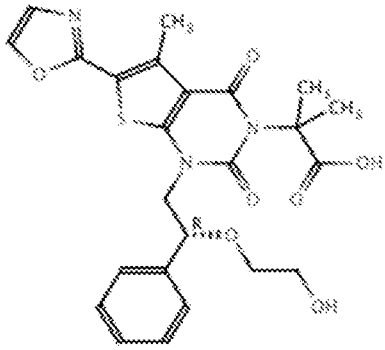
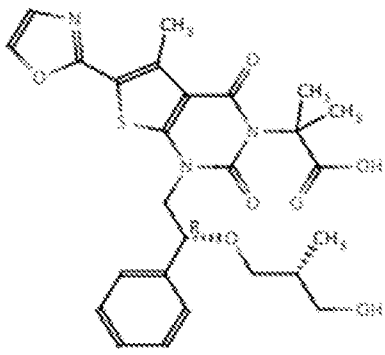
Cmpd #	Compound Structure	m/z
I-147		482 (M+1)
I-148		566 (M+1)
I-149		550 (M+1)
I-150		550 (M+1)

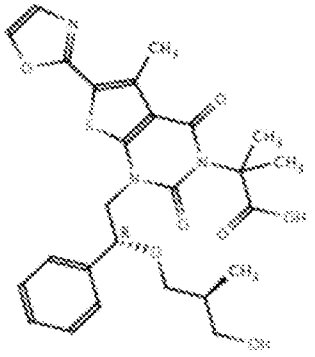
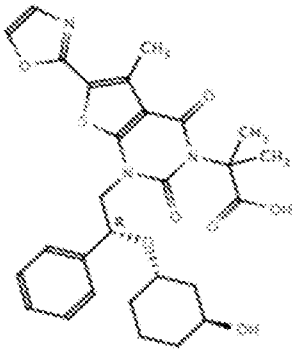
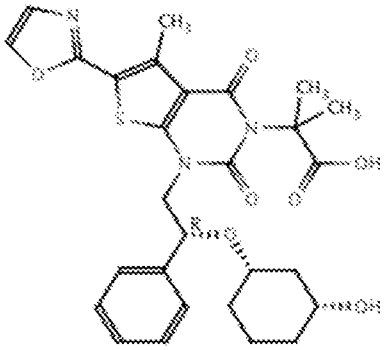
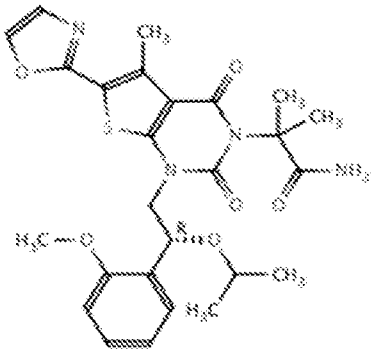
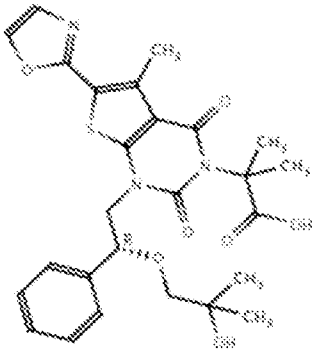
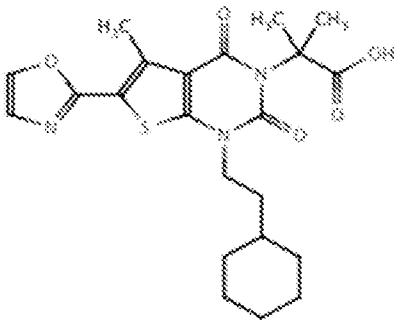
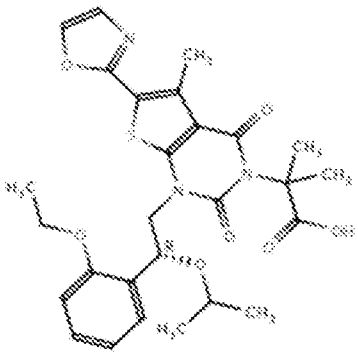
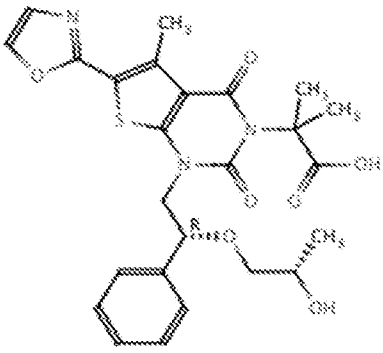
Cmpd #	Compound Structure	m/z
I-151		464 (M-NH2)
I-152		552 (M+1)
I-153		494 (M+1)
I-154		479 (M+1)

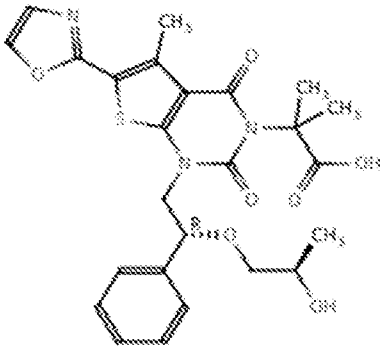
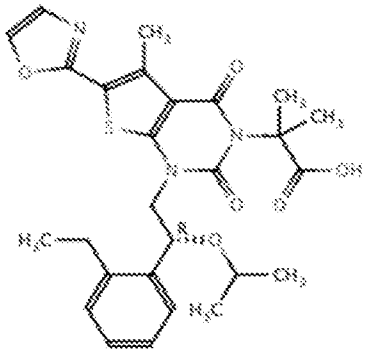
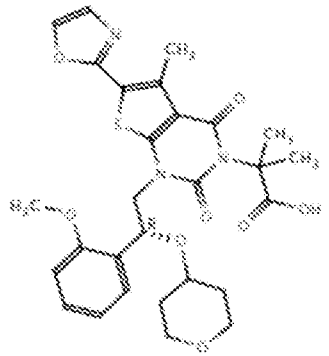
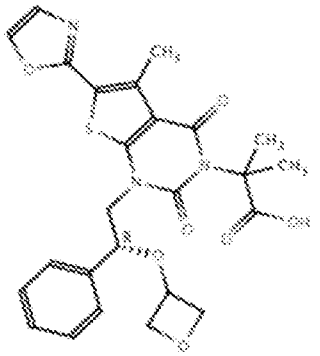
Cmpd #	Compound Structure	m/z
I-155		574 (M+1)
I-156		532 (M+1)
I-157		498 (M+1)
I-158		528 (M+1)

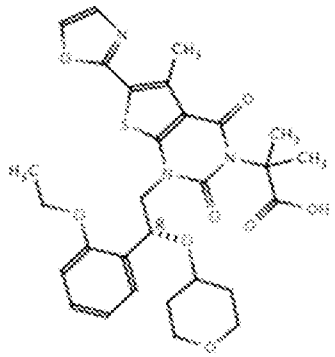
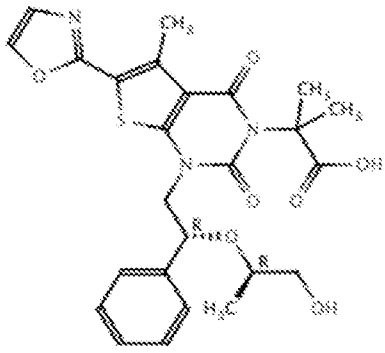
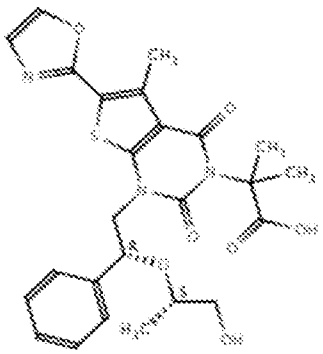
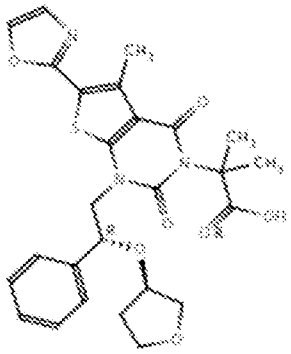
Cmpd #	Compound Structure	m/z
I-159		528 (M+1)
I-160		598 (M+1)
I-161		598 (M+1)
I-162		540 (M+1)

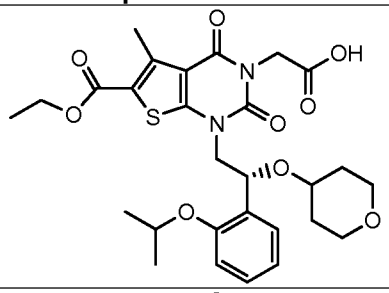
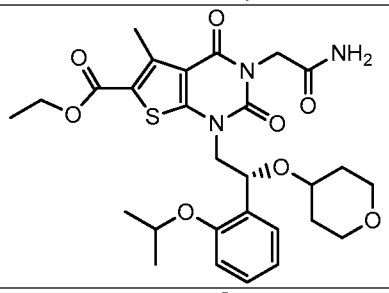
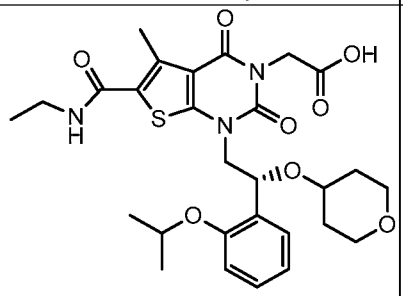
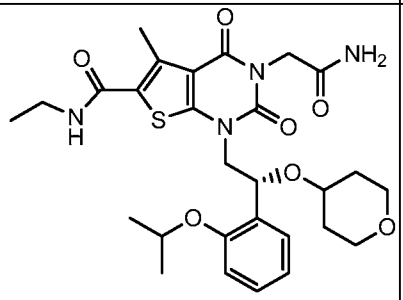
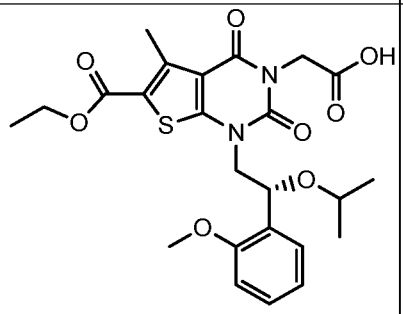
Cmpd #	Compound Structure	m/z
I-163		568 (M+1)
I-164		554 (M+1)
I-165		554 (M+1)
I-166		553 (M+1)

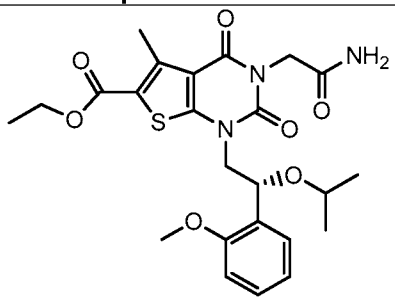
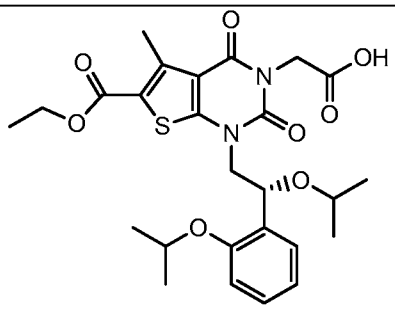
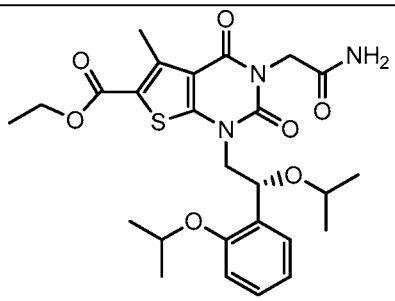
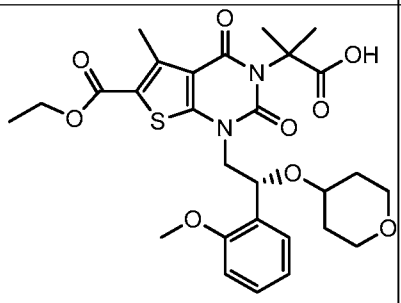
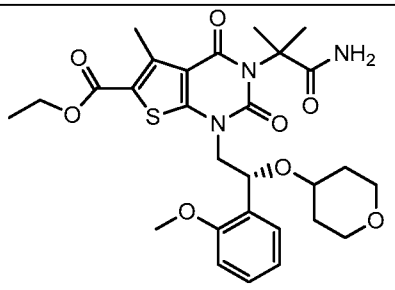
Cmpd #	Compound Structure	m/z
I-167		553 (M+1)
I-168		568 (M+1)
I-169		500 (M+1)
I-170		528 (M+1)

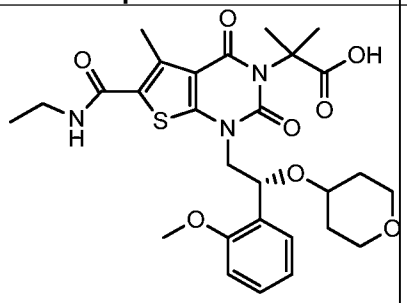
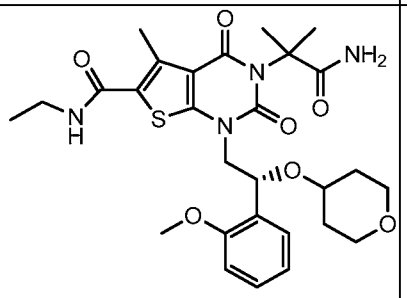
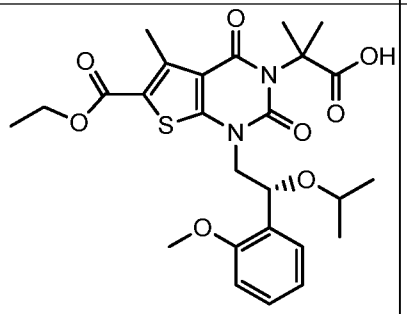
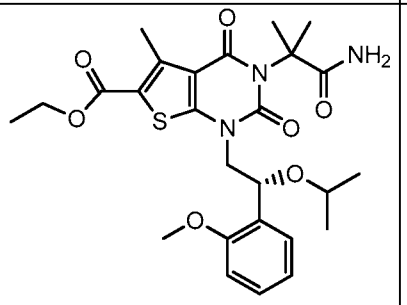
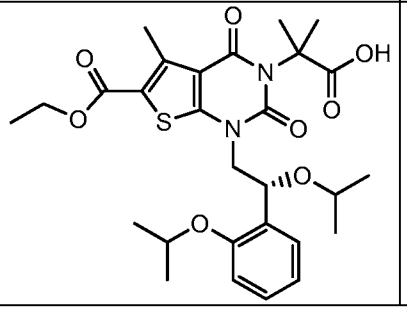
Cmpd #	Compound Structure	m/z
I-171		528 (M+1)
I-172		554 (M+1)
I-173		554 (M+1)
I-174		510 (M-NH_2)
I-175		528 (M+1)
I-176		446 (M+1)
I-177		542 (M+1)
I-178		514 (M+1)

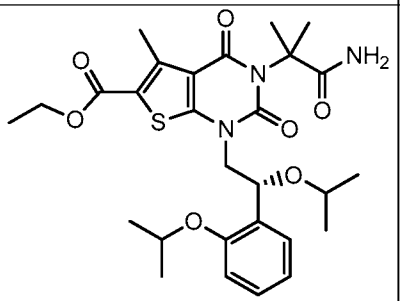
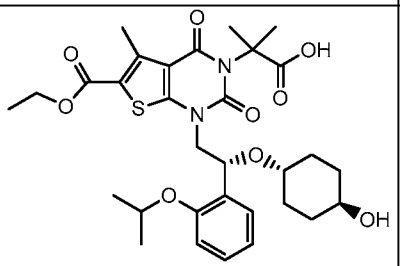
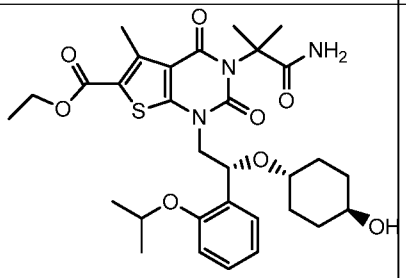
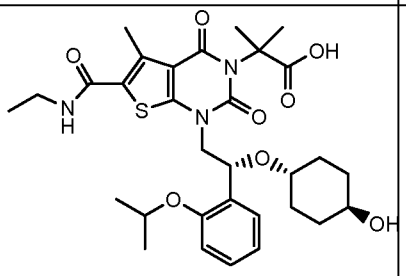
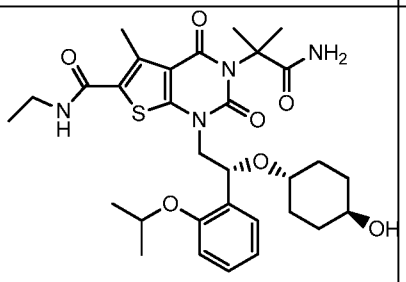
Cmpd #	Compound Structure	m/z
I-179		514 (M+1)
I-180		526 (M+1)
I-181		570 (M+1)
I-182		512 (M+1)

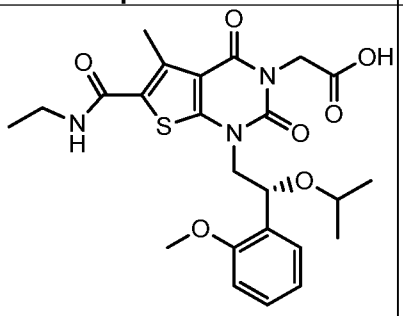
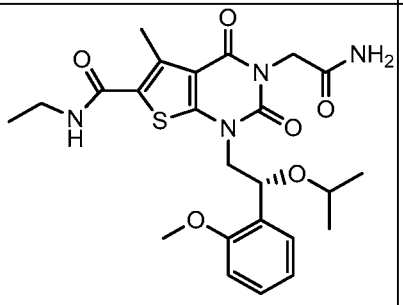
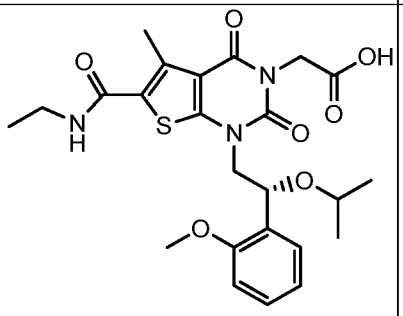
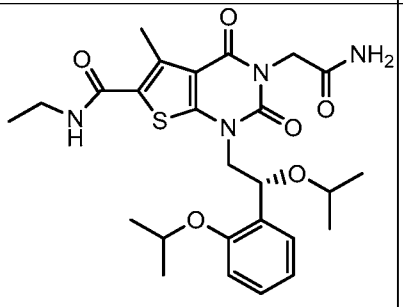
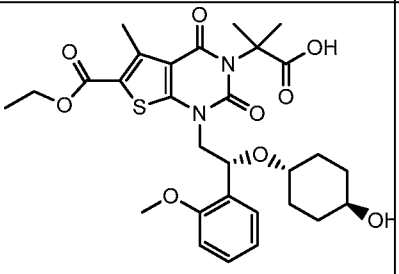
Cmpd #	Compound Structure	m/z
I-183		606 (M+Na)
I-184		514 (M+1)
I-185		514 (M+1)
I-186		526 (M+1)

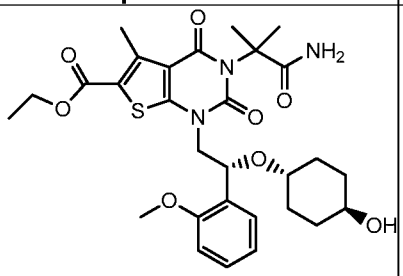
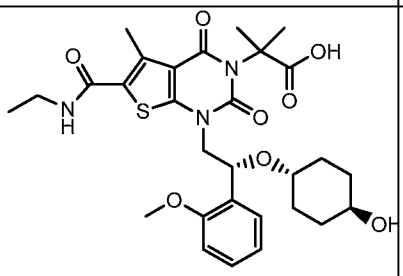
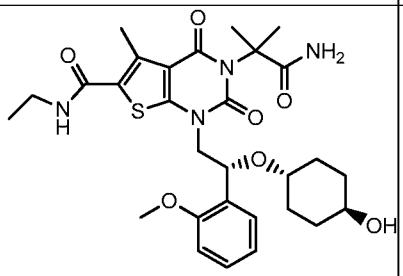
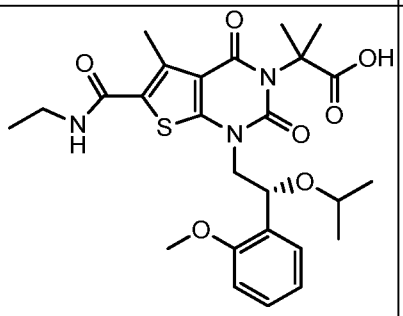
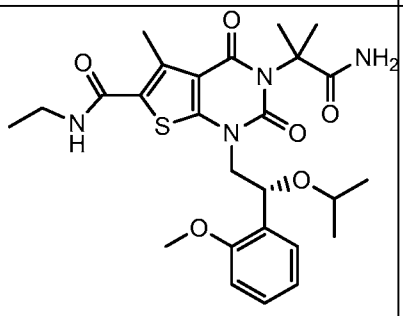
Cmpd #	Compound Structure	m/z
I-187		
I-188		
I-189		
I-190		
I-191		

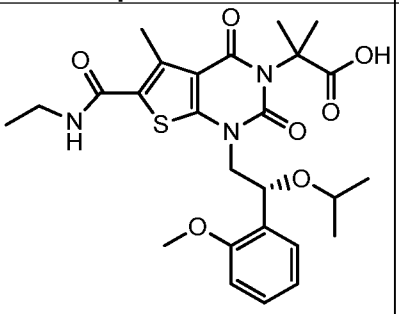
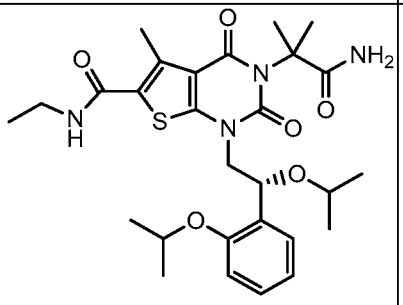
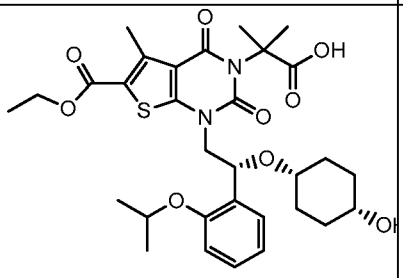
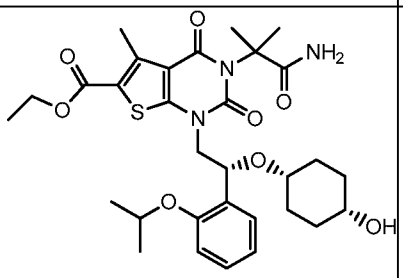
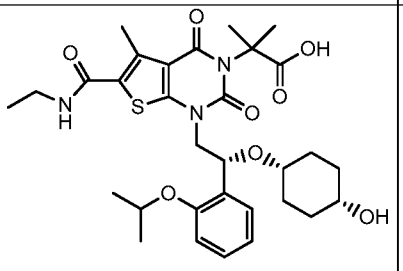
Cmpd #	Compound Structure	m/z
I-192		
I-193		
I-194		
I-195		
I-196		

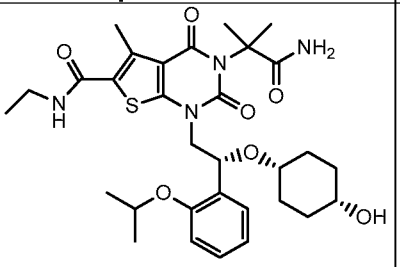
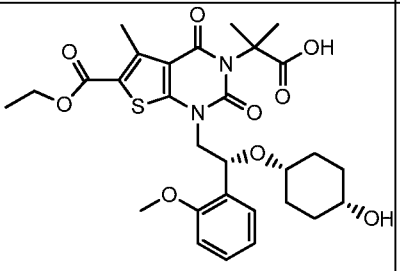
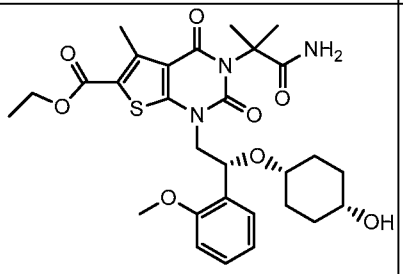
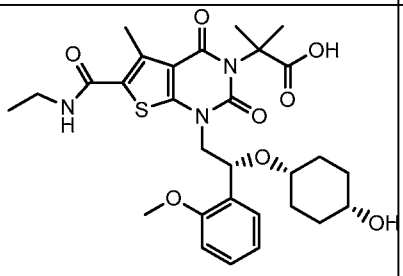
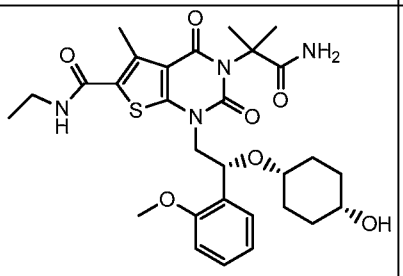
Cmpd #	Compound Structure	m/z
I-197		
I-198		
I-199		
I-200		
I-201		

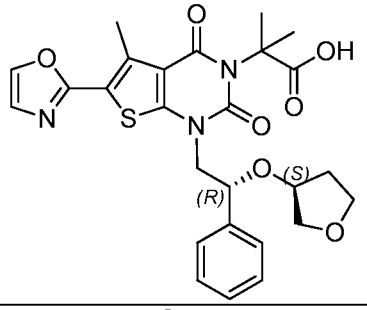
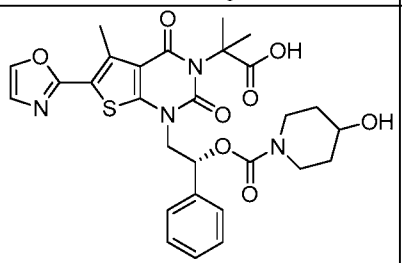
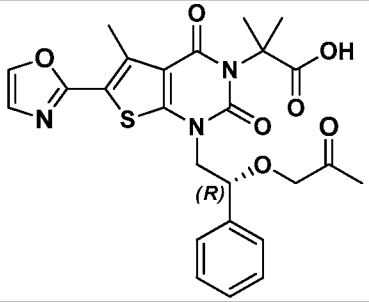
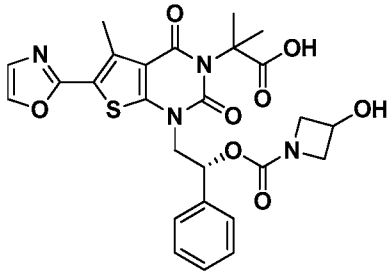
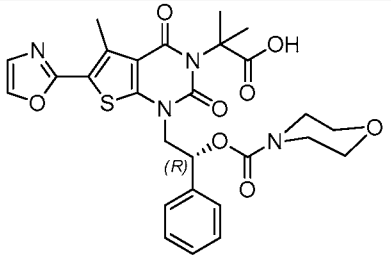
Cmpd #	Compound Structure	m/z
I-202		
I-203		
I-204		
I-205		
I-206		

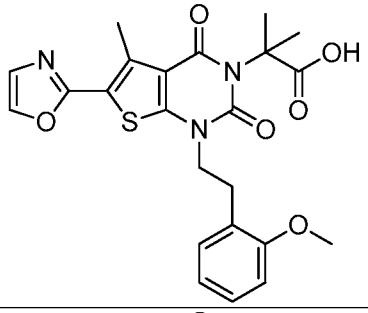
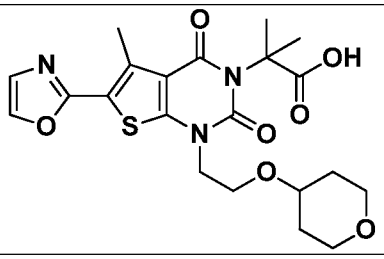
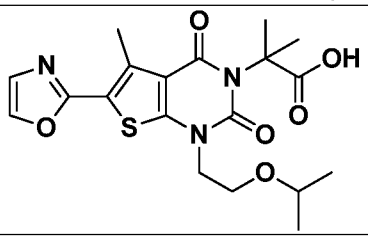
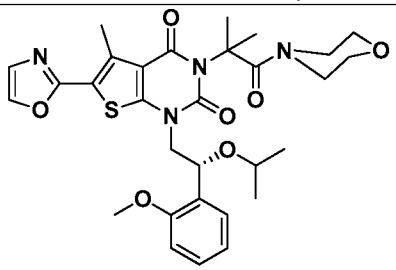
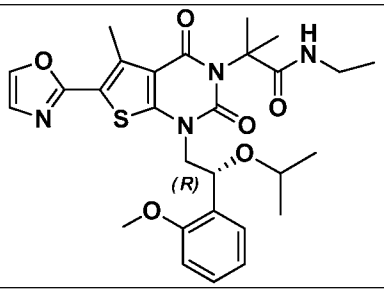
Cmpd #	Compound Structure	m/z
I-207		
I-208		
I-209		
I-210		
I-211		

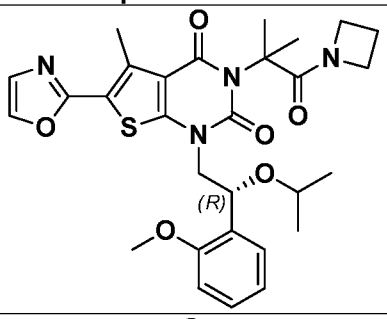
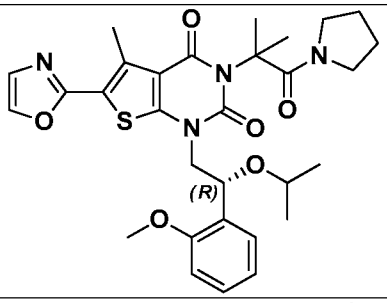
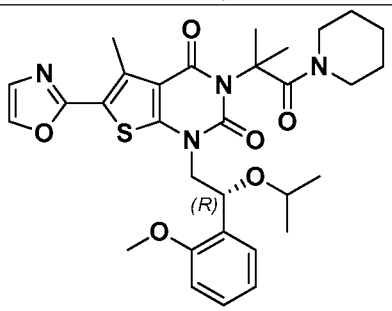
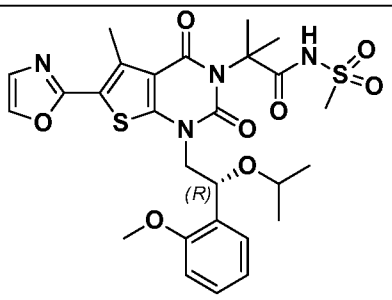
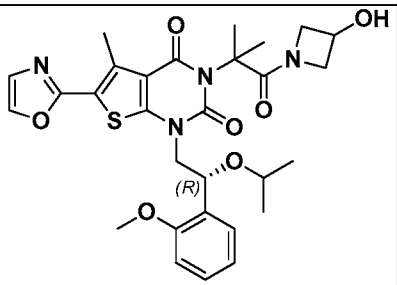
Cmpd #	Compound Structure	m/z
I-212		
I-213		
I-214		
I-215		
I-216		

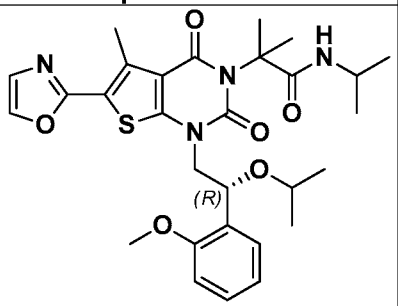
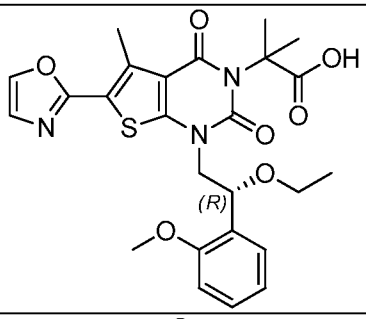
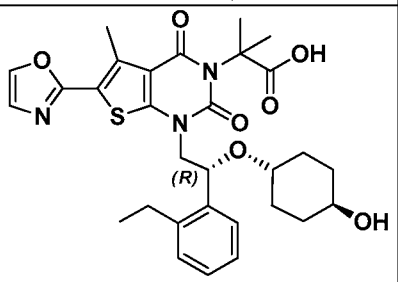
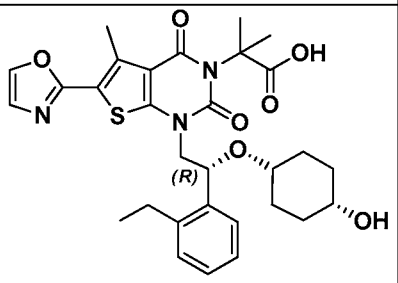
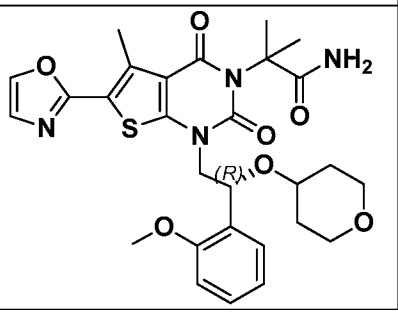
Cmpd #	Compound Structure	m/z
I-217		
I-218		
I-219		
I-220		
I-221		

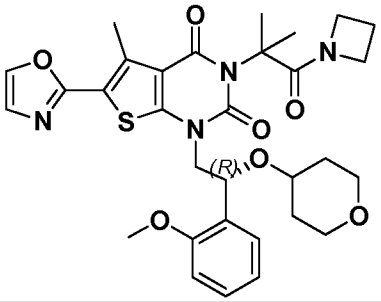
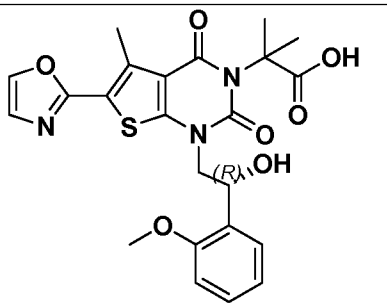
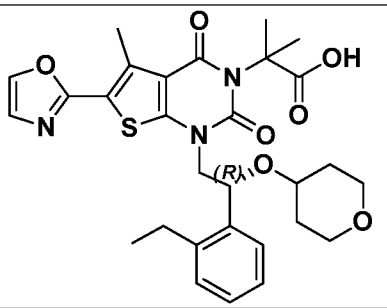
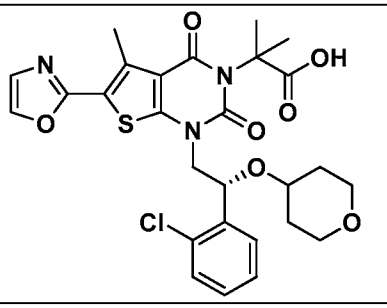
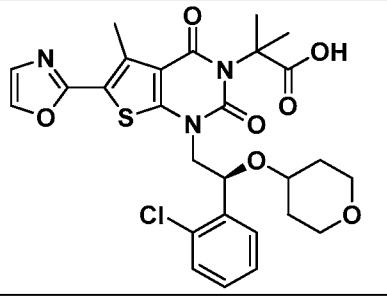
Cmpd #	Compound Structure	m/z
I-222		
I-223		
I-224		
I-225		
I-226		

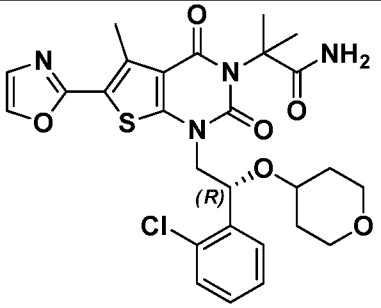
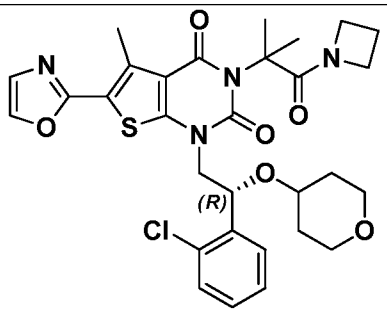
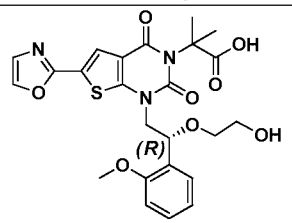
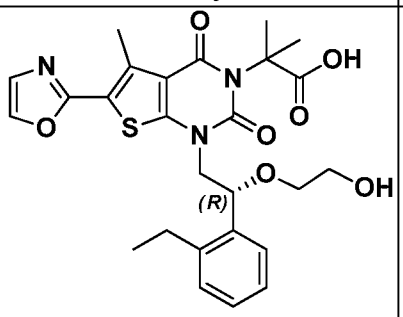
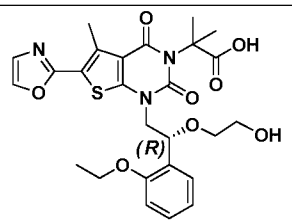
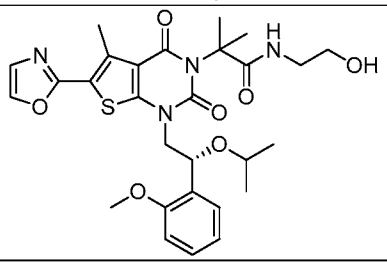
Cmpd #	Compound Structure	m/z
I-227		526 (M+H)$^+$,
I-228		583 (M+H)$^+$
I-229		512 (M+H)$^+$
I-230		555 (M+H)$^+$
I-231		569 (M+H)$^+$

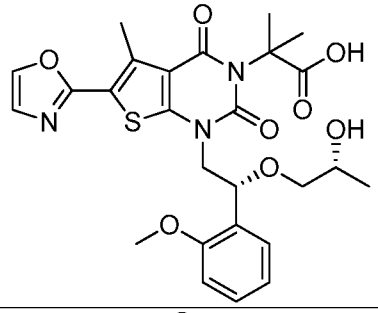
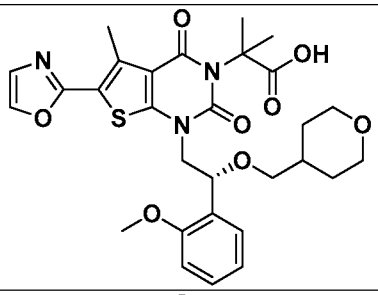
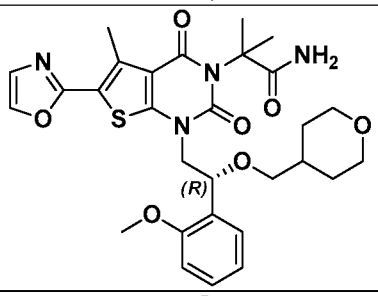
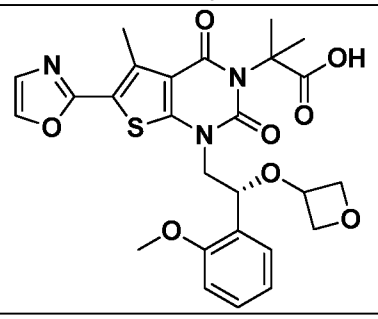
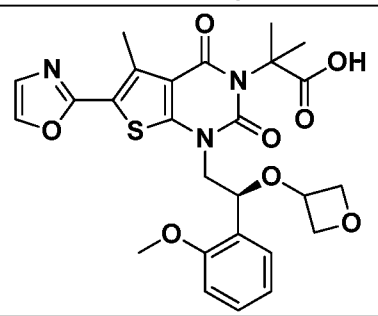
Cmpd #	Compound Structure	m/z
I-232		470 (M+H)$^+$
I-233		464 (M+H)$^+$
I-234		423 (M+H)$^+$
I-235		619 (M+Na)$^+$
I-236		577 (M+Na)$^+$

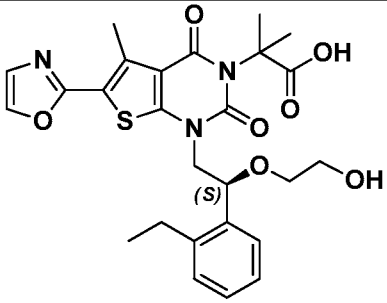
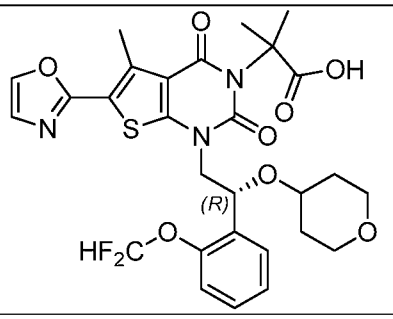
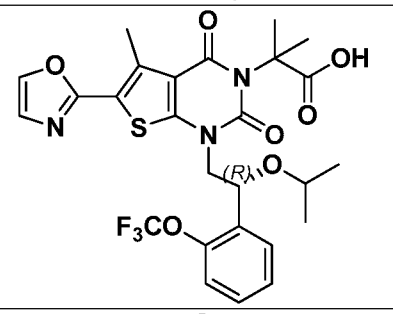
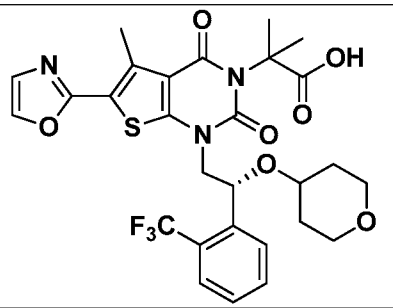
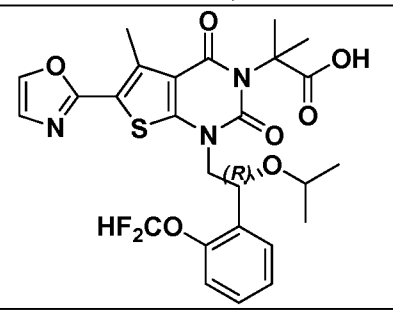
Cmpd #	Compound Structure	m/z
I-237		568 $(M+H)^+$
I-238		603 $(M+Na)^+$
I-239		617 $(M+Na)^+$
I-240		605 $(M+H)^+$
I-241		605 $(M+Na)^+$

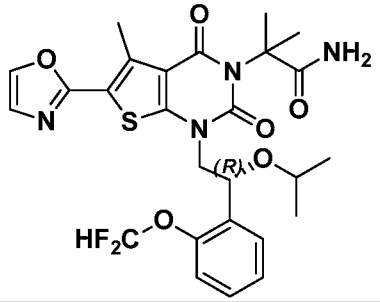
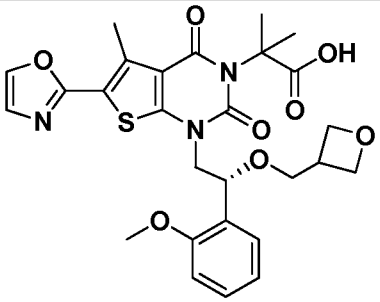
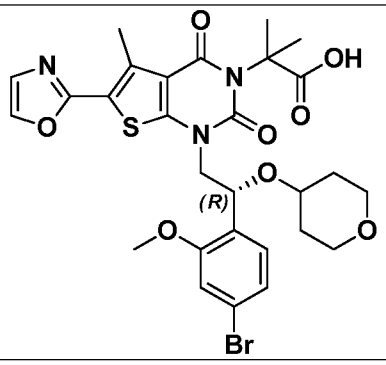
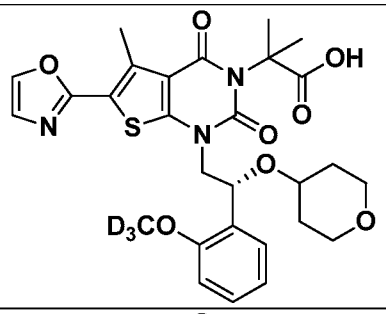
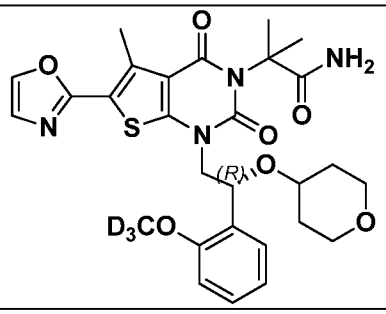
Cmpd #	Compound Structure	m/z
I-242		591 $(M+Na)^+$
I-243		514 $(M+H)^+$
I-244		582 $(M+H)^+$
I-245		582 $(M+H)^+$
I-246		591 $(M+Na)^+$

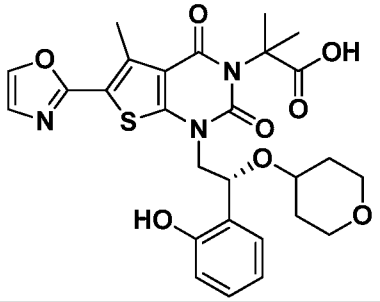
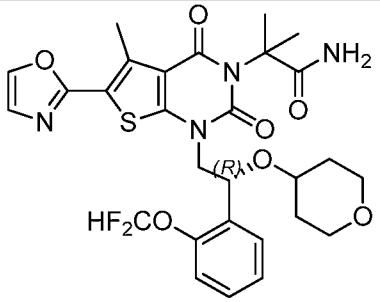
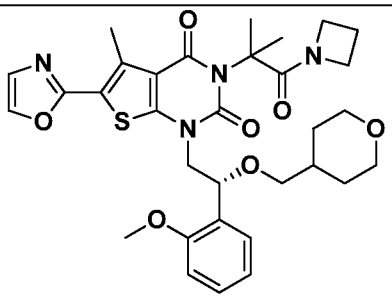
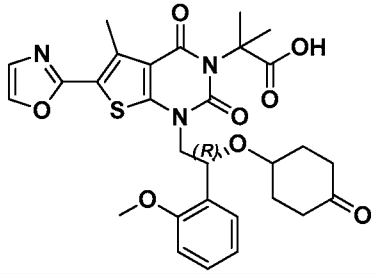
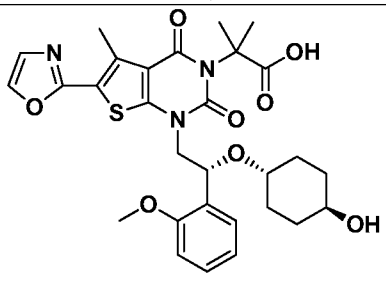
Cmpd #	Compound Structure	m/z
I-247		609 (M+H)$^+$
I-248		586 (M+H)$^+$
I-249		568 (M+H)$^+$
I-250		574 (M+H)$^+$
I-251		574 (M+H)$^+$

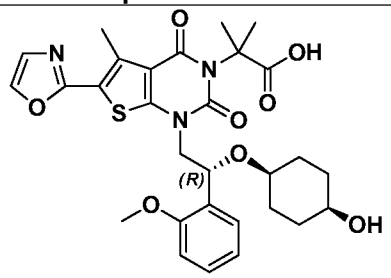
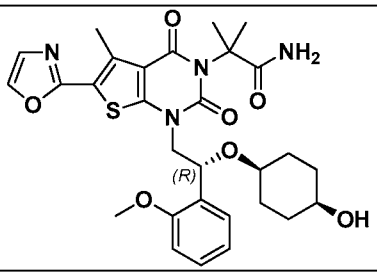
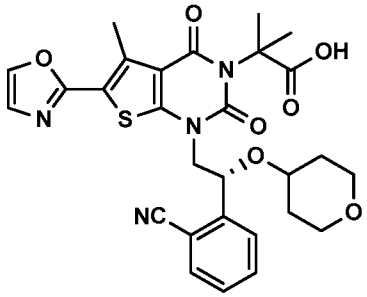
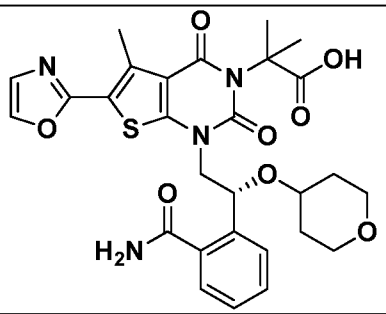
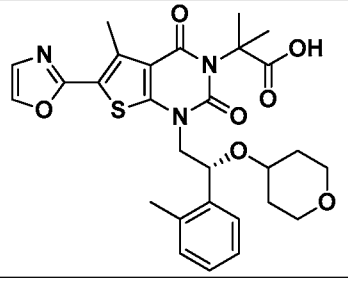
Cmpd #	Compound Structure	m/z
I-252		595 (M+Na)$^+$
I-253		613 (M+H)$^+$
I-254		530 (M+H)$^+$
I-255		528 (M+H)$^+$
I-256		544 (M+H)$^+$
I-257		571 (M+H)$^+$

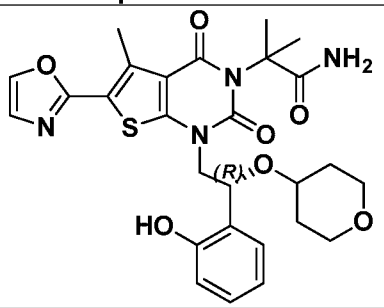
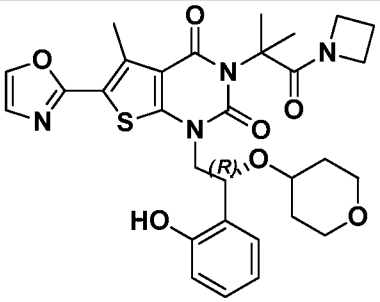
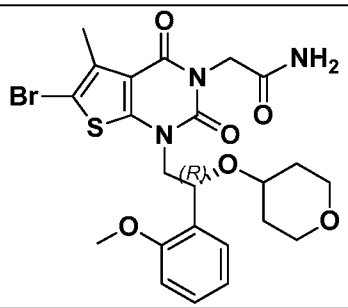
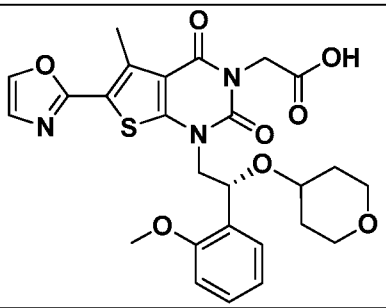
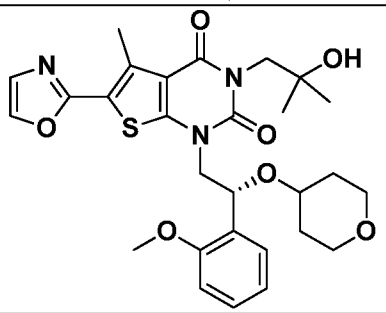
Cmpd #	Compound Structure	m/z
I-258		544 (M+H)$^+$
I-259		584 (M+H)$^+$
I-260		583 (M+H)$^+$
I-261		542 (M+H)$^+$
I-262		542 (M+H)$^+$

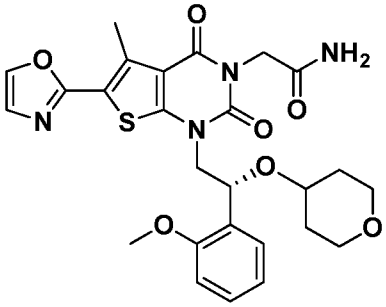
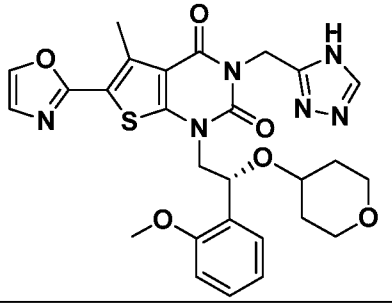
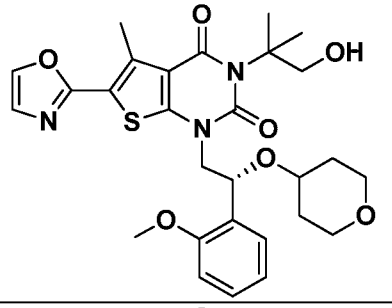
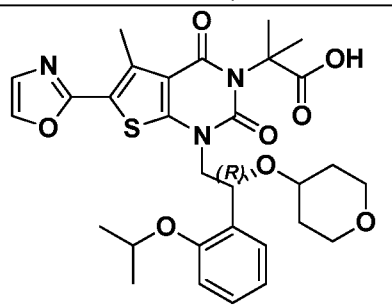
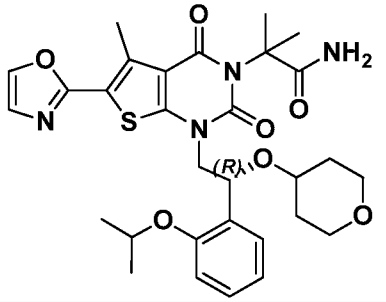
Cmpd #	Compound Structure	m/z
I-263		528 (M+H)$^+$
I-264		607 (M+H)$^+$
I-265		582 (M+H)$^+$
I-266		608 (M+H)$^+$
I-267		564 (M+H)$^+$

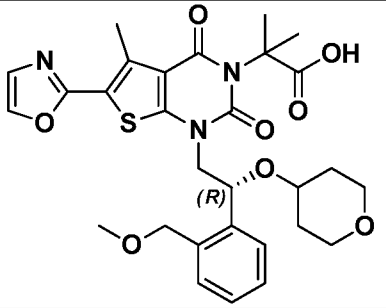
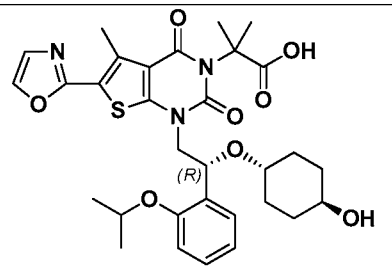
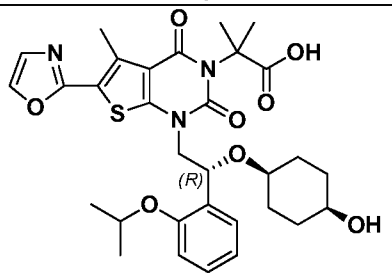
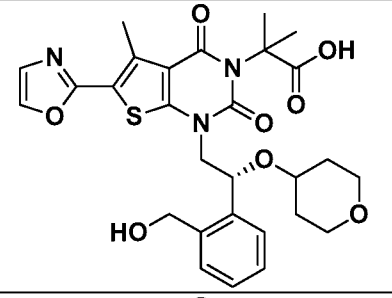
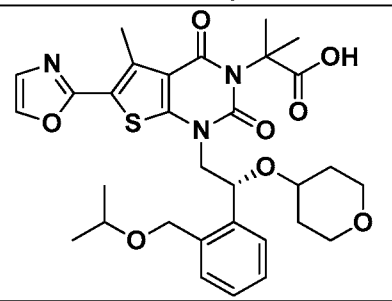
Cmpd #	Compound Structure	m/z
I-268		563 (M+H)$^+$
I-269		556 (M+H)$^+$
I-270		650 (M+H)$^+$
I-271		573 (M+H)$^+$
I-272		594 (M+Na)$^+$

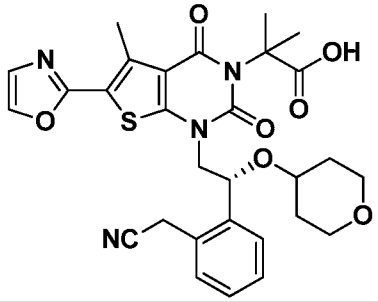
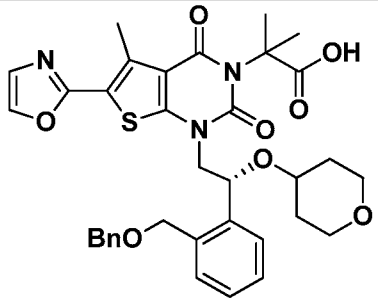
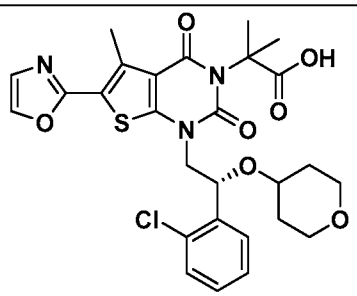
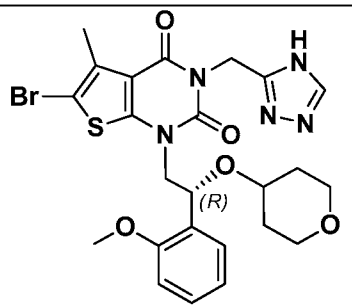
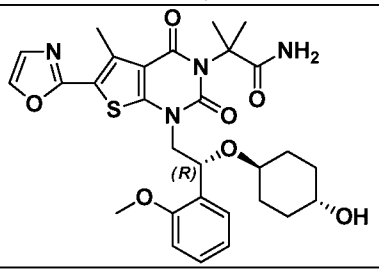
Cmpd #	Compound Structure	m/z
I-273		556 (M+H)$^+$
I-274		627 (M+Na)$^+$
I-275		623 (M+H)$^+$
I-276		582 (M+H)$^+$
I-277		584 (M+H)$^+$

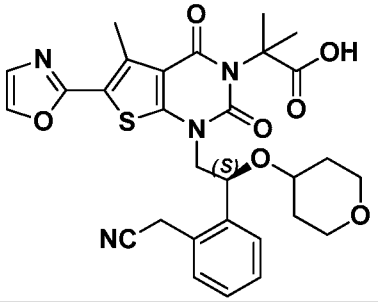
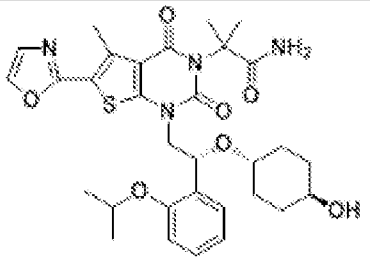
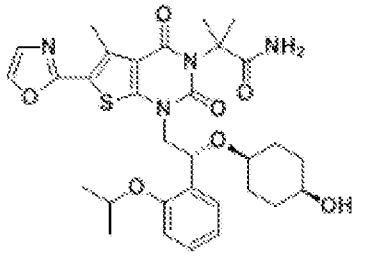
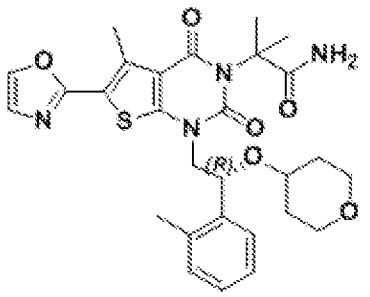
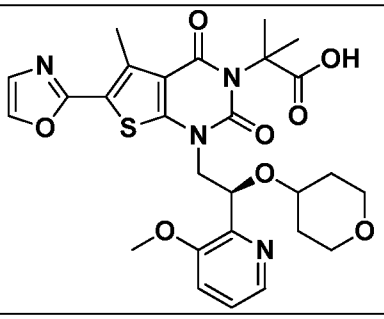
Cmpd #	Compound Structure	m/z
I-278		584 $(M+H)^+$
I-279		605 $(M+Na)^+$
I-280		565 $(M+H)^+$
I-281		583 $(M+H)^+$
I-282		554 $(M+H)^+$

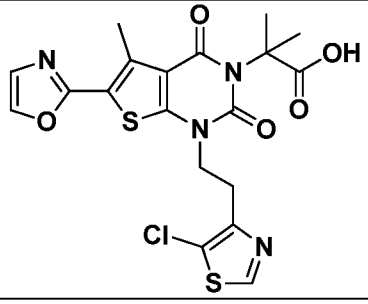
Cmpd #	Compound Structure	m/z
I-283		577 $(M+Na)^+$
I-284		595 $(M+H)^+$
I-285		554, 552 $(M+H^+)$
I-286		542 $(M+H)^+$
I-287		556 $(M+H)^+$

Cmpd #	Compound Structure	m/z
I-288		541 $(M+H)^+$
I-289		565 $(M+H)^+$
I-290		556 $(M+H)^+$
I-291		598 $(M+H)^+$
I-292		619 $(M+Na)^+$

Cmpd #	Compound Structure	m/z
I-293		606 $(M+Na)^+$
I-294		612 $(M+H)^+$
I-295		612 $(M+H)^+$
I-296		592 $(M+Na)^+$
I-297		634 $(M+Na)^+$

Cmpd #	Compound Structure	m/z
I-298		579 (M+H)$^+$
I-299		
I-300		574 (M+H)$^+$
I-301		576 (M+H)$^+$
I-302		605 (M+Na)$^+$

Cmpd #	Compound Structure	m/z
I-303		579 (M+H)$^+$
I-304		633 (M+Na)$^+$
I-305		633 (M+Na)$^+$
I-306		575 (M+Na)$^+$
I-307		593 (M+Na)$^+$

Cmpd #	Compound Structure	m/z
I-308		481 (M+H)$^+$

[0092] In certain embodiments, the present invention provides any compound selected from those depicted in Table 1, above, or a pharmaceutically acceptable salt thereof.

4. Uses, Formulation and Administration and Pharmaceutically acceptable compositions

[0093] According to another embodiment, the invention provides a composition comprising a compound of this invention or a pharmaceutically acceptable salt, ester, or salt of ester thereof and a pharmaceutically acceptable carrier, adjuvant, or vehicle. The amount of compound in compositions of this invention is such that is effective to measurably inhibit ACC, in a biological sample or in a patient. In certain embodiments, the amount of compound in compositions of this invention is such that is effective to measurably inhibit ACC, in a biological sample or in a patient. In certain embodiments, a composition of this invention is formulated for administration to a patient in need of such composition. In some embodiments, a composition of this invention is formulated for oral administration to a patient.

[0094] The term "patient," as used herein, means an animal, preferably a mammal, and most preferably a human.

[0095] The term "pharmaceutically acceptable carrier, adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based

substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[0096] A "pharmaceutically acceptable derivative" means any non-toxic salt, ester, salt of an ester or other derivative of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof.

[0097] As used herein, the term "inhibitorily active metabolite or residue thereof" means that a metabolite or residue thereof is also an inhibitor of ACC.

[0098] Compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

[0099] For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[00100] Pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[00101] Alternatively, pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[00102] Pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[00103] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

[00104] For topical applications, provided pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, provided pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[00105] For ophthalmic use, provided pharmaceutically acceptable compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be formulated in an ointment such as petrolatum.

[00106] Pharmaceutically acceptable compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[00107] Most preferably, pharmaceutically acceptable compositions of this invention are formulated for oral administration. Such formulations may be administered with or without food. In some embodiments, pharmaceutically acceptable compositions of this invention are administered without food. In other embodiments, pharmaceutically acceptable compositions of this invention are administered with food.

[00108] The amount of compounds of the present invention that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration. Preferably, provided compositions should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the inhibitor can be administered to a patient receiving these compositions.

[00109] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present invention in the composition will also depend upon the particular compound in the composition.

Uses of Compounds and Pharmaceutically Acceptable Compositions

[00110] Acetyl-CoA carboxylase (ACC) catalyzes the ATP-dependent carboxylation of acetyl-CoA to form malonyl-CoA. This reaction, which proceeds in two half-reactions, a biotin carboxylase (BC) reaction and a carboxyltransferase (CT) reaction, is the first committed step in

fatty acid (FA) biosynthesis and is the rate-limiting reaction for the pathway. In addition to its role as a substrate in FA biosynthesis, malonyl-CoA, the product of the ACC-catalyzed reaction, also plays an important regulatory role in controlling mitochondrial FA uptake through allosteric inhibition of carnitine palmitoyltransferase I (CPT-I), the enzyme catalyzing the first committed step in mitochondrial FA oxidation. Malonyl-CoA, therefore, is a key metabolic signal for the control of FA production and utilization in response to dietary changes and altered nutritional requirements in animals, for example during exercise, and therefore plays a key role in controlling the switch between carbohydrate and fat utilization in liver and skeletal muscle [Harwood, 2005].

[00111] In mammals, ACC exists as two tissue-specific isozymes, ACC1 which is present in lipogenic tissues (liver, adipose) and ACC2, which is present in oxidative tissues (liver, heart, skeletal muscle). ACC1 and ACC2 are encoded by separate genes, display distinct cellular distributions, and share 75% overall amino acid sequence identity, except for an extension at the N-terminus of ACC2 that direct ACC2 to the mitochondrial membrane. ACC1, which lacks this targeting sequence, is localized to the cytoplasm. In the heart and skeletal muscle, which have a limited capacity to synthesize fatty acids, the malonyl-CoA formed by ACC2 functions to regulate FA oxidation. In the liver, the malonyl-CoA formed in the cytoplasm through the actions of ACC1 is utilized for FA synthesis and elongation leading to triglyceride formation and VLDL production, whereas the malonyl-CoA formed at the mitochondrial surface by ACC2 acts to regulate FA oxidation [Tong and Harwood, *J. Cellular Biochem.* 99: 1476, 2006]. This compartmentalization of malonyl-CoA results from a combination of synthesis proximity [Abu-Elheiga *et al.,* PNAS (USA) 102: 12011, 2005] and the rapid action of malonyl-CoA decarboxylase [Cheng *et al., J. Med. Chem.* 49:1517, 2006].

[00112] Simultaneous inhibition of the enzymatic activities of ACC1 and ACC2 offers the ability to inhibit *de novo* FA production in lipogenic tissues (e.g. liver & adipose) while at the same time stimulating FA oxidation in oxidative tissues (e.g. liver & skeletal muscle) and therefore offers an attractive modality for favorably affecting, in a concerted manner, a multitude of cardiovascular risk factors associated with obesity, diabetes, insulin resistance, and the metabolic syndrome.

[00113] Several lines of evidence strongly support the concept of direct inhibition of ACC activity as an important therapeutic target for treating obesity, diabetes, insulin resistance, and the metabolic syndrome.

[00114] Abu-Elheiga *et al.* [*Proc. Natl. Acad. Sci.* USA 100:10207-10212, 2003] demonstrated that ACC2 knock-out mice exhibit reduced skeletal and cardiac muscle malonyl-CoA, increased muscle FA oxidation, reduced hepatic fat, reduced total body fat, elevated skeletal muscle uncoupling protein-3 (UCP3) which is indicative of increased energy expenditure, reduced body weight, reduced plasma free FAs, reduced plasma glucose, and reduced tissue glycogen, and are protected from diet-induced diabetes and obesity.

[00115] Savage *et al.* [*J. Clin. Invest.* 116: 817, 2006], using ACC1 and ACC2 antisense oligonucleotides, demonstrated stimulation of FA oxidation in isolated rat hepatocytes and in rats fed high-fat diets, and lowering of hepatic triglycerides, improvements in insulin sensitivity, reductions in hepatic glucose production, and increases in UCP1 mRNA in high fat-fed rats. These effects were greater when both ACC1 and ACC2 expression were suppressed than when either ACC1 or ACC2 expression alone was suppressed.

[00116] Harwood *et al.* [J. *Biol. Chem.* 278: 37099, 2003] demonstrated that the isozyme-nonselective ACC inhibitor, CP-640186, which equally inhibits ACC1 and ACC2 (IC_{50} = ~60 nM) isolated from rat, mouse, monkey and human without inhibiting either pyruvate carboxylase or propionyl-CoA carboxylase, reduced FA synthesis, triglyceride synthesis and secretion in Hep-G2 cells without affecting cholesterol synthesis, and reduced apoB secretion without affecting apoA1 secretion. CP-640186 also stimulated FA oxidation in C2C12 cells and in rat muscle slices and increased CPT-I activity in Hep-G2 cells. In experimental animals, CP-640186 acutely reduced malonyl-CoA concentration in both lipogenic and oxidative tissues in both the fed and fasted state, reduced liver and adipose tissue FA synthesis, and increased whole body FA oxidation. In sucrose-fed rats treated with CP-640186 for three weeks, CP-640186 time- and dose-dependently reduced liver, muscle and adipose triglycerides, reduced body weight due to selective fat reduction without reducing lean body mass, reduced leptin levels, reduced the hyperinsulinemia produced by the high sucrose diet without changing plasma glucose levels, and improved insulin sensitivity.

[00117] Saha *et al.* [*Diabetes* 55:A288, 2006] demonstrated stimulation of insulin sensitivity in insulin-resistant rat muscle tissue by CP-640186 within 30 min of compound administration,

and studies by Furler *et al.* [*Diabetes* 55:A333, 2006] used dual tracer analysis to show that acute (46 min) treatment of rats with CP-640186 stimulated FA clearance without decreasing glucose clearance.

[00118] ACC is the rate-limiting enzyme in fatty acid synthesis and its product, malonyl CoA, serves as an important regulator of fatty acid oxidation. Hence, ACC inhibitors both reduce *de novo* lipid synthesis and promote the oxidation of existing fat. This dual effect on lipid metabolism raises the possibility that ACC inhibitors will be substantially more effective in reducing excess fat than other mechanisms. Furthermore, ACC inhibitors will impact insulin sensitivity, plasma and tissue triglycerides, and fasting plasma glucose as a consequence of whole-body and tissue-specific fat mass reduction without the need for poly-pharmacy.

[00119] ACC inhibitors need only access the liver and muscle in the peripheral compartment. Avoiding the CNS will address many of side effects associated with the late-stage obesity programs targeting CNS receptors. ACC inhibitors are also expected to have superior safety profiles to existing metabolic disease agents. For example, it is unlikely that an ACC inhibitor will precipitate life-threatening hypoglycemia as is often seen with insulin mimetics, insulin secretagogues, and insulin degradation inhibitors. Also, since ACC inhibitors will reduce whole-body fat mass, they will be superior to the glitazones that increase whole-body fat mass as part of their mechanism of action.

[00120] A peripherally acting agent that causes significant weight loss and improves other metabolic endpoints fits well within the US FDA's requirements for approval of a new obesity agent. However, if an approval for obesity continues to be challenging in 5-7 years, ACC inhibitors could be approved for familial combined hyperlipidemia and non-alcoholic steatohepatitis (NASH). There are currently no marketed ACC inhibitors, so an isozyme-nonselective ACC inhibitor would represent first-in-class therapy for treating obesity and metabolic syndrome.

[00121] The activity of a compound utilized in this invention as an inhibitor of ACC or treatment for obesity or metabolic syndrome, may be assayed *in vitro* or *in vivo*. An in vivo assessment of the efficacy of the compounds of the invention may be made using an animal model of obesity or metabolic syndrome, e.g., a rodent or primate model. Cell-based assays may be performed using, e.g., a cell line isolated from a tissue that expresses ACC. Additionally, biochemical or mechanism-based assays, e.g., transcription assays using a purified protein,

Northern blot, RT-PCR, etc., may be performed. *In vitro* assays include assays that determine cell morphology, protein expression, and/or the cytotoxicity, enzyme inhibitory activity, and/or the subsequent functional consequences of treatment of cells with compounds of the invention. Alternate *in vitro* assays quantitate the ability of the inhibitor to bind to protein or nucleic acid molecules within the cell. Inhibitor binding may be measured by radiolabelling the inhibitor prior to binding, isolating the inhibitor/target molecule complex and determining the amount of radiolabel bound. Alternatively, inhibitor binding may be determined by running a competition experiment where new inhibitors are incubated with purified proteins or nucleic acids bound to known radioligands. Detailed conditions for assaying a compound utilized in this invention as an inhibitor of ACC are set forth in the Examples below. The aforementioned assays are exemplary and not intended to limit the scope of the invention. The skilled practitioner can appreciate that modifications can be made to conventional assays to develop equivalent assays that obtain the same result.

[00122] As used herein, the terms "treatment," "treat," and "treating" refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof, as described herein. In some embodiments, treatment may be administered after one or more symptoms have developed. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example to prevent or delay their recurrence.

[00123] The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a metabolic disorder or condition, cancer, a bacterial infection, a fungal infection, a parasitic infection (e.g. malaria), an autoimmune disorder, a neurodegenerative or neurological disorder, schizophrenia, a bone-related disorder, liver disease, or a cardiac disorder.

[00124] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a disease associated with ACC (Tong *et al.* "Acetyl-coenzyme A carboxylase: crucial metabolic enzyme and attractive target for drug discovery" Cell and Molecular Life Sciences (2005) 62, 1784-1803).

[00125] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a metabolic disorder, disease, or condition. In some embodiments, the metabolic disorder is obesity, metabolic syndrome, diabetes or diabetes-related disorders including Type 1 diabetes (insulin-dependent diabetes mellitus, IDDM) and Type 2 diabetes (non-insulin-dependent diabetes mellitus, NIDDM), impaired glucose tolerance, insulin resistance, hyperglycemia, diabetic complications, including, but not limited to atherosclerosis, coronary heart disease, stroke, peripheral vascular disease, nephropathy, hypertension, neuropathy and nephropathy; obesity comorbidities including but not limited to metabolic syndrome, dyslipidemia, hypertension, insulin resistance, diabetes (including Type 1 and Type 2 diabetes), coronary artery disease, and heart failure. In some embodiments, the metabolic disorder, disease or condition is non-alcoholic fatty liver disease or hepatic insulin resistance.

[00126] In some embodiments, the present invention provides a method of treating a metabolic disorder, disease, or condition described herein, comprising administering a compound of the invention in conjunction with one or more pharmaceutical agents. Suitable pharmaceutical agents that may be used in combination with the compounds of the present invention include anti-obesity agents (including appetite suppressants), anti-diabetic agents, anti-hyperglycemic agents, lipid lowering agents, and anti-hypertensive agents.

[00127] Suitable lipid lowering agents that can be used in conjunction with compounds of the present invention include but are not limited to, bile acid sequestrants, HMG-CoA reductase inhibitors, HMG-CoA synthase inhibitors, cholesterol absorption inhibitors, acyl coenzyme A-cholesterol acyl transferase (ACAT) inhibitors, CETP inhibitors, squalene synthetase inhibitors, PPAR-alpha agonists, FXR receptor modulators, LXR receptor modulators, lipoprotein synthesis inhibitors, renin-angiotensin system inhibitors, PPAR-delta partial agonists, bile acid reabsorption inhibitors, PPAR-gamma agonists, triglyceride synthesis inhibitors, microsomal triglyceride transport inhibitors, transcription modulators, squalene epoxidase inhibitors, low density lipoprotein receptor inducers, platelet aggregation inhibitors, 5-LO or FLAP inhibitors, niacin, and niacin-bound chromium.

[00128] Suitable anti-hypertensive agents that can be used in conjunction with compounds of the present invention include but are not limited to diuretics, beta-adrenergic blockers, calcium

channel blockers, angiotensin converting enzyme (ACE) inhibitors, neutral endopeptidase inhibitors, endothelin antagonists, vasodilators, angiotensin II receptor antagonists, alpha/beta adrenergic blockers, alpha 1 blockers, alpha 2 agonists, aldosterone inhibitors, mineralocorticoid receptor inhibitors, renin inhibitors, and angiopoietin 2 binding agents.

[00129] Suitable anti-diabetic agents that can be used in conjunction with compounds of the present invention include but are not limited to other acetyl-CoA carboxylase (ACC) inhibitors, DGAT-1 inhibitors, AZD7687, LCQ908, DGAT-2 inhibitors, monoacylglycerol O-acyltransferase inhibitors, PDE-10 inhibitors, AMPK activators, sulfonylureas (e.g. acetohexamide, chlorpropamide, diabinese, glibenclamide, glipizide, glyburide, blimipiride, gliclazide, glipentide, gliquidone, glisolamide, tolazamide, tolbutamide), meglitinides, alpha-amylase inhibitors (e.g. tendamistat, treastatin, AL-3688), alpha-glucoside hydrolase inhibitors (e.g. acarbose), alpha-glucosidase inhibitors (e.g. adiposine, camiglibose, emiglitate, miglitol, voglibose, pradimicin-Q, sarbostatin), PPAR-gamma agonists (e.g. balaglitazone, ciglitazone, darglitazone, englitazone, isaglitazone, pioglitazone, rosiglitazone, troglitazone), PPAR-alpha/gamma agonists (e.g. CLX-0940, GW-1536, GW-1929, GW-2433, KRP-297, L-796449, LR-90, MK-0767, SB-219994), biguanides (e.g. metformin, buformin), GLP-1 modulators (exendin-3, exendin-4), liraglutide, albiglutide, exenatide (Byetta), taspoglutide, lixisenatide, dulaglutide, semaglutide, N,N-9924, TTP-054, PTP-1B inhibitors (trodusquemine, hyrtiosal extract), SIRT-1 inhibitors (e.g. resveratrol, GSK2245840, GSK184072), DPP-IV inhibitors (e.g. sitagliptin, vildagliptin, alogliptin, dutogliptin, linagliptin, saxagliptin), insulin secretagogues, fatty acid oxidation inhibitors, A2 antagonists, JNK inhibitors, glucokinase activators (e.g. TTP-399, TTP-355, TTP-547, AZD1656, ARRY403, MK-0599, TAK-329, AZD5658, GKM-001), insulin, insulin mimetics, glycogen phosphorylase inhibitors (e.g. GSK1362885), VPAC2 receptor agonists, SGLT2 inhibitors (dapagliflozin, canagliflozin, BI-10733, tofogliflozin, ASP-1941, THR1474, TS-071, ISIS388626, LX4211), glucagon receptor modulators, GPR119 modulators (e.g. MBX-2982, GSK1292263, APD597, PSN821), FGF21 derivatives, TGR5 (GPBAR1) receptor agonists (e.g. INT777), GPR40 agonists (e.g. TAK-875), GPR120 agonists, nicotinic acid receptor (HM74A) activators, SGLT1 inhibitors (e.g. GSK1614235), carnitine palmitoyl transferase enzyme inhibitors, fructose 1,6-diphosphatase inhibitors, aldose reductase inhibitors, mineralocorticoid receptor inhibitors, TORC2 inhibitors, CCR2 inhibitors, CCR5 inhibitors, PKC (e.g. PKC-alpha, PKC-beta, PKC-gamma) inhibitors, fatty acid synthetase

inhibitors, serine palmitoyl transferase inhibitors, GPR81 modulators, GPR39 modulators, GPR43 modulators, GPR41 modulators, GPR105 modulators, Kv1.3 inhibitors, retinol binding protein 4 inhibitors, glucocorticoid receptor modulators, somatostatin receptor (e.g. SSTR1, SSTR2, SSTR3, SSTR5) inhibitors, PDHK2 inhibitors, PDHK4 inhibitors, MAP4K4 inhibitors, IL1-beta modulators, and RXR-alpha modulators.

[00130] Suitable anti-obesity agents include but are not limited to, 11-beta-hydroxysteroid dehydrogenase 1 inhibitors, stearoyl-CoA desaturase (SCD-1) inhibitors, MCR-4 agonists, CCK-A agonists, monoamine reuptake inhibitors (e.g. sibutramine), sympathomimetic agents, beta-3-adrenergic receptor agonists, dopamine receptor agonists (e.g. bromocriptine), melanocyte-stimulating hormone and analogs thereof, 5-HT_{2C} agonists (e.g. lorcaserin / Belviq), melanin concentrating hormone antagonists, leptin, leptin analogs, leptin agonists, galanin antagonists, lipase inhibitors (e.g. tetrahydrolipstatin / Orlistat), anorectic agents (e.g. bombesin agonists), NPY antagonists (e.g. velneperit), PYY_{3-36} (and analogs thereof), BRS3 modulators, opioid receptor mixed antagonists, thyromimetic agents, dehydroepiandrosterone, glucocorticoid agonists or antagonists, orexin antagonists, GLP-1 agonists, ciliary neurotrophic factors (e.g. Axokine), human agouti-related protein (AGRP) inhibitors, H3 antagonists or inverse agonists, neuromedin U agonists, MTP/ApoB inhibitors (e.g. gut-selective MTP inhibitors such as dirlotapide, JTT130, Usistapide, SLX4090), MetAp2 inhibitors (e.g. ZGN-433), agents with mixed modulatory activity at two or more of glucagon, GIP, and GLP1 receptors (e.g. MAR-701, ZP2929), norepinephrine reuptake inhibitors, opioid antagonists (e.g. naltrexone), CB1 receptor antagonists or inverse agonists, ghrelin agonists or antagonists, oxyntomodulin and analogs thereof, monoamine uptake inhibitors (e.g. tesofensine), and combination agents (e.g. buproprion plus zonisamide (Empatic), pramlintide plus metreleptin, buproprion plus naltrexone (Contrave), phentermine plus topiramate (Qsymia).

[00131] In some embodiments, the anti-obesity agents used in combination with compounds of the invention are selected from gut-selective MTP inhibitors (e.g. dirlotapide, mitratapide, implitapide, R56918), CCK-A agonists, 5-HT_{2C} agonists (e.g. lorcaserin / Belviq), MCR4 agonists, lipase inhibitors (e.g. Cetilistat), PYY_{3-36} (including analogs and PEGylated analogs thereof), opioid antagonists (e.g. naltrexone), oleoyl estrone, obinepitide, pramlintide, tesofensine, leptin, bromocriptine, orlistat, AOD-9604, and sibutramine.

[00132] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a LKB1 or Kras associated disease. In some embodiments, the LKB1 or Kras associated disease is selected from hepatocellular carcinoma, LKB1 mutant cancers, LKB1 loss of heterozygosity (LOH) driven cancers, Kras mutant cancers, Peutz-Jeghers syndrome (PJS), Cowden's disease (CD), and tubeous sclerosis (TS) (Makowski *et al.* "Role of LKB1 in Lung Cancer Development" British Journal of Cancer (2008) 99, 683-688). In some embodiments, the LKB1 or Kras associated disease is a Kras positive/LKB1 deficient lung tumor.

[00133] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a cancer, or inhibiting the growth of or inducing apoptosis in cancer cells (Wang *et al.* "Acetyl-CoA Carboxylase-alpha Inhibitor TOFA Induces Human Cancer Cell Apoptosis" Biochem Biophys Res Commun. (2009) 385(3), 302-306; Chajes *et al.* "Acetyl-CoA Carboxylase alpha Is Essential to Breast Cancer Cell Survival" Cancer Res. (2006) 66, 5287-5294; Beckers *et al.* "Chemical Inhibition of Acetyl-CoA Carboxylase Induces Growth Arrest and Cytotoxicity Selectivity in Cancer Cells" Cancer Res. (2007) 8180-8187; Brusselmans *et al.* "RNA Interference-Mediated Silencing of the Acetyl-CoA-Carboxylase-alpha Gene Induces Growth Inhibition and Apoptosis of Prostate Cancer Cells" Cancer Res. (2005) 65, 6719-6725; Brunet *et al.* "BRCA1 and Acetyl-CoA Carboxylase: The Metabolic Syndrom of Breast Cancer" Molecular Carcinogenesis (2008) 47, 157-163; Cairns *et al.* "Regulation of Cancer Cell Metabolism" (2011) 11, 85-95; Chiaradonna *et al.* "From Cancer Metabolism to New Biomarkers and Drug Targets" Biotechnology Advances (2012) 30, 30-51).

[00134] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a melanoma. In some embodiments, the melanoma is one bearing an activated MAPK pathway (Petti *et al.* "AMPK activators inhibit the proliferation of human melanomas bearing the activated MAPK pathway" Melanoma Research (2012) 22, 341-350).

[00135] Compounds of the present invention find special utility in triple negative breast cancer, as the tumor suppressor protein BRCA1 binds and stabilizes the inactive form of ACC, thus upregulating de novo lipid synthesis, resulting in cancer cell proliferation Brunet et al. "BRCA1 and acetyl-CoA carboxylase: the metabolic syndrome of breast cancer" Mol. Carcinog. (2008) 47(2), 157-163.

[00136] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a liposarcoma. Liposarcomas have been shown to depend on *de* novo long-chain fatty acid synthesis for growth, and inhibition of ACC by soraphen A inhibited lipogenesis as well as tumor cell growth (Olsen *et al.* "Fatty acid synthesis is a therapeutic target in human liposarcoma" International J. of Oncology (2010) 36, 1309-1314).

[00137] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a liver disease. In some embodiments, the liver disease is selected from hepatitis C, hepatocellular carcinoma, familial combined hyperlipidemia and non-alcoholic steatohepatitis (NASH), liver cancer, cholangiocarcinoma, angiosarcoma, hemangiosarcoma, and progressive familial intrahepatic cholestasis.

[00138] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a bacterial infection or inhibiting the growth of bacteria.

[00139] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a fungal infection or inhibiting the growth of fungal cells (Shen *et al.* "A Mechanism for the Potent Inhibition of Eukaryotic Acetyl-Coenzyme A Carboxylase by Soraphen A, a Macrocyclic Polyketide Natural Product" Molecular Cell (2004) 16, 881-891).

[00140] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration

effective for treating or lessening the severity of a bacterial infection (Tong, L. et al. J. Cell. Biochem. (2006) 99, 1476-1488).

[00141] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a viral infection (Munger et al. Nat. Biotechnol. (2008) 26, 1179-1186). In some embodiments, the viral infection is Hepatitis C.

[00142] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a neurological disease (Henderson et al. Neurotherapeutics (2008) 5, 470-480; Costantini et al. Neurosci. (2008) 9 Suppl. 2:S16; Baranano et al. Curr. Treat. Opin. Neurol. (2008) 10, 410-419).

[00143] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a parasitic infection or inhibiting the growth of parasites (e.g. malaria and toxoplasma: Gornicki *et al.* "Apicoplast fatty acid biosynthesis as a target for medical intervention in apicomplexan parasites" International Journal of Parasitology (2003) 33, 885-896; Zuther *et al.* "Growth of *Toxoplasma gondii* is inhibited by aryloxyphenoxypropionate herbicides targeting acetyl-CoA carboxylase" PNAS (1999) 96 (23) 13387-13392).

[00144] In some embodiments, the compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a cardiac disorder. In some embodiments, the cardiac disorder is cardiac hypertrophy. In some embodiments the cardiac disorder is treated or its severity lessened by the cardioprotective mechanism resulting from increased fatty acid oxidation via ACC inhibition (Kolwicz *et al.* "Cardiac-specific deletion of acetyl CoA carboxylase 2 (ACC2) prevents metabolic remodeling during pressure-overload hypertrophy" Circ. Res. (2012); DOI: 10.1161/CIRCRESAHA.112.268128).

[00145] In certain embodiments, the compounds and compositions, according to the method of the present invention, may be used as herbicides. In some embodiments, the present invention provides a method to inhibit the growth or viability of plants comprising treating plants with compounds of the present invention. In some embodiments of the present invention, compounds

of the present invention can be used to inhibit the growth or viability of plants by inhibiting ACC. In some embodiments, the method of the present invention comprises using compounds of the present invention to inhibit fatty acid production in or increase fatty acid oxidation in plants.

[00146] The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. The compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[00147] The pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00148] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl

alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00149] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00150] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00151] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[00152] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00153] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00154] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

[00155] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and

granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00156] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00157] According to one embodiment, the invention relates to a method of inhibiting ACC in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound.

[00158] In certain embodiments, the invention relates to a method of modulating fatty acid levels in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound.

[00159] The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[00160] Inhibition of enzymes in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to biological assays, gene expression studies, and biological target identification.

[00161] Another embodiment of the present invention relates to a method of inhibiting ACC in a patient comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound.

[00162] According to another embodiment, the invention relates to a method of inhibiting fatty acid production, stimulating fatty acid oxidation, or both, in a patient comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound. According to certain embodiments, the invention relates to a method of inhibiting fatty acid production, stimulating fatty acid oxidation, or both in a patient, leading to decreasing obesity or alleviating symptoms of metabolic syndrome, comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound. In other embodiments, the present invention provides a method for treating a disorder mediated by ACC, in a patient in need thereof, comprising the step of administering to said patient a compound according to the present invention or pharmaceutically acceptable composition thereof. Such disorders are described in detail herein.

[00163] In some embodiments the compounds and compositions of the present invention may be used in a method of treating obesity or another metabolic disorder. In certain embodiments the compounds and compositions of the present invention may be used to treat obesity or other metabolic disorder in a mammal. In certain embodiments the mammal is a human patient. In certain embodiments the compounds and compositions of the present invention may be used to treat obesity or other metabolic disorder in a human patient.

[00164] In some embodiments the present invention provides a method of treating obesity or another metabolic disorder, comprising administering a compound or composition of the present invention to a patient with obesity or another metabolic disorder. In certain embodiments the method of treating obesity or another metabolic disorder comprises administering compounds and compositions of the present invention to a mammal. In certain embodiments the mammal is a human. In some embodiments the metabolic disorder is dyslipidemia or hyperlipidemia. In some embodiments, the obesity is a symptom of Prader-Willi syndrome, Bardet-Biedl syndrome, Cohen syndrome or MOMO syndrome. In some embodiments, the obesity is a side effect of the

administration of another medication, including but not limited to insulin, sulfunylureas, thiazolidinediones, antipsychotics, antidepressants, steroids, anticonvulsants (including phenytoin and valproate), pizotifen, or hormonal contraceptives.

[00165] In certain embodiments, the present invention provides a method of treating cancer or another proliferative disorder, comprising administering a compound or composition of the present invention to a patient with cancer or another proliferative disorder. In certain embodiments, the method of treating cancer or another proliferative disorder comprises administering compounds and compositions of the present invention to a mammal. In certain embodiments, the mammal is a human.

[00166] As used herein, the terms "inhibition of cancer" and "inhibition of cancer cell proliferation" refer to the inhibition of the growth, division, maturation or viability of cancer cells, and/or causing the death of cancer cells, individually or in aggregate with other cancer cells, by cytotoxicity, nutrient depletion, or the induction of apoptosis.

[00167] Examples of tissues containing cancerous cells whose proliferation is inhibited by the compounds and compositions described herein and against which the methods described herein are useful include but are not limited to breast, prostate, brain, blood, bone marrow, liver, pancreas, skin, kidney, colon, ovary, lung, testicle, penis, thyroid, parathyroid, pituitary, thymus, retina, uvea, conjunctiva, spleen, head, neck, trachea, gall bladder, rectum, salivary gland, adrenal gland, throat, esophagus, lymph nodes, sweat glands, sebaceous glands, muscle, heart, and stomach.

[00168] In some embodiments, the cancer treated by compounds or compositions of the invention is a melanoma, liposarcoma, lung cancer, breast cancer, prostate cancer, leukemia, kidney cancer, esophageal cancer, brain cancer, lymphoma or colon cancer. In certain embodiments, the cancer is a primary effusion lymphoma (PEL). In certain preferred embodiments the cancer to be treated by compounds or compositions of the invention is one bearing an activated MAPK pathway. In some embodiments the cancer bearing an activated MAPK pathway is a melanoma. In certain preferred embodiments the cancer treated by compounds or compositions of the invention is one associated with BRCA1 mutation. In an especially preferred embodiment, the cancer treated by compounds or compositions of the invention is a triple negative breast cancer.

[00169] In certain embodiments, the disease which can be treated by compounds of the invention are neurological disorders. In some embodiments, the neurological disorder is Alzheimer's Disease, Parkinson's Disease, epilepsy, ischemia, Age Associated Memory Impairment, Mild Cognitive Impairment, Friedreich's Ataxia, GLUT1-deficient epilepsy, Leprechaunism, Rabson-Mendenhall Syndrome, Coronary Arterial Bypass Graft dementia, anaesthesia-induced memory loss, amyotrophic lateral sclerosis, gliomaor Huntington's Disease.

[00170] In certain embodiments, the disease which can be treated by compounds of the invention is an infectious disease. In some embodiments, the infectious disease is a viral infection. In some embodiments the viral infection is cytomegalovirus infection or influenza infection. In some embodiments, the infectious disease is a fungal infection. In some embodiments, the infectious disease is a bacterial infection.

[00171] In some embodiments, compounds of the present invention can be used in the treatment of

[00172] Depending upon the particular condition, or disease, to be treated, additional therapeutic agents, which are normally administered to treat that condition, may be administered in combination with compounds and compositions of this invention. As used herein, additional therapeutic agents that are normally administered to treat a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated".

[00173] In certain embodiments, a provided compound, or composition thereof, is administered in combination with another inhibitor of ACC or antiobesity agent. In some embodiments, a provided compound, or composition thereof, is administered in combination with one or more other therapeutic agents. Such therapeutic agents agents include, but are not limited to agents such as orlistat (Xenical), CNS stimulants, Qsymia, or Belviq.

[00174] In certain embodiments, a provided compound, or a composition thereof, is administered in combination with another anti-cancer, cytotoxin, or chemotherapeutic agent, to a patient in need thereof.

[00175] In certain embodiments, the anti-cancer or chemotherapeutic agents used in combination with compounds or compositions of the invention include, but are not limited to metformin, phenformin, buformin, imatinib, nilotinib, gefitinib, sunitinib, carfilzomib, salinosporamide A, retinoic acid, cisplatin, carboplatin, oxaliplatin, mechlorethamine, cyclophosphamide, chlorambucil, ifosfamide, azathioprine, mercaptopurine, doxifluridine,

fluorouracil, gemcitabine, methotrexate, tioguanine, vincristine, vinblastine, vinorelbine, vindesine, podophyllotoxin, etoposide, teniposide, tafluposide, paclitaxel, docetaxel, irinotecan, topotecan, amsacrine, actinomycin, doxorubicin, daunorubicin, valrubicin, idarubicin, epirubicin, plicamycin, mitomycin, mitoxantrone, melphalan, busulfan, capecitabine, pemetrexed, epothilones, 13-cis-Retinoic Acid, 2-CdA, 2-Chlorodeoxyadenosine, 5-Azacitidine, 5-Fluorouracil, 5-FU, 6-Mercaptopurine, 6-MP, 6-TG, 6-Thioguanine, Abraxane, Accutane ®, Actinomycin-D, Adriamycin ®, Adrucil ®, Afinitor ®, Agrylin ®, Ala-Cort ®, Aldesleukin, Alemtuzumab, ALIMTA, Alitretinoin, Alkaban-AQ ®, Alkeran ®, All-transretinoic Acid, Alpha Interferon, Altretamine, Amethopterin, Amifostine, Aminoglutethimide, Anagrelide, Anandron ®, Anastrozole, Arabinosylcytosine, Ara-C, Aranesp ®, Aredia ®, Arimidex ®, Aromasin ®, Arranon ®, Arsenic Trioxide, Arzerra™, Asparaginase, ATRA, Avastin ®, Azacitidine, BCG, BCNU, Bendamustine, Bevacizumab, Bexarotene, BEXXAR ®, Bicalutamide, BiCNU, Blenoxane ®, Bleomycin, Bortezomib, Busulfan, Busulfex ®, C225, Calcium Leucovorin, Campath ®, Camptosar ®, Camptothecin-11, Capecitabine, Carac ™, Carboplatin, Carmustine, Carmustine Wafer, Casodex ®, CC-5013, CCI-779, CCNU, CDDP, CeeNU, Cerubidine ®, Cetuximab, Chlorambucil, Citrovorum Factor, Cladribine, Cortisone, Cosmegen ®, CPT-11, Cytadren ®, Cytosar-U ®, Cytoxan ®, Dacarbazine, Dacogen, Dactinomycin, Darbepoetin Alfa, Dasatinib, Daunomycin, Daunorubicin Hydrochloride, Daunorubicin Liposomal, DaunoXome ®, Decadron, Decitabine, Delta-Cortef ®, Deltasone ®, Denileukin, Diftitox, DepoCyt ™, Dexamethasone, Dexamethasone Acetate, Dexamethasone Sodium Phosphate, Dexasone, Dexrazoxane, DHAD, DIC, Diodex, Docetaxel, Doxil ®, Doxorubicin, Doxorubicin Liposomal, Droxia ™, DTIC, DTIC-Dome ®, Duralone ®, Efudex ®, Eligard ™, Ellence ™, Eloxatin ™, Elspar ®, Emcyt ®, Epirubicin, Epoetin Alfa, Erbitux, Erlotinib, Erwinia L-asparaginase, Estramustine, Ethyol, Etopophos ®, Etoposide, Etoposide Phosphate, Eulexin ®, Everolimus, Evista ®, Exemestane, Fareston ®, Faslodex ®, Femara ®, Filgrastim, Floxuridine, Fludara ®, Fludarabine, Fluoroplex ®, Fluorouracil, Fluorouracil (cream), Fluoxymesterone, Flutamide, Folinic Acid, FUDR ®, Fulvestrant, G-CSF, Gefitinib, Gemcitabine, Gemtuzumab, ozogamicin, ,Gemzar Gleevec ™, Gliadel ® Wafer, GM-CSF, Goserelin, Granulocyte - Colony Stimulating Factor, Granulocyte Macrophage Colony Stimulating Factor, Halotestin ®, Herceptin ®, Hexadrol, Hexalen ®, Hexamethylmelamine, HMM, Hycamtin ®, Hydrea ®, Hydrocort Acetate ®, Hydrocortisone, Hydrocortisone Sodium Phosphate, Hydrocortisone Sodium Succinate,

Hydrocortone Phosphate, Hydroxyurea, Ibritumomab, Ibritumomab, Tiuxetan, Idamycin ®, Idarubicin Ifex ®, IFN-alpha, Ifosfamide, IL-11, IL-2, Imatinib mesylate, Imidazole Carboxamide, Interferon alfa, Interferon Alfa-2b (PEG Conjugate), Interleukin-2, Interleukin-11, Intron A® (interferon alfa-2b), Iressa ®, Irinotecan, Isotretinoin, Ixabepilone, Ixempra ™, Kidrolase ®, Lanacort ®, Lapatinib, L-asparaginase, LCR, Lenalidomide, Letrozole, Leucovorin, Leukeran, Leukine ™, Leuprolide, Leurocristine, Leustatin ™, Liposomal Ara-C, Liquid Pred ®, Lomustine, L-PAM, L-Sarcolysin, Lupron ®, Lupron Depot ®, Matulane ®, Maxidex, Mechlorethamine, Mechlorethamine Hydrochloride, Medralone ®, Medrol ®, Megace ®, Megestrol, Megestrol Acetate, Melphalan, Mercaptopurine, Mesna, Mesnex ™, Methotrexate, Methotrexate Sodium, Methylprednisolone, Meticorten ®, Mitomycin, Mitomycin-C, Mitoxantrone, M-Prednisol ®, MTC, MTX, Mustargen ®, Mustine, Mutamycin ®, Myleran ®, Mylocel ™, Mylotarg ®, Navelbine ®, Nelarabine, Neosar ®, Neulasta ™, Neumega ®, Neupogen ®, Nexavar ®, Nilandron ®, Nilotinib, Nilutamide, Nipent ®, Nitrogen Mustard, Novaldex ®, Novantrone ®, Nplate, Octreotide, Octreotide acetate, Ofatumumab, Oncospar ®, Oncovin ®, Ontak ®, Onxal ™, Oprelvekin, Orapred ®, Orasone ®, Oxaliplatin, Paclitaxel, Paclitaxel Protein-bound, Pamidronate, Panitumumab, Panretin ®, Paraplatin ®, Pazopanib, Pediapred ®, PEG Interferon, Pegaspargase, Pegfilgrastim, PEG-INTRON ™, PEG-L-asparaginase, PEMETREXED, Pentostatin, Phenylalanine Mustard, Platinol ®, Platinol-AQ ®, Prednisolone, Prednisone, Prelone ®, Procarbazine, PROCRIT ®, Proleukin ®, Prolifeprospan 20 with Carmustine Implant, Purinethol ®, Raloxifene, Revlimid ®, Rheumatrex ®, Rituxan ®, Rituximab, Roferon-A ® (Interferon Alfa-2a), Romiplostim, Rubex ®, Rubidomycin hydrochloride, Sandostatin ®, Sandostatin LAR ®, Sargramostim, Solu-Cortef ®, Solu-Medrol ®, Sorafenib, SPRYCEL ™, STI-571, Streptozocin, SU11248, Sunitinib, Sutent ®, Tamoxifen, Tarceva ®, Targretin ®, Tasigna ®, Taxol ®, Taxotere ®, Temodar ®, Temozolomide, Temsirolimus, Teniposide, TESPA, Thalidomide, Thalomid ®, TheraCys ®, Thioguanine, Thioguanine Tabloid ®, Thiophosphoamide, Thioplex ®, Thiotepa, TICE ®, Toposar ®, Topotecan, Toremifene, Torisel ®, Tositumomab, Trastuzumab, Treanda ®, Tretinoin, Trexall ™, Trisenox ®, TSPA, TYKERB ®, VCR, Vectibix ™, Velban ®, Velcade ®, VePesid ®, Vesanoid ®, Viadur ™, Vidaza ®, Vinblastine, Vinblastine Sulfate, Vincasar Pfs ®, Vincristine, Vinorelbine, Vinorelbine tartrate, VLB, VM-26, Vorinostat, Votrient, VP-16, Vumon ®, Xeloda

®, Zanosar ®, Zevalin ™, Zinecard ®, Zoladex ®, Zoledronic acid, Zolinza, Zometa ®, or combinations of any of the above.

[00176] In certain embodiments, compounds of the present invention may be administered together with a biguanide selected from metformin, phenformin, or buformin, to a patient in need thereof. In certain embodiments, the patient administered a combination of a compound of the invention and a biguanide is suffering from a cancer, obesity, a liver disease, diabetes or two or more of the above.

[00177] In certain embodiments, a combination of 2 or more therapeutic agents may be administered together with compounds of the invention. In certain embodiments, a combination of 3 or more therapeutic agents may be administered with compounds of the invention.

[00178] Other examples of agents the inhibitors of this invention may also be combined with include, without limitation: vitamins and nutritional supplements, cancer vaccines, treatments for neutropenia (e.g. G-CSF, filgrastim, lenograstim), treatments for thrombocytopenia (e.g. blood transfusion, erythropoietin), PI3 kinase (PI3K) inhibitors, MEK inhibitors, AMPK activators, PCSK9 inhibitors, SREBP site 1 protease inhibitors, HMG CoA-reductase inhibitors, antiemetics (e.g. 5-HT_3 receptor antagonists, dopamine antagonists, NK1 receptor antagonists, histamine receptor antagonists, cannabinoids, benzodiazepines, or anticholinergics), treatments for Alzheimer's Disease such as Aricept® and Excelon®; treatments for Parkinson's Disease such as L-DOPA/carbidopa, entacapone, ropinrole, pramipexole, bromocriptine, pergolide, trihexephendyl, and amantadine; agents for treating Multiple Sclerosis (MS) such as beta interferon (e.g., Avonex® and Rebif®), Copaxone®, and mitoxantrone; treatments for asthma such as albuterol and Singulair®; agents for treating schizophrenia such as zyprexa, risperdal, seroquel, and haloperidol; anti-inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophophamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, and anti-Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins, fibrates, cholesterol absorption inhibitors, bile acid sequestrants, and niacin; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents;

agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors; agents for treating immunodeficiency disorders such as gamma globulin; and anti-diabetic agents such as biguanides (metformin, phenformin, buformin), thiazolidinediones (rosiglitazone, pioglitazone, troglitazone), sulfonylureas (tolbutamide, acetohexamide, tolazamide, chlorpropamide, glipizide, glyburide, glimepiride, gliclazide), meglitinides (repaglinide, nateglinide), alpha-glucosidase inhibitors (miglitol, acarbose), incretin mimetics (exenatide, liraglutide, taspoglutide), gastric inhibitory peptide analogs, DPP-4 inhibitors (vildagliptin, sitagliptin, saxagliptin, linagliptin, alogliptin), amylin analogs (pramlintide), and insulin and insulin analogs.

[00179] In certain embodiments, compounds of the present invention, or a pharmaceutically acceptable composition thereof, are administered in combination with antisense agents, a monoclonal or polyclonal antibody or an siRNA therapeutic.

[00180] Those additional agents may be administered separately from an inventive compound-containing composition, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with a compound of this invention in a single composition. If administered as part of a multiple dosage regime, the two active agents may be submitted simultaneously, sequentially or within a period of time from one another, normally within five hours from one another.

[00181] As used herein, the term "combination," "combined," and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with this invention. For example, a compound of the present invention may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form. Accordingly, the present invention provides a single unit dosage form comprising a compound of formula **I**, an additional therapeutic agent, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[00182] The amount of both, an inventive compound and additional therapeutic agent (in those compositions which comprise an additional therapeutic agent as described above) that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Preferably, compositions of this invention should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of an inventive can be administered.

[00183] In those compositions which comprise an additional therapeutic agent, that additional therapeutic agent and the compound of this invention may act synergistically. Therefore, the amount of additional therapeutic agent in such compositions will be less than that required in a monotherapy utilizing only that therapeutic agent. In such compositions a dosage of between 0.01 - 100 μg/kg body weight/day of the additional therapeutic agent can be administered.

[00184] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[00185] The invention further refers to an agricultural composition comprising at least one compound of formula I as defined above or an agriculturally acceptable salt thereof and a liquid or solid carrier. Suitable carriers, as well as auxiliaries and further active compounds which may also be contained in the composition of the invention are defined below.

[00186] Suitable "agriculturally acceptable salts" include but are not limited to the salts of those cations or the acid addition salts of those acids whose cations and anions, respectively, have no adverse effect on the fungicidal action of the compounds of formula I. Thus, suitable cations are in particular the ions of the alkali metals, preferably sodium and potassium, of the alkaline earth metals, preferably calcium, magnesium and barium, and of the transition metals, preferably manganese, copper, zinc and iron, and also the ammonium ion which, if desired, may carry one to four C_1-C_4-alkyl substituents and/or one phenyl or benzyl substituent, preferably diisopropylammonium, tetramethylammonium, tetrabutylammonium, trimethylbenzylammonium. Additional agriculturally acceptable salts include phosphonium ions, sulfonium ions, preferably tri(C_1-C_4-alkyl)sulfonium and sulfoxonium ions, preferably tri(C_1-C_4-alkyl)sulfoxonium. Anions of useful acid addition salts are primarily chloride, bromide, fluoride, hydrogen- sulfate, sulfate, dihydrogenphosphate, hydrogenphosphate, phosphate, nitrate, bicarbonate, carbonate, hexafluorosilicate, hexafluorophosphate, benzoate, and also the anions of C_1-C_4-alkanoic acids, preferably formate, acetate, propionate and butyrate. Such agriculturally acceptable acid addition salts can be formed by reacting compounds of formula I bearing a basic

ionizable group with an acid of the corresponding anion, preferably hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid or nitric acid.

[00187] The compounds of formula I and the compositions according to the invention, respectively, are suitable as fungicides. They are distinguished by an outstanding effectiveness against a broad spectrum of phytopathogenic fungi, including soil-borne fungi, which derive especially from the classes of the Plasmodiophoromycetes, Peronosporomycetes (syn. Oomycetes), Chytridiomycetes, Zygomycetes, Ascomycetes, Basidiomycetes and Deuteromycetes (syn. Fungi imperfecti). Some are systemically effective and they can be used in crop protection as foliar fungicides, fungicides for seed dressing and soil fungicides. Moreover, they are suitable for controlling harmful fungi, which inter alia occur in wood or roots of plants.

[00188] In some embodiments, the compounds of formula I and the compositions according to the invention are particularly important in the control of phytopathogenic fungi on various cultivated plants, such as cereals, e.g. wheat, rye, barley, triticale, oats or rice; beet, e.g. sugar beet or fodder beet; fruits, such as pomes, stone fruits or soft fruits, e.g. apples, pears, plums, peaches, almonds, cherries, strawberries, raspberries, blackberries or gooseberries; leguminous plants, such as lentils, peas, alfalfa or soybeans; oil plants, such as rape, mustard, olives, sunflowers, coconut, cocoa beans, castor oil plants, oil palms, ground nuts or soybeans; cucurbits, such as squashes, cucumber or melons; fiber plants, such as cotton, flax, hemp or jute; citrus fruit, such as oranges, lemons, grapefruits or mandarins; vegetables, such as spinach, lettuce, asparagus, cabbages, carrots, onions, tomatoes, potatoes, cucurbits or paprika; lauraceous plants, such as avocados, cinnamon or camphor; energy and raw material plants, such as corn, soybean, rape, sugar cane or oil palm; corn; tobacco; nuts; coffee; tea; bananas; vines (table grapes and grape juice grape vines); hop; turf; natural rubber plants or ornamental and forestry plants, such as flowers, shrubs, broad-leaved trees or evergreens, e.g. conifers; and on the plant propagation material, such as seeds, and the crop material of these plants.

[00189] In some embodiments, compounds of formula I and compositions thereof, respectively are used for controlling a multitude of fungi on field crops, such as potatoes sugar beets, tobacco, wheat, rye, barley, oats, rice, corn, cotton, soybeans, rape, legumes, sunflowers, coffee or sugar cane; fruits; vines; ornamentals; or vegetables, such as cucumbers, tomatoes, beans or squashes.

[00190] The term "plant propagation material" is to be understood to denote all the generative parts of the plant such as seeds and vegetative plant material such as cuttings and tubers (e.g. potatoes), which can be used for the multiplication of the plant. This includes seeds, roots, fruits, tubers, bulbs, rhizomes, shoots, sprouts and other parts of plants, including seedlings and young plants, which are to be transplanted after germination or after emergence from soil. These young plants may also be protected before transplantation by a total or partial treatment by immersion or pouring.

[00191] In some embodiments, treatment of plant propagation materials with compounds of formula I and compositions thereof, respectively, is used for controlling a multitude of fungi on cereals, such as wheat, rye, barley and oats; rice, corn, cotton and soybeans.

[00192] The term "cultivated plants" is to be understood as including plants which have been modified by breeding, mutagenesis or genetic engineering including but not limiting to agricultural biotech products on the market or in development. Genetically modified plants are plants, which genetic material has been so modified by the use of recombinant DNA techniques that under natural circumstances cannot readily be obtained by cross breeding, mutations or natural recombination. Typically, one or more genes have been integrated into the genetic material of a genetically modified plant in order to improve certain properties of the plant. Such genetic modifications also include but are not limited to targeted post-translational modification of protein(s), oligo- or polypeptides e.g. by glycosylation or polymer additions such as prenylated, acetylated or farnesylated moieties or PEG moieties.

[00193] Plants that have been modified by breeding, mutagenesis or genetic engineering, e.g. have been rendered tolerant to applications of specific classes of herbicides, such as hydroxyphenylpyruvate dioxygenase (HPPD) inhibitors; acetolactate synthase (ALS) inhibitors, such as sulfonyl ureas (see e.g. US 6,222,100, WO 01/82685, WO 00/26390, WO 97/41218, WO 98/02526, WO 98/02527, WO 04/106529, WO 05/20673, WO 03/14357, WO 03/13225, WO 03/14356, WO 04/16073) or imida- zolinones (see e.g. US 6,222,100, WO 01/82685, WO 00/026390, WO 97/41218, WO 98/002526, WO 98/02527, WO 04/106529, WO 05/20673, WO 03/014357, WO 03/13225, WO 03/14356, WO 04/16073); enolpyruvylshikimate-3-phosphate synthase (EPSPS) inhibitors, such as glyphosate (see e.g. WO 92/00377); glutamine synthetase (GS) inhibitors, such as glufosinate (see e.g. EP-A 242 236, EP-A 242 246) or oxynil herbicides (see e.g. US 5,559,024) as a result of conventional methods of breeding or genetic engineering.

Several cultivated plants have been rendered tolerant to herbicides by conventional methods of breeding (mutagenesis), e.g. Clearfield® summer rape (Canola, BASF SE, Germany) being tolerant to imidazolinones, e.g. imazamox. Genetic engineering methods have been used to render cultivated plants, such as soybean, cotton, corn, beets and rape, tolerant to herbicides such as glyphosate and glufosinate, some of which are commercially available under the trade names RoundupReady® (glyphosate-tolerant, Monsanto, U.S.A.) and LibertyLink® (glufosinate-tolerant, Bayer CropScience, Germany).

[00194] Furthermore, plants are also covered that, by the use of recombinant DNA techniques, are capable to synthesize one or more insecticidal proteins, especially those known from the bacterial genus Bacillus, particularly from Bacillus thuringiensis, such as δ-endotoxins, e.g. CrylA(b), CrylA(c), CrylF, CrylF(a2), CryllA(b), CrylllA, CrylllB(bi) or Cryθc; vegetative insecticidal proteins (VIP), e.g. VIP1 , VIP2, VIP3 or VIP3A; insecticidal proteins of bacteria colonizing nematodes, e.g. Photorhabdus spp. or Xenor-habdus spp.; toxins produced by animals, such as scorpion toxins, arachnid toxins, wasp toxins, or other insect-specific neurotoxins; toxins produced by fungi, such Streptomycetes toxins, plant lectins, such as pea or barley lectins; agglutinins; proteinase inhibitors, such as trypsin inhibitors, serine protease inhibitors, patatin, cystatin or pa- pain inhibitors; ribosome-inactivating proteins (RIP), such as ricin, maize-RIP, abrin, luffin, saporin or bryodin; steroid metabolism enzymes, such as 3-hydroxysteroid oxidase, ecdysteroid-IDP-glycosyl-transferase, cholesterol oxidases, ecdysone inhibitors or HMG-CoA-reductase; ion channel blockers, such as blockers of sodium or calcium channels; juvenile hormone esterase; diuretic hormone receptors (helicokinin receptors); stilben synthase, bibenzyl synthase, chitinases or glucanases. In the context of the present invention these insecticidal proteins or toxins are to be understood expressly also as pre-toxins, hybrid proteins, truncated or otherwise modified proteins. Hybrid proteins are characterized by a new combination of protein domains, (see, e.g. WO 02/015701). Further examples of such toxins or genetically modified plants capable of synthesizing such toxins are disclosed, e.g., in EP-A 374 753, WO 93/007278, WO 95/34656, EP-A 427 529, EP-A 451 878, WO 03/18810 und WO 03/52073. The methods for producing such genetically modified plants are generally known to the person skilled in the art and are described, e.g., in the publications mentioned above. These insecticidal proteins contained in the genetically modified plants impart to the plants producing these proteins tolerance to harmful pests from all taxonomic groups of arthropods, especially to

beetles (Coleoptera), two-winged insects (Diptera), and moths (Lepidoptera) and to nematodes (Nematoda). Genetically modified plants capable to synthesize one or more insecticidal proteins are, e.g., described in the publications mentioned above, and some of them are commercially available such as YieldGard® (corn cultivars producing the CryiAb toxin), YieldGard® Plus (corn cultivars producing Cry1 Ab and Cry3Bb1 toxins), Starlink® (corn cultivars producing the Cry9c toxin), Her- culex® RW (corn cultivars producing Cry34Ab1 , Cry35Ab1 and the enzyme Phosphi- nothricin-N-Acetyltransferase [PAT]); NuCOTN® 33B (cotton cultivars producing the Cry1 Ac toxin), Bollgard® I (cotton cultivars producing the CryiAc toxin), Bollgard® Il (cotton cultivars producing CryiAc and Cry2Ab2 toxins); VIPCOT® (cotton cultivars producing a VIP-toxin); NewLeaf® (potato cultivars producing the Cry3A toxin); Bt-Xtra®, NatureGard®, KnockOut®, BiteGard®, Protecta®, Bt 1 1 (e.g. Agrisure® CB) and Bt176 from Syngenta Seeds SAS, France, (corn cultivars producing the CryiAb toxin and PAT enyzme), MIR604 from Syngenta Seeds SAS, France (corn cultivars producing a modified version of the Cry3A toxin, c.f. WO 03/018810), MON 863 from Monsanto Europe S.A., Belgium (corn cultivars producing the Cry3Bb1 toxin), IPC 531 from Monsanto Europe S.A., Belgium (cotton cultivars producing a modified version of the CryiAc toxin) and 1507 from Pioneer Overseas Corporation, Belgium (corn cultivars producing the Cry1 F toxin and PAT enzyme).

[00195] Furthermore, plants are also covered that, by the use of recombinant DNA techniques, are capable to synthesize one or more proteins to increase the resistance or tolerance of those plants to bacterial, viral or fungal pathogens. Examples of such proteins are the so-called "pathogenesis-related proteins" (PR proteins, see, e.g. EP-A 392225), plant disease resistance genes (e.g. potato cultivars, which express resistance genes acting against Phytophthora infestans derived from the Mexican wild potato Solanum bulbocastanum) or T4-lysozym (e.g. potato cultivars capable of synthesizing these proteins with increased resistance against bacteria such as Erwinia amylvora). The methods for producing such genetically modified plants are generally known to the person skilled in the art and are described, e.g., in the publications mentioned above.

[00196] Furthermore, plants are also covered that, by the use of recombinant DNA techniques, are capable to synthesize one or more proteins to increase the productivity (e.g. biomass production, grain yield, starch content, oil content or protein content), tolerance to drought,

salinity or other growth-limiting environmental factors or tolerance to pests and fungal, bacterial or viral pathogens of those plants.

[00197] Furthermore, plants are also covered that, by the use of recombinant DNA techniques, contain a modified amount of substances of content or new substances of content, specifically to improve human or animal nutrition, e.g. oil crops that produce health- promoting long-chain omega-3 fatty acids or unsaturated omega-9 fatty acids (e.g. Nexera® rape, DOW Agro Sciences, Canada).

[00198] Furthermore, plants are also covered that, by the use of recombinant DNA techniques, contain a modified amount of substances of content or new substances of content, specifically to improve raw material production, e.g. potatoes that produce increased amounts of amylopectin (e.g. Amflora® potato, BASF SE, Germany).

[00199] The compounds of formula I and compositions thereof, respectively, are particularly suitable for controlling the following plant diseases:

[00200] Albugo spp. (white rust) on ornamentals, vegetables (e.g. A. Candida) and sunflowers (e.g. A. tragopogonis); Altemaria spp. (Alternaria leaf spot) on vegetables, rape {A. brassicola or brassicae), sugar beets (A. tenuis), fruits, rice, soybeans, potatoes (e.g. A. solani or A. alternata), tomatoes (e.g. A. solani or A. alternata) and wheat; Aphanomyces spp. on sugar beets and vegetables; Ascochyta spp. on cereals and vegetables, e.g. A. tritici (anthracnose) on wheat and A. hordei on barley; Bipolaris and Drechslera spp. (teleomorph: Cochliobolus spp.), e.g. Southern leaf blight (D. maydis) or Northern leaf blight (β. zeicola) on corn, e.g. spot blotch (β. sorokiniana) on cereals and e.g. B. oryzae on rice and turfs; Blumeria (formerly Erysiphe) graminis (powdery mildew) on cereals (e.g. on wheat or barley); Botrytis cinerea (teleomorph: Botryotinia fuckeliana: grey mold) on fruits and berries (e.g. strawberries), vegetables (e.g. lettuce, carrots, celery and cabbages), rape, flowers, vines, forestry plants and wheat; Bremia lactucae (downy mildew) on lettuce; Ceratocystis (syn. Ophiostoma) spp. (rot or wilt) on broad-leaved trees and evergreens, e.g. C. ulmi (Dutch elm disease) on elms; Cercospora spp. (Cercospora leaf spots) on corn (e.g. Gray leaf spot: C. zeaemaydis), rice, sugar beets (e.g. C. beticola), sugar cane, vegetables, coffee, soybeans (e.g. C. sojina or C. kikuchii) and rice; Cladosporium spp. on tomatoes (e.g. C. fulvum: leaf mold) and cereals, e.g. C. herbarum (black ear) on wheat; Claviceps purpurea (ergot) on cereals; Cochliobolus (anamorph: Helminthosporium of Bipolaris) spp. (leaf spots) on corn (C. carbonum), cereals (e.g. C. sativus,

anamorph: B. sorokiniana) and rice (e.g. C. miyabeanus, anamorph: H. oryzae); Colletotrichum (teleomorph: Glomerella) spp. (an- thracnose) on cotton (e.g. C. gossypii), corn (e.g. C. graminicola: Anthracnose stalk rot), soft fruits, potatoes (e.g. C. coccodes: black dot), beans (e.g. C. lindemuthianum) and soybeans (e.g. C. truncatum or C. gloeosporioides); Corticium spp., e.g. C. sasakii (sheath blight) on rice; Corynespora cassiicola (leaf spots) on soybeans and ornamentals; Cycloconium spp., e.g. C. oleaginum on olive trees; Cylindrocarpon spp. (e.g. fruit tree canker or young vine decline, teleomorph: Nectria or Neonectria spp.) on fruit trees, vines (e.g. C. liriodendri, teleomorph: Neonectria liriodendri. Black Foot Disease) and ornamentals; Dematophora (teleomorph: Rosellinia) necatrix (root and stem rot) on soybeans; Diaporthe spp., e.g. D. phaseolorum (damping off) on soybeans; Drechslera (syn. Helminthosporium, teleomorph: Pyrenophora) spp. on corn, cereals, such as barley (e.g. D. teres, net blotch) and wheat (e.g. D. tritici-repentis: tan spot), rice and turf; Esca (dieback, apoplexy) on vines, caused by Formitiporia (syn. Phellinus) punctata, F. mediterranea, Phaeomoniella chlamydospora (earlier Phaeo- acremonium chlamydosporum), Phaeoacremonium aleophilum and/or Botryosphaeria obtusa; Elsinoe spp. on pome fruits (E. pyri), soft fruits (E. veneta: anthracnose) and vines (E ampelina: anthracnose); Entyloma oryzae (leaf smut) on rice; Epicoccum spp. (black mold) on wheat; Erysiphe spp. (powdery mildew) on sugar beets (E. betae), vegetables (e.g. E. pisi), such as cucurbits (e.g. E. cichoracearum), cabbages, rape (e.g. E. cruciferarum); Eutypa lata (Eutypa canker or dieback, anamorph: Cytosporina lata, syn. Libertella blepharis) on fruit trees, vines and ornamental woods; Exserohilum (syn. Helminthosporium) spp. on corn (e.g. E. turcicum); Fusarium (teleomorph: Gibberella) spp. (wilt, root or stem rot) on various plants, such as F. graminearum or F. culmorum (root rot, scab or head blight) on cereals (e.g. wheat or barley), F. oxysporum on tomatoes, F. solani on soybeans and F. verticillioides on corn; Gaeumannomyces graminis (take-all) on cereals (e.g. wheat or barley) and corn; Gibberella spp. on cereals (e.g. G. zeae) and rice (e.g. G. fujikuroi: Bakanae disease); Glomerella cingulata on vines, pome fruits and other plants and G. gossypii on cotton; Grain- staining complex on rice; Guignardia bidwellii (black rot) on vines; Gymnosporangium spp. on rosaceous plants and junipers, e.g. G. sabinae (rust) on pears; Helminthosporium spp. (syn. Drechslera, teleomorph: Cochliobolus) on corn, cereals and rice; Hemileia spp., e.g. H. vastatrix (coffee leaf rust) on coffee; lsariopsis clavispora (syn. Cladosporium vitis) on vines; Macrophomina phaseolina (syn. phaseoli) (root and stem rot) on soybeans and cotton; Microdochium (syn. Fusarium) nivale

(pink snow mold) on cereals (e.g. wheat or barley); Microsphaera diffusa (powdery mildew) on soybeans; Monilinia spp., e.g. M. laxa, M. fructicola and M. fructigena (bloom and twig blight, brown rot) on stone fruits and other rosaceous plants; Mycosphaerella spp. on cereals, bananas, soft fruits and ground nuts, such as e.g. M. graminicola (anamorph: Septoria tritici, Septoria blotch) on wheat or M. fijiensis (black Sigatoka disease) on bananas; Peronospora spp. (downy mildew) on cabbage (e.g. P. brassicae), rape (e.g. P. parasitica), onions (e.g. P. destructor), tobacco (P. tabacina) and soybeans (e.g. P. manshurica); Phakopsora pachyrhizi and P. meibomiae (soybean rust) on soybeans; Phialophora spp. e.g. on vines (e.g. P. tracheiphila and P. tetraspora) and soybeans (e.g. P. gregata: stem rot); Phoma lingam (root and stem rot) on rape and cabbage and P. betae (root rot, leaf spot and damping-off) on sugar beets; Phomopsis spp. on sunflowers, vines (e.g. P. viticola: can and leaf spot) and soybeans (e.g. stem rot: P. phaseoli, teleomorph: Diaporthe phaseolorum); Physoderma maydis (brown spots) on corn; Phytophthora spp. (wilt, root, leaf, fruit and stem root) on various plants, such as paprika and cucurbits (e.g. P. capsici), soybeans (e.g. P. megasperma, syn. P. sojae), potatoes and tomatoes (e.g. P. infestans: late blight) and broad-leaved trees (e.g. P. ramorum: sudden oak death); Plasmodiophora brassicae (club root) on cabbage, rape, radish and other plants; Plasmopara spp., e.g. P. viticola (grapevine downy mildew) on vines and P. halstediiou sunflowers; Podosphaera spp. (powdery mildew) on rosaceous plants, hop, pome and soft fruits, e.g. P. leucotricha on apples; Polymyxa spp., e.g. on cereals, such as barley and wheat (P. graminis) and sugar beets (P. betae) and thereby transmitted viral diseases; Pseudocercosporella herpotrichoides (eyespot, teleomorph: Tapesia yallundae) on cereals, e.g. wheat or barley; Pseudoperonospora (downy mildew) on various plants, e.g. P. cubensis on cucurbits or P. humili on hop; Pseudopezicula tracheiphila (red fire disease or , rotbrenner' , anamorph: Phialo- phora) on vines; Puccinia spp. (rusts) on various plants, e.g. P. triticina (brown or leaf rust), P. striiformis (stripe or yellow rust), P. hordei (dwarf rust), P. graminis (stem or black rust) or P. recondita (brown or leaf rust) on cereals, such as e.g. wheat, barley or rye, and asparagus (e.g. P. asparagi); Pyrenophora (anamorph: Drechslera) tritici- repentis (tan spot) on wheat or P. feres (net blotch) on barley; Pyricularia spp., e.g. P. oryzae (teleomorph: Magnaporthe grisea, rice blast) on rice and P. grisea on turf and cereals; Pythium spp. (damping-off) on turf, rice, corn, wheat, cotton, rape, sunflowers, soybeans, sugar beets, vegetables and various other plants (e.g. P. ultimum or P. aphanidermatum); Ramularia spp., e.g. R. collo-cygni (Ramularia leaf spots, Physiological leaf

spots) on barley and R. beticola on sugar beets; Rhizoctonia spp. on cotton, rice, potatoes, turf, corn, rape, potatoes, sugar beets, vegetables and various other plants, e.g. R. solani (root and stem rot) on soybeans, R. solani (sheath blight) on rice or R. cerealis (Rhizoctonia spring blight) on wheat or barley; Rhizopus stolonifer (black mold, soft rot) on strawberries, carrots, cabbage, vines and tomatoes; Rhynchosporium secalis (scald) on barley, rye and triticale; Sarocladium oryzae and S. attenuatum (sheath rot) on rice; Sclerotinia spp. (stem rot or white mold) on vegetables and field crops, such as rape, sunflowers (e.g. S. sclerotiorum) and soybeans (e.g. S. rolfsii or S. sclerotiorum); Septoria spp. on various plants, e.g. S. glycines (brown spot) on soybeans, S. tritici (Septoria blotch) on wheat and S. (syn. Stagonospora) nodorum (Stagonospora blotch) on cereals; Uncinula (syn. Erysiphe) necator (powdery mildew, anamorph: Oidium tuckeri) on vines; Setospaeria spp. (leaf blight) on corn (e.g. S. turcicum, syn. Helminthosporium turcicum) and turf; Sphacelotheca spp. (smut) on corn, (e.g. S. miliaria: head smut), sorghum und sugar cane; Sphaerotheca fuliginea (powdery mildew) on cucurbits; Spongospora subterranea (powdery scab) on potatoes and thereby transmitted viral diseases; Stagonospora spp. on cereals, e.g. S. nodorum (Stagonospora blotch, teleomorph: Leptosphaeria [syn. Phaeosphaeria] nodorum) on wheat; Synchytrium endobioticum on potatoes (potato wart disease); Taphrina spp., e.g. T. deformans (leaf curl disease) on peaches and T. pruni (plum pocket) on plums; Thielaviopsis spp. (black root rot) on tobacco, pome fruits, vegetables, soybeans and cotton, e.g. T. basicola (syn. Chalara elegans); Tilletia spp. (common bunt or stinking smut) on cereals, such as e.g. T. tritici (syn. T. caries, wheat bunt) and T. controversa (dwarf bunt) on wheat; Typhula incamata (grey snow mold) on barley or wheat; Urocystis spp., e.g. U. occulta (stem smut) on rye; Uromyces spp. (rust) on vegetables, such as beans (e.g. U. appendiculatus, syn. U. phaseoli) and sugar beets (e.g. U. betae); Ustilago spp. (loose smut) on cereals (e.g. U. nuda and U. avaenae), corn (e.g. U. maydis: corn smut) and sugar cane; Venturia spp. (scab) on apples (e.g. V. inaequalis) and pears; and Verticillium spp. (wilt) on various plants, such as fruits and ornamentals, vines, soft fruits, vegetables and field crops, e.g. V. dahliae on strawberries, rape, potatoes and tomatoes.

[00201] The compounds of formula I and compositions thereof, respectively, are also suitable for controlling harmful fungi in the protection of stored products or harvest and in the protection of materials. The term "protection of materials" is to be understood to denote the protection of technical and non-living materials, such as adhesives, glues, wood, paper and paperboard,

textiles, leather, paint dispersions, plastics, colling lubricants, fiber or fabrics, against the infestation and destruction by harmful microorganisms, such as fungi and bacteria. As to the protection of wood and other materials, the particular attention is paid to the following harmful fungi: Ascomycetes such as Ophiostoma spp., Ceratocystis spp., Aureobasidium pullulans, Sclerophoma spp., Chaetomium spp., Humicola spp., Petriella spp., Trichurus spp.; Basidiomycetes such as Coniophora spp., Coriolus spp., Gloeophyllum spp., Lentinus spp., Pleurotus spp., Poria spp., Serpula spp. and Tyromyces spp., Deuteromycetes such as Aspergillus spp., Cladosporium spp., Penicillium spp., Trichorma spp., Altemaria spp., Paecilomyces spp. and Zygomycetes such as Mucor spp., and in addition in the protection of stored products and harvest the following yeast fungi are worthy of note: Candida spp. and Saccharomyces cerevisae.

[00202] The compounds of formula I and compositions thereof, respectively, may be used for improving the health of a plant. The invention also relates to a method for improving plant health by treating a plant, its propagation material and/or the locus where the plant is growing or is to grow with an effective amount of compounds of formula I or compositions thereof, respectively.

[00203] The term "plant health" is to be understood to denote a condition of the plant and/or its products which is determined by several indicators alone or in combination with each other such as yield (e.g. increased biomass and/or increased content of valuable ingredients), plant vigor (e.g. improved plant growth and/or greener leaves ("greening effect")), quality (e.g. improved content or composition of certain ingredients) and tolerance to abiotic and/or biotic stress. The above identified indicators for the health condition of a plant may be interdependent or may result from each other.

[00204] The compounds of formula I can be present in different crystal modifications whose biological activity may differ. They are likewise subject matter of the present invention.

[00205] The compounds of formula I are employed as such or in form of compositions by treating the fungi or the plants, plant propagation materials, such as seeds, soil, surfaces, materials or rooms to be protected from fungal attack with a fungicidally effective amount of the active substances. The application can be carried out both before and after the infection of the plants, plant propagation materials, such as seeds, soil, surfaces, materials or rooms by the fungi.

[00206] Plant propagation materials may be treated with compounds of formula I as such or a composition comprising at least one compound of formula I prophylactically either at or before planting or transplanting.

[00207] The invention also relates to agrochemical compositions comprising a solvent or solid carrier and at least one compound of formula I and to the use for controlling harmful fungi.

[00208] An agrochemical composition comprises a fungicidally effective amount of a compound I and/or II. The term "effective amount" denotes an amount of the composition or of the compound of formula I, which is sufficient for controlling harmful fungi on cultivated plants or in the protection of materials and which does not result in a substantial damage to the treated plants. Such an amount can vary in a broad range and is dependent on various factors, such as the fungal species to be controlled, the treated cultivated plant or material, the climatic conditions and the specific compound of formula I used.

[00209] The compounds of formula I and salts thereof can be converted into customary types of agrochemical compositions, e.g. solutions, emulsions, suspensions, dusts, powders, pastes and granules. The composition type depends on the particular intended purpose; in each case, it should ensure a fine and uniform distribution of the compound according to the invention.

[00210] Examples for composition types are suspensions (SC, OD, FS), emulsifiable concentrates (EC), emulsions (EW, EO, ES), pastes, pastilles, wettable powders or dusts (WP, SP, SS, WS, DP, DS) or granules (GR, FG, GG, MG), which can be water- soluble or wettable, as well as gel formulations for the treatment of plant propagation materials such as seeds (GF).

[00211] Usually the composition types (e.g. SC, OD, FS, EC, WG, SG, WP, SP, SS, WS, GF) are employed diluted. Composition types such as DP, DS, GR, FG, GG and MG are usually used undiluted.

[00212] The compositions are prepared in a known manner (cf. US 3,060,084, EP-A 707 445 (for liquid concentrates), Browning: "Agglomeration", Chemical Engineering, Dec. 4, 1967, 147-48, Perry's Chemical Engineer's Handbook, 4th Ed., McGraw-Hill, New York, 1963, pp. 8-57 et seq., WO 91/13546, US 4,172,714, US 4,144,050, US 3,920,442, US 5,180,587, US 5,232,701 , US 5,208,030, GB 2,095,558, US 3,299,566, Klingman: Weed Control as a Science (J. Wiley & Sons, New York, 1961), Hance et al.: Weed Control Handbook (8th Ed., Blackwell Scientific, Oxford, 1989) and Mollet, H. and Grubemann, A.: Formulation technology (Wiley VCH Verlag, Weinheim, 2001).

[00213] The agrochemical compositions may also comprise auxiliaries which are customary in agrochemical compositions. The auxiliaries used depend on the particular application form and active substance, respectively.

[00214] Examples for suitable auxiliaries are solvents, solid carriers, dispersants or emulsifiers (such as further solubilizers, protective colloids, surfactants and adhesion agents), organic and inorganic thickeners, bactericides, anti-freezing agents, anti-foaming agents, if appropriate colorants and tackifiers or binders (e.g. for seed treatment formulations). Suitable solvents are water, organic solvents such as mineral oil fractions of medium to high boiling point, such as kerosene or diesel oil, furthermore coal tar oils and oils of vegetable or animal origin, aliphatic, cyclic and aromatic hydrocarbons, e.g. toluene, xylene, paraffin, tetrahydronaphthalene, alkylated naphthalenes or their derivatives, alcohols such as methanol, ethanol, propanol, butanol and cyclohexanol, glycols, ketones such as cyclohexanone and gamma-butyrolactone, fatty acid dimethylamides, fatty acids and fatty acid esters and strongly polar solvents, e.g. amines such as N- methylpyrrolidone.

[00215] Solid carriers are mineral earths such as silicates, silica gels, talc, kaolins, limestone, lime, chalk, bole, loess, clays, dolomite, diatomaceous earth, calcium sulfate, magnesium sulfate, magnesium oxide, ground synthetic materials, fertilizers, such as, e.g., ammonium sulfate, ammonium phosphate, ammonium nitrate, ureas, and products of vegetable origin, such as cereal meal, tree bark meal, wood meal and nutshell meal, cellulose powders and other solid carriers.

[00216] Suitable surfactants (adjuvants, wetters, tackifiers, dispersants or emulsifiers) are alkali metal, alkaline earth metal and ammonium salts of aromatic sulfonic acids, such as ligninsoulfonic acid (Borresperse® types, Borregard, Norway) phenolsulfonic acid, naphthalenesulfonic acid (Morwet® types, Akzo Nobel, U.S.A.), dibutylnaphthalene- sulfonic acid (Nekal® types, BASF, Germany), and fatty acids, alkylsulfonates, alkyl- arylsulfonates, alkyl sulfates, laurylether sulfates, fatty alcohol sulfates, and sulfated hexa-, hepta- and octadecanolates, sulfated fatty alcohol glycol ethers, furthermore condensates of naphthalene or of naphthalenesulfonic acid with phenol and formaldehyde, polyoxy-ethylene octylphenyl ether, ethoxylated isooctylphenol, octylphenol, nonylphenol, alkylphenyl polyglycol ethers, tributylphenyl polyglycol ether, tristearyl- phenyl polyglycol ether, alkylaryl polyether alcohols, alcohol and fatty alcohol/ethylene oxide condensates, ethoxylated castor oil, polyoxyethylene alkyl ethers, ethoxylated polyoxypropylene, lauryl alcohol polyglycol ether acetal, sorbitol esters, lignin-sulfite waste liquors and proteins, denatured proteins, polysaccharides (e.g. methylcellulose), hydrophobically modified starches, polyvinyl alcohols (Mowiol® types, Clariant, Switzerland), polycarboxylates (Sokolan® types, BASF, Germany), polyalkoxylates,

polyvinyl- amines (Lupasol® types, BASF, Germany), polyvinylpyrrolidone and the copolymers therof.

[00217] Examples for thickeners (i.e. compounds that impart a modified flowability to compositions, i.e. high viscosity under static conditions and low viscosity during agitation) are polysaccharides and organic and anorganic clays such as Xanthan gum (Kelzan®, CP Kelco, U.S.A.), Rhodopol® 23 (Rhodia, France), Veegum® (RT. Vanderbilt, U.S.A.) or Attaclay® (Engelhard Corp., NJ, USA).

[00218] Bactericides may be added for preservation and stabilization of the composition. Examples for suitable bactericides are those based on dichlorophene and benzylalcohol hemi formal (Proxel® from ICI or Acticide® RS from Thor Chemie and Kathon® MK from Rohm & Haas) and isothiazolinone derivatives such as alkylisothiazolinones and benzisothiazolinones (Acticide® MBS from Thor Chemie).

[00219] Examples for suitable anti-freezing agents are ethylene glycol, propylene glycol, urea and glycerin.

[00220] Examples for anti-foaming agents are silicone emulsions (such as e.g. Silikon® SRE, Wacker, Germany or Rhodorsil®, Rhodia, France), long chain alcohols, fatty acids, salts of fatty acids, fluoroorganic compounds and mixtures thereof.

[00221] Suitable colorants are pigments of low water solubility and water-soluble dyes. Examples to be mentioned und the designations rhodamin B, C. I. pigment red 112, C. I. solvent red 1 , pigment blue 15:4, pigment blue 15:3, pigment blue 15:2, pigment blue 15:1 , pigment blue 80, pigment yellow 1 , pigment yellow 13, pigment red 112, pigment red 48:2, pigment red 48:1 , pigment red 57:1 , pigment red 53:1 , pigment orange 43, pigment orange 34, pigment orange 5, pigment green 36, pigment green 7, pigment white 6, pigment brown 25, basic violet 10, basic violet 49, acid red 51 , acid red 52, acid red 14, acid blue 9, acid yellow 23, basic red 10, basic red 108.

[00222] Examples for tackifiers or binders are polyvinylpyrrolidons, polyvinylacetates, polyvinyl alcohols and cellulose ethers (Tylose®, Shin-Etsu, Japan).

[00223] Powders, materials for spreading and dusts can be prepared by mixing or concomitantly grinding the compounds of formula I and, if appropriate, further active substances, with at least one solid carrier.

[00224] Granules, e.g. coated granules, impregnated granules and homogeneous granules, can be prepared by binding the active substances to solid carriers. Examples of solid carriers are mineral earths such as silica gels, silicates, talc, kaolin, attaclay, limestone, lime, chalk, bole, loess, clay, dolomite, diatomaceous earth, calcium sulfate, magnesium sulfate, magnesium oxide, ground synthetic materials, fertilizers, such as, e.g., ammonium sulfate, ammonium phosphate, ammonium nitrate, ureas, and products of vegetable origin, such as cereal meal, tree bark meal, wood meal and nutshell meal, cellulose powders and other solid carriers.

[00225] Examples for composition types include, but are not limited to: 1. Composition types for dilution with water, i) Water-soluble concentrates (SL, LS): 10 parts by weight of a compound of formula I according to the invention are dissolved in 90 parts by weight of water or in a water-soluble solvent. As an alternative, wetting agents or other auxiliaries are added. The active substance dissolves upon dilution with water. In this way, a composition having a content of 10% by weight of active substance is obtained. ii) Dispersible concentrates (DC): 20 parts by weight of a compound of formula I according to the invention are dissolved in 70 parts by weight of cyclohexanone with addition of 10 parts by weight of a dispersant, e.g. polyvinylpyrrolidone. Dilution with water gives a dispersion. The active substance content is 20% by weight. iii) Emulsifiable concentrates (EC): 15 parts by weight of a compound of formula I according to the invention are dissolved in 75 parts by weight of xylene with addition of calcium dodecylbenzenesulfonate and castor oil ethoxylate (in each case 5 parts by weight). Dilution with water gives an emulsion. The composition has an active substance content of 15% by weight. iv) Emulsions (EW, EO, ES): 25 parts by weight of a compound of formula I according to the invention are dissolved in 35 parts by weight of xylene with addition of calcium dodecylbenzenesulfonate and castor oil ethoxylate (in each case 5 parts by weight). This mixture is introduced into 30 parts by weight of water by means of an emulsifying machine (Ultraturrax) and made into a homogeneous emulsion. Dilution with water gives an emulsion. The composition has an active substance content of 25% by weight. v) Suspensions (SC, OD, FS): In an agitated ball mill, 20 parts by weight of a compound of formula I according to the invention are comminuted with addition of 10 parts by weight of dispersants and wetting agents and 70 parts by weight of water or an organic solvent to give a fine active sub- stance suspension. Dilution with water gives a stable suspension of the active substance. The active substance content in the composition is 20% by weight. vi) Water-dispersible granules and water-soluble

granules (WG, SG) 50 parts by weight of a compound of formula I according to the invention are ground finely with addition of 50 parts by weight of dispersants and wetting agents and prepared as water-dispersible or water-soluble granules by means of technical appliances (e.g. extrusion, spray tower, fluidized bed). Dilution with water gives a stable dispersion or solution of the active substance. The composition has an active substance content of 50% by weight. vii) Water-dispersible powders and water-soluble powders (WP, SP, SS, WS) 75 parts by weight of a compound of formula I according to the invention are ground in a rotor-stator mill with addition of 25 parts by weight of dispersants, wetting agents and silica gel. Dilution with water gives a stable dispersion or solution of the active substance. The active substance content of the composition is 75% by weight. viii) Gel (GF): In an agitated ball mill, 20 parts by weight of a compound of formula I according to the invention are comminuted with addition of 10 parts by weight of dispersants, 1 part by weight of a gelling agent wetters and 70 parts by weight of water or of an organic solvent to give a fine suspension of the active substance. Dilution with water gives a stable suspension of the active substance, whereby a composition with 20% (w/w) of active substance is obtained.

[00226] 2. Composition types to be applied undiluted: ix) Dustable powders (DP, DS): 5 parts by weight of a compound of formula I according to the invention are ground finely and mixed intimately with 95 parts by weight of finely divided kaolin. This gives a dustable composition having an active substance content of 5% by weight. x) Granules (GR, FG, GG, MG): 0.5 parts by weight of a compound of formula I according to the invention is ground finely and associated with 99.5 parts by weight of carriers. Current methods are extrusion, spray-drying or the fluidized bed. This gives granules to be applied undiluted having an active substance content of 0.5% by weight. xi) ULV solutions (UL) 10 parts by weight of a compound of formula I according to the invention are dissolved in 90 parts by weight of an organic solvent, e.g. xylene. This gives a composition to be applied undiluted having an active substance content of 10% by weight.

[00227] The agrochemical compositions generally comprise between 0.01 and 95%, preferably between 0.1 and 90%, most preferably between 0.5 and 90%, by weight of active substance. The active substances are employed in a purity of from 90% to 100%, preferably from 95% to 100% (according to NMR spectrum).

[00228] Water-soluble concentrates (LS), flowable concentrates (FS), powders for dry treatment (DS), water-dispersible powders for slurry treatment (WS), water-soluble powders (SS), emulsions (ES) emulsifiable concentrates (EC) and gels (GF) are usually employed for the purposes of treatment of plant propagation materials, particularly seeds. These compositions can be applied to plant propagation materials, particularly seeds, diluted or undiluted. The compositions in question give, after two-to-tenfold dilution, active substance concentrations of from 0.01 to 60% by weight, preferably from 0.1 to 40% by weight, in the ready-to-use preparations. Application can be carried out before or during sowing. Methods for applying or treating agrochemical compounds and compositions thereof, respectively, on to plant propagation material, especially seeds, are known in the art, and include dressing, coating, pelleting, dusting, soaking and in- furrow application methods of the propagation material. In a preferred embodiment, the compounds or the compositions thereof, respectively, are applied on to the plant propagation material by a method such that germination is not induced, e.g. by seed dressing, pelleting, coating and dusting.

[00229] In a preferred embodiment, a suspension-type (FS) composition is used for seed treatment. Typcially, a FS composition may comprise 1-800 g/l of active substance, 1-200 g/l Surfactant, 0 to 200 g/l antifreezing agent, 0 to 400 g/l of binder, 0 to 200 g/l of a pigment and up to 1 liter of a solvent, preferably water.

[00230] The active substances can be used as such or in the form of their compositions, e.g. in the form of directly sprayable solutions, powders, suspensions, dispersions, emulsions, dispersions, pastes, dustable products, materials for spreading, or granules, by means of spraying, atomizing, dusting, spreading, brushing, immersing or pouring. The application forms depend entirely on the intended purposes; it is intended to ensure in each case the finest possible distribution of the active substances according to the invention. Aqueous application forms can be prepared from emulsion concentrates, pastes or wettable powders (sprayable powders, oil dispersions) by adding water. To prepare emulsions, pastes or oil dispersions, the substances, as such or dissolved in an oil or solvent, can be homogenized in water by means of a wetter, tackifier, dispersant or emulsifier. Alternatively, it is possible to prepare concentrates composed of active substance, wetter, tackifier, dispersant or emulsifier and, if appropriate, solvent or oil, and such concentrates are suitable for dilution with water.

[00231] The active substance concentrations in the ready-to-use preparations can be varied within relatively wide ranges. In general, they are from 0.0001 to 10%, preferably from 0.001 to 1 % by weight of active substance.

[00232] The active substances may also be used successfully in the ultra-low-volume process (ULV), it being possible to apply compositions comprising over 95% by weight of active substance, or even to apply the active substance without additives.

[00233] When employed in plant protection, the amounts of active substances applied are, depending on the kind of effect desired, from 0.001 to 2 kg per ha, preferably from 0.005 to 2 kg per ha, more preferably from 0.05 to 0.9 kg per ha, in particular from 0.1 to 0.75 kg per ha.

[00234] In treatment of plant propagation materials such as seeds, e.g. by dusting, coating or drenching seed, amounts of active substance of from 0.1 to 1000 g, preferably from 1 to 1000 g, more preferably from 1 to 100 g and most preferably from 5 to 100 g, per 100 kilogram of plant propagation material (preferably seed) are generally required.

[00235] When used in the protection of materials or stored products, the amount of active substance applied depends on the kind of application area and on the desired effect. Amounts customarily applied in the protection of materials are, e.g., 0.001 g to 2 kg, preferably 0.005 g to 1 kg, of active substance per cubic meter of treated material.

[00236] Various types of oils, wetters, adjuvants, herbicides, bactericides, other fungicides and/or pesticides may be added to the active substances or the compositions comprising them, if appropriate not until immediately prior to use (tank mix). These agents can be admixed with the compositions according to the invention in a weight ratio of 1 :100 to 100:1 , preferably 1 :10 to 10:1.

[00237] Adjuvants which can be used are in particular organic modified polysiloxanes such as Break Thru S 240®; alcohol alkoxylates such as Atplus 245®, Atplus MBA 1303®, PIurafac LF 300® and Lutensol ON 30®; EO/PO block polymers, e.g. Pluronic RPE 2035® and Genapol B®; alcohol ethoxylates such as Lutensol XP 80®; and dioctyl sulfosuccinate sodium such as Leophen RA®.

[00238] The compositions according to the invention can, in the use form as fungicides, also be present together with other active substances, e.g. with herbicides, insecticides, growth regulators, fungicides or else with fertilizers, as pre-mix or, if appropriate, not until immediately prior to use (tank mix).

[00239] Mixing the compounds of formula I or the compositions comprising them in the use form as fungicides with other fungicides results in many cases in an expansion of the fungicidal spectrum of activity being obtained or in a prevention of fungicide resistance development. Furthermore, in many cases, synergistic effects are obtained.

[00240] The following list of active substances, in conjunction with which the compounds according to the invention can be used, is intended to illustrate the possible combinations but does not limit them:

[00241] A) strobilurins azoxystrobin, dimoxystrobin, enestroburin, fluoxastrobin, kresoxim-methyl, meto- minostrobin, orysastrobin, picoxystrobin, pyraclostrobin, pyribencarb, trifloxystrobin, 2-(2-(6-(3-chloro-2-methyl-phenoxy)-5-fluoro-pyrimidin-4-yloxy)-phenyl)-2-methoxyimino-N-methyl-acetamide, 3-methoxy-2-(2-(N-(4-methoxy-phenyl)- cyclopropane-carboximidoylsulfanylmethyl)-phenyl)-acrylic acid methyl ester, methyl (2-chloro-5-[1-(3-methylbenzyloxyimino)ethyl]benzyl)carbamate and 2-(2-(3-(2,6-dichlorophenyl)-1-methyl-allylideneaminooxymethyl)-phenyl)-2-methoxyimino-N-methyl-acetamide;

[00242] B) carboxamides and carboxanilides: benalaxyl, benalaxyl-M, benodanil, bixafen, boscalid, carboxin, fenfuram, fenhexamid, flutolanil, furametpyr, isopyrazam, isotianil, kiralaxyl, me- pronil, metalaxyl, metalaxyl-M (mefenoxam), ofurace, oxadixyl, oxycarboxin, pen-thiopyrad, sedaxane, tecloftalam, thifluzamide, tiadinil, 2-amino-4-methyl- thiazole-5-carboxanilide, 2-chloro-N-(1,1,3-trimethyl-indan-4-yl)-nicotinamide, N- (3',4',5'-trifluorobiphenyl-2-yl)-3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxamide, N-(4'-trifluoromethylthiobiphenyl-2-yl)-3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxamide, N-(2-(1,3-dimethyl-butyl)-phenyl)-1 ,3-dimethyl-5-fluoro-1H-pyrazole-4-carboxamide and N-(2-(1,3,3-trimethyl-butyl)-phenyl)-1,3-dimethyl-5-fluoro-1H-pyrazole-4-carboxamide; carboxylic morpholides: dimethomorph, flumorph, pyrimorph; benzoic acid amides: flumetover, fluopicolide, fluopyram, zoxamide, N-(3-Ethyl-3,5,5-trimethyl-cyclohexyl)-3-formylamino-2-hydroxy-benzamide; other carboxamides: carpropamid, dicyclomet, mandiproamid, oxytetracyclin, silthiofarm and N-(6-methoxy-pyridin-3-yl) cyclopropanecarboxylic acid amide;

[00243] C) azoles and triazoles: azaconazole, bitertanol, bromuconazole, cyproconazole, difenoconazole, diniconazole, diniconazole-M, epoxiconazole, fenbuconazole, fluquinconazole, flusilazole, flutriafol, hexaconazole, imibenconazole, ipconazole, metconazole, myclobutanil, oxpoconazole, paclobutrazole, penconazole, propiconazole, prothioconazole, simeconazole,

tebuconazole, tetraconazole, triadimefon, triadimenol, triticonazole, uniconazole, 1-(4-chloro-phenyl)-2-([1,2,4]triazol-1-yl)-cycloheptanol; imidazoles: cyazofamid, imazalil, pefurazoate, prochloraz, triflumizol; benzimidazoles: benomyl, carbendazim, fuberidazole, thiabendazole; - others: ethaboxam, etridiazole, hymexazole and 2-(4-chloro-phenyl)-N-[4-(3,4-dimethoxy-phenyl)-isoxazol-5-yl]-2-prop-2-ynyloxy-acetamide;

[00244] D) heterocyclic compounds pyridines: fluazinam, pyrifenox, 3-[5-(4-chloro-phenyl)-2,3-dimethyl-isoxazolidin- 3-yl]-pyridine, 3-[5-(4-methyl-phenyl)-2,3-dimethyl-isoxazolidin-3-yl]-pyridine, 2,3,5,6-tetra-chloro-4-methanesulfonyl-pyridine, 3,4,5-trichloropyridine-2,6-di-carbonitrile, N-(1-(5-bromo-3-chloro-pyridin-2-yl)-ethyl)-2,4-dichloronicotinamide, N-[(5-bromo-3-chloro-pyridin-2-yl)-methyl]-2,4-dichloro-nicotinamide; pyrimidines: bupirimate, cyprodinil, diflumetorim, fenarimol, ferimzone, mepanipyrim, nitrapyrin, nuarimol, pyrimethanil; piperazines: triforine; pyrroles: fenpiclonil, fludioxonil; morpholines: aldimorph, dodemorph, dodemorph-acetate, fenpropimorph, tridemorph; piperidines: fenpropidin; - dicarboximides: fluoroimid, iprodione, procymidone, vinclozolin; non-aromatic 5-membered heterocycles: famoxadone, fenamidone, flutianil, octhilinone, probenazole, 5-amino-2-isopropyl-3-oxo-4-ortho-tolyl-2,3-dihydro-pyrazole-1-carbothioic acid S-allyl ester; others: acibenzolar-S-methyl, amisulbrom, anilazin, blasticidin-S, captafol, captan, chinomethionat, dazomet, debacarb, diclomezine, difenzoquat, difenzoquat- methylsulfate, fenoxanil, Folpet, oxolinic acid, piperalin, proquinazid, pyroquilon, quinoxyfen, triazoxide, tricyclazole, 2-butoxy-6-iodo-3-propylchromen-4-one, 5-chloro-1-(4,6-dimethoxy-pyrimidin-2-yl)-2-methyl-1H-benzimidazole, 5-chloro-7-(4-methylpiperidin-1-yl)-6-(2,4,6-trifluorophenyl)-[1,2,4]triazolo[1,5-a]pyrimidine and 5-ethyl-6-octyl-[1,2,4]triazolo[1,5-a]pyrimidine-7-ylamine;

[00245] E) carbamates thio- and dithiocarbamates: ferbam, mancozeb, maneb, metam, methasulphocarb, metiram, propineb, thiram, zineb, ziram; carbamates: benthiavalicarb, diethofencarb, iprovalicarb, propamocarb, propamo- carb hydrochlorid, valiphenal and N-(1-(1-(4-cyano-phenyl)ethanesulfonyl)-but-2-yl) carbamic acid-(4-fluorophenyl) ester;

[00246] F) other active substances - guanidines: guanidine, dodine, dodine free base, guazatine, guazatine-acetate, iminoctadine, iminoctadine-triacetate, iminoctadine-tris(albesilate); antibiotics: kasugamycin, kasugamycin hydrochloride-hydrate, streptomycin, pol- yoxine, validamycin A; nitrophenyl derivates: binapacryl, dinobuton, dinocap, nitrthal-isopropyl, tecna-zen, organometal compounds: fentin salts, such as fentin-acetate, fentin chloride or fentin

hydroxide; sulfur-containing heterocyclyl compounds: dithianon, isoprothiolane; organophosphorus compounds: edifenphos, fosetyl, fosetyl-aluminum, iproben-fos, phosphorous acid and its salts, pyrazophos, tolclofos-methyl; organochlorine compounds: chlorothalonil, dichlofluanid, dichlorophen, flusulfamide, hexachlorobenzene, pencycuron, pentachlorphenole and its salts, phthalide, quintozene, thiophanate-methyl, tolylfluanid, N-(4-chloro-2-nitro-phenyl)-N-ethyl-4-methyl-benzenesulfonamide; inorganic active substances: Bordeaux mixture, copper acetate, copper hydroxide, copper oxychloride, basic copper sulfate, sulfur; biphenyl, bronopol, cyflufenamid, cymoxanil, diphenylamin, metrafenone, mildiomycin, oxin-copper, prohexadione-calcium, spiroxamine, tolylfluanid, N-(cyclopropylmethoxyimino-(6-difluoro-methoxy-2,3-difluoro-phenyl)-methyl)-2-phenylacetamide, N'-(4-(4-chloro-3-trifluoromethyl-phenoxy)-2,5-dimethyl-phenyl)-N-ethyl-N-methylformamidine, N'-(4-(4-fluoro-3-trifluoromethyl-phenoxy)-2,5-dimethyl-phenyl)-N-ethyl-N-methyl formamidine, N'-(2-methyl-5-trifluoromethyl-4-(3-trimethylsilanyl-propoxy)-phenyl)-N-ethyl-N-methylformamidine, N'-(5-difluoromethyl-2-methyl-4-(3-trimethylsilanyl-propoxy)-phenyl)-N-ethyl-N-methylformamidine, 2-{1-[2-(5-methyl-3-trifluoromethyl-pyrazole-1-yl)-acetyl]-piperidin-4-yl}-thiazole-4-carboxylic acid methyl-(1,2,3,4-tetrahydro-naphthalen-1-yl)-amide, 2-{1-[2-(5- methyl-S-trifluoromethyl-pyrazole-i-yO-acety^-piperidin^-ylJ-thiazole^-carboxylic acid methyl-(R)-1 ,2,3,4-tetrahydro-naphthalen-1-yl-amide, acetic acid 6-tert-butyl- 8-fluoro-2,3-dimethyl-quinolin-4-yl ester and methoxy-acetic acid 6-tert-butyl-8- fluoro-2,3-dimethyl-quinolin-4-yl ester.

[00247] G) growth regulators abscisic acid, amidochlor, ancymidol, 6-benzylaminopurine, brassinolide, butralin, chlormequat (chlormequat chloride), choline chloride, cyclanilide, daminozide, dikegulac, dimethipin, 2,6-dimethylpuridine, ethephon, flumetralin, flurprimidol, fluthiacet, forchlorfenuron, gibberellic acid, inabenfide, indole-3-acetic acid , maleic hydrazide, mefluidide, mepiquat (mepiquat chloride), naphthaleneacetic acid, N-6-benzyladenine, paclobutrazol, prohexadione (prohexadione-calcium), prohydrojasmon, thidiazuron, triapenthenol, tributyl phosphorotrithioate, 2,3,5-tri-iodobenzoic acid , trinexapac-ethyl and uniconazole;

[00248] H) herbicides acetamides: acetochlor, alachlor, butachlor, dimethachlor, dimethenamid, flufen- acet, mefenacet, metolachlor, metazachlor, napropamide, naproanilide, pethox- amid, pretilachlor, propachlor, thenylchlor; amino acid derivatives: bilanafos,

glyphosate, glufosinate, sulfosate; aryloxyphenoxypropionates: clodinafop, cyhalofop-butyl, fenoxaprop, fluazifop, haloxyfop, metamifop, propaquizafop, quizalofop, quizalofop-P-tefuryl; Bipyridyls: diquat, paraquat; (thio)carbamates: asulam, butylate, carbetamide, desmedipham, dimepiperate, eptam (EPTC), esprocarb, molinate, orbencarb, phenmedipham, prosulfocarb, pyributicarb, thiobencarb, triallate; cyclohexanediones: butroxydim, clethodim, cycloxydim, profoxydim, sethoxydim, tepraloxydim, tralkoxydim; - dinitroanilines: benfluralin, ethalfluralin, oryzalin, pendimethalin, prodiamine, trifluralin; diphenyl ethers: acifluorfen, aclonifen, bifenox, diclofop, ethoxyfen, fomesafen, lactofen, oxyfluorfen; hydroxybenzonitriles: bomoxynil, dichlobenil, ioxynil; - imidazolinones: imazamethabenz, imazamox, imazapic, imazapyr, imazaquin, imazethapyr; phenoxy acetic acids: clomeprop, 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4-DB, dichlorprop, MCPA, MCPA-thioethyl, MCPB, Mecoprop; pyrazines: chloridazon, flufenpyr-ethyl, fluthiacet, norflurazon, pyridate; pyridines: aminopyralid, clopyralid, diflufenican, dithiopyr, fluridone, fluroxypyr, picloram, picolinafen, thiazopyr; sulfonyl ureas: amidosulfuron, azimsulfuron, bensulfuron, chlorimuron-ethyl, chlorsulfuron, cinosulfuron, cyclosulfamuron, ethoxysulfuron, flazasulfuron, flucetosulfuron, flupyrsulfuron, foramsulfuron, halosulfuron, imazosulfuron, iodosulfu- ron, mesosulfuron, metsulfuron-methyl, nicosulfuron, oxasulfuron, primisulfuron, prosulfuron, pyrazosulfuron, rimsulfuron, sulfometuron, sulfosulfuron, thifensulfuron, triasulfuron, tribenuron, trifloxysulfuron, triflusulfuron, tritosulfuron, 1-((2-chloro-6-propyl-imidazo[1,2-b]pyridazin-3-yl)sulfonyl)-3-(4,6-dimethoxy-pyrmidin-2-yl)urea; triazines: ametryn, atrazine, cyanazine, dimethametryn, ethiozin, hexazinone, metamitron, metribuzin, prometryn, simazine, terbuthylazine, terbutryn, triaziflam; ureas: chlorotoluron, daimuron, diuron, fluometuron, isoproturon, linuron, metha-benzthiazuron,tebuthiuron; other acetolactate synthase inhibitors: bispyribac-sodium, cloransulam-methyl, diclosulam, florasulam, flucarbazone, flumetsulam, metosulam, ortho-sulfamuron, penoxsulam, propoxycarbazone, pyribambenz-propyl, pyribenzoxim, pyriftalid, pyriminobac-methyl, pyrimisulfan, pyrithiobac, pyroxasulfone, pyroxsulam; others: amicarbazone, aminotriazole, anilofos, beflubutamid, benazolin, bencar- bazone,benfluresate, benzofenap, bentazone, benzobicyclon, bromacil, bromo- butide, butafenacil, butamifos, cafenstrole, carfentrazone, cinidon-ethlyl, chlor- thal, cinmethylin, clomazone, cumyluron, cyprosulfamide, dicamba, difenzoquat, diflufenzopyr, Drechslera monoceras, endothal, ethofumesate, etobenzanid, fen- trazamide, flumiclorac-pentyl, flumioxazin, flupoxam,

flurochloridone, flurtamone, indanofan, isoxaben, isoxaflutole, lenacil, propanil, propyzamide, quinclorac, quinmerac, mesotrione, methyl arsonic acid, naptalam, oxadiargyl, oxadiazon, oxaziclomefone, pentoxazone, pinoxaden, pyraclonil, pyraflufen-ethyl, pyrasulfo- tole, pyrazoxyfen, pyrazolynate, quinoclamine, saflufenacil, sulcotrione, sulfentra- zone, terbacil, tefuryltrione, tembotrione, thiencarbazone, topramezone, 4- hydroxy-3-[2-(2-methoxy-ethoxymethyl)-6-trifluoromethyl-pyridine-3-carbonyl]- bicyclo[3.2.1]oct-3-en-2-one, (3-[2-chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4- trifluoromethyl-3,6-dihydro-2H-pyrimidin-1-yl)-phenoxy]-pyridin-2-yloxy)-acetic acid ethyl ester, 6-amino-5-chloro-2-cyclopropyl-pyrimidine-4-carboxylic acid methyl ester, 6-chloro-3-(2-cyclopropyl-6-methyl-phenoxy)-pyridazin-4-ol, 4-amino-3-chloro-6-(4-chloro-phenyl)-5-fluoro-pyridine-2-carboxylic acid, 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxy-phenyl)-pyridine-2-carboxylic acid methyl ester, and 4-amino-3-chloro-6-(4-chloro-3-dimethylamino-2-fluoro-phenyl)- pyridine-2-carboxylic acid methyl ester.

[00249] I) insecticides - organo(thio)phosphates: acephate, azamethiphos, azinphos-methyl, chlorpyrifos, chlorpyrifos-methyl, chlorfenvinphos, diazinon, dichlorvos, dicrotophos, dimethoate, disulfoton, ethion, fenitrothion, fenthion, isoxathion, malathion, methamido- phos, methidathion, methyl-parathion, mevinphos, monocrotophos, oxydemeton- methyl, paraoxon, parathion, phenthoate, phosalone, phosmet, phosphamidon, phorate, phoxim, pirimiphos-methyl, profenofos, prothiofos, sulprophos, tetra- chlorvinphos, terbufos, triazophos, trichlorfon; carbamates: alanycarb, aldicarb, bendiocarb, benfuracarb, carbaryl, carbofuran, carbosulfan, fenoxycarb, furathiocarb, methiocarb, methomyl, oxamyl, pirimicarb, propoxur, thiodicarb, triazamate; pyrethroids: allethrin, bifenthrin, cyfluthrin, cyhalothrin, cyphenothrin, cypermethrin, alpha-cypermethrin, beta-cypermethrin, zeta-cypermethrin, deltamethrin, esfenvalerate, etofenprox, fenpropathrin, fenvalerate, imiprothrin, lambda- cyhalothrin, permethrin, prallethrin, pyrethrin I and II, resmethrin, silafluofen, tau- fluvalinate, tefluthrin, tetramethrin, tralomethrin, transfluthrin, profluthrin, dimefluthrin; insect growth regulators: a) chitin synthesis inhibitors: benzoylureas: chlorfluazuron, cyramazin, diflubenzuron, flucycloxuron, flufenoxuron, hexaflumuron, lufenuron, novaluron, teflubenzuron, triflumuron; buprofezin, diofenolan, hexythiazox, etoxazole, clofentazine; b) ecdysone antagonists: halofenozide, methoxyfenozide, tebufenozide, azadirachtin; c) juvenoids: pyriproxyfen, methoprene, fenoxycarb; d) lipid biosynthesis inhibitors: spirodiclofen, spiromesifen, spirotetramat; nicotinic receptor agonists/antagonists compounds: clothianidin, dinotefuran, imi- dacloprid, thiamethoxam,

nitenpyram, acetamiprid, thiacloprid, 1-(2-chloro- thiazol-5-ylmethyl)-2-nitrimino-3,5-dimethyl-[1,3,5]triazinane; GABA antagonist compounds: endosulfan, ethiprole, fipronil, vaniliprole, pyrafluprole, pyriprole, 5-amino-1 -(2,6-dichloro-4-methyl-phenyl)-4-sulfinamoyl-1H-pyrazole-3-carbothioic acid amide; macrocyclic lactone insecticides: abamectin, emamectin, milbemectin, lepimectin, spinosad, spinetoram; mitochondrial electron transport inhibitor (METI) I acaricides: fenazaquin, pyrida- ben, tebufenpyrad, tolfenpyrad, flufenerim; METI II and III compounds: acequinocyl, fluacyprim, hydramethylnon; Uncouplers: chlorfenapyr; - oxidative phosphorylation inhibitors: cyhexatin, diafenthiuron, fenbutatin oxide, propargite; moulting disruptor compounds: cryomazine; mixed function oxidase inhibitors: piperonyl butoxide; sodium channel blockers: indoxacarb, metaflumizone; - others: benclothiaz, bifenazate, cartap, flonicamid, pyridalyl, pymetrozine, sulfur, thiocyclam, flubendiamide, chlorantraniliprole, cyazypyr (HGW86), cyenopyrafen, flupyrazofos, cyflumetofen, amidoflumet, imicyafos, bistrifluron, and pyrifluquinazon.

[00250] The present invention furthermore relates to agrochemical compositions comprising a mixture of at least one compound of formula I (component 1) and at least one further active substance useful for plant protection, e.g. selected from the groups A) to I) (component 2), in particular one further fungicide, e.g. one or more fungicide from the groups A) to F), as described above, and if desired one suitable solvent or solid carrier. Those mixtures are of particular interest, since many of them at the same application rate show higher efficiencies against harmful fungi. Furthermore, combating harmful fungi with a mixture of compounds of formula I and at least one fungicide from groups A) to F), as described above, is more efficient than combating those fungi with individual compounds of formula I or individual fungicides from groups A) to F). By applying compounds of formula I together with at least one active substance from groups A) to I) a synergistic effect can be obtained, i.e. more than simple addition of the individual effects is obtained (synergistic mixtures).

[00251] According to this invention, applying the compounds of formula I together with at least one further active substance is to be understood to denote that at least one compound of formula I and at least one further active substance occur simultaneously at the site of action (i.e. the harmful fungi to be controlled or their habitats such as infected plants, plant propagation materials, particularly seeds, surfaces, materials or the soil as well as plants, plant propagation materials, particularly seeds, soil, surfaces, materials or rooms to be protected from fungal

attack) in a fungicidally effective amount. This can be obtained by applying the compounds of formula I and at least one further active substance simultaneously, either jointly (e.g. as tank-mix) or separately, or in succession, wherein the time interval between the individual applications is selected to ensure that the active substance applied first still occurs at the site of action in a sufficient amount at the time of application of the further active substance(s). The order of application is not essential for working of the present invention.

[00252] In binary mixtures, i.e. compositions according to the invention comprising one compound I (component 1) and one further active substance (component 2), e.g. one active substance from groups A) to I), the weight ratio of component 1 and component 2 generally depends from the properties of the active substances used, usually it is in the range of from 1 :100 to 100:1 , regularly in the range of from 1 :50 to 50:1 , preferably in the range of from 1 :20 to 20:1 , more preferably in the range of from 1 :10 to 10:1 and in particular in the range of from 1 :3 to 3:1.

[00253] In ternary mixtures, i.e. compositions according to the invention comprising one compound I (component 1) and a first further active substance (component 2) and a second further active substance (component 3), e.g. two active substances from groups A) to I), the weight ratio of component 1 and component 2 depends from the properties of the active substances used, preferably it is in the range of from 1:50 to 50:1 and particularly in the range of from 1 :10 to 10:1 , and the weight ratio of component 1 and component 3 preferably is in the range of from 1:50 to 50:1 and particularly in the range of from 1:10 to 10:1.

[00254] The components can be used individually or already partially or completely mixed with one another to prepare the composition according to the invention. It is also possible for them to be packaged and used further as combination composition such as a kit of parts.

[00255] In one embodiment of the invention, the kits may include one or more, including all, components that may be used to prepare a subject agrochemical composition. E. g., kits may include one or more fungicide component(s) and/or an adjuvant component and/or an insecticide component and/or a growth regulator component and/or a herbicide. One or more of the components may already be combined together or pre-formulated. In those embodiments where more than two components are provided in a kit, the components may already be combined together and as such are packaged in a single container such as a vial, bottle, can, pouch, bag or canister. In other embodiments, two or more components of a kit may be packaged separately,

i.e., not pre- formulated. As such, kits may include one or more separate containers such as vials, cans, bottles, pouches, bags or canisters, each container containing a separate component for an agrochemical composition. In both forms, a component of the kit may be applied separately from or together with the further components or as a component of a combination composition according to the invention for preparing the composition according to the invention.

[00256] The user applies the composition according to the invention usually from a predosage device, a knapsack sprayer, a spray tank or a spray plane. Here, the agrochemical composition is made up with water and/or buffer to the desired application concentration, it being possible, if appropriate, to add further auxiliaries, and the ready-to-use spray liquor or the agrochemical composition according to the invention is thus obtained. In some embodiments, 50 to 500 liters of the ready-to-use spray liquor are applied per hectare of agricultural useful area. In some embodiments 100 to 400 liters of the ready-to-use spray liquor are applied per hectare. In some embodiments, the invention provides a kit for greenhouse application of a ready-to-use composition of the invention.

[00257] According to one embodiment, individual components of the composition according to the invention such as parts of a kit or parts of a binary or ternary mixture may be mixed by the user himself in a spray tank and further auxiliaries may be added, if appropriate (tank mix). In a further embodiment, either individual components of the composition according to the invention or partially premixed components, e.g. components comprising compounds of formula I and/or active substances from the groups A) to I), may be mixed by the user in a spray tank and further auxiliaries and additives may be added, if appropriate (tank mix).

[00258] In a further embodiment, either individual components of the composition according to the invention or partially premixed components, e.g. components comprising compounds of formula I and/or active substances from the groups A) to I), can be applied jointly (e.g. after tankmix) or consecutively.

[00259] In some embodiments the invention provides a mixture comprising a compound of formula I (component 1) and at least one active substance selected from the strobilurines of group A) (component 2) and particularly selected from azoxystrobin, dimoxystrobin, fluoxastrobin, kresoxim-methyl, orysastrobin, picoxystrobin, pyraclostrobin and trifloxystrobin.

[00260] In some embodiments the invention provides a mixture comprising a compound of formula I (component 1) and at least one active substance selected from the carboxamides of

group B) (component 2). In some embodiments, the carboxamide is selected from the group consisting of bixafen, boscalid, sedaxane, fenhexamid, metalaxyl, isopyrazam, mefenoxam, ofurace, dimethomorph, flumorph, fluopicolid (picobenzamid), zoxamide, carpropamid, mandipropamid and N-(3',4',5'-trifluorobiphenyl-2-yl)-3-difluoromethyl-1-methyl-1H-pyrazole-4-carboxamide.

[00261] In some embodiments the invention provides a mixture comprising a compound of formula I (component 1) and at least one active substance selected from the azoles of group C) (component 2). In some embodiments, the azole is selected from the group consisting of cyproconazole, difenoconazole, epoxicona- zole, fluquinconazole, flusilazole, flutriafol, metconazole, myclobutanil, penconazole, propiconazole, prothioconazole, triadimefon, triadimenol, tebuconazole, tetraconazole, triticonazole, prochloraz, cyazofamid, benomyl, carbendazim and ethaboxam.

[00262] In some embodiments the invention provides a mixture comprising a compound of formula I (component 1) and at least one active substance selected from the heterocyclic compounds of group D) (component 2). In some embodiments, the heterocyclic compounds of group D) are selected from the group consisting of fluazinam, cyprodinil, fenarimol, mepanipyrim, pyrimethanil, triforine, fludioxonil, dodemorph, fenpropimorph, tridemorph, fenpropidin, iprodione, vinclozolin, famoxadone, fenamidone, probenazole, proquina- zid, acibenzolar-S-methyl, captafol, folpet, fenoxanil, quinoxyfen and 5-ethyl-6-octyl-[1,2,4]triazolo[1,5-a]pyrimidine-7-ylamine.

[00263] In some embodiments the invention provides a mixture comprising a compound of formula I (component 1) and at least one active substance selected from the carbamates of group E) (component 2). In some embodiments, the carbamates are selected from the group consisting of mancozeb, metiram, propineb, thiram, iprovalicarb, benthiavalicarb and propamocarb.

[00264] In some embodiments the invention provides a mixture comprising a compound of formula I (component 1) and at least one active substance selected from the fungicides given in group F) (component 2). In some embodiments, the fungicides of group F) are selected from the group consisting of dithianon, fentin salts, such as fentin acetate, fosetyl, fosetyl-aluminium, H3PO3 and salts thereof, chlorthalonil, dichlofluanid, thiophanat-methyl, copper acetate, copper hydroxide, copper oxychloride, copper sulfate, sulfur, cymoxanil, metrafenone and spiroxamine.

[00265] The active substances referred to as component 2, their preparation and their activity against harmful fungi is known in the art. In some embodiments these substances are commercially available. The compounds described by IUPAC nomenclature, their preparation and their fungicidal activity are also known in the art (cf. Can. J. Plant Sci. 48(6), 587-94, 1968; EP-A 141 317; EP-A 152 031 ; EP-A 226 917; EP-A 243 970; EP-A 256 503; EP-A 428 941 ; EP-A 532 022; EP-A 1 028 125; EP-A 1 035 122; EP-A 1 201 648; EP-A 1 122 244, JP 2002316902; DE 19650197; DE 10021412; DE 102005009458; US 3,296,272; US 3,325,503; WO 98/46608; WO 99/14187; WO 99/24413; WO 99/27783; WO 00/29404; WO 00/46148; WO 00/65913; WO 01/54501 ; WO 01/56358; WO 02/22583; WO 02/40431 ; WO 03/10149; WO 03/1 1853; WO 03/14103; WO 03/16286; WO 03/53145; WO 03/61388; WO 03/66609; WO 03/74491 ; WO 04/49804; WO 04/83193; WO 05/120234; WO 05/123689; WO 05/123690; WO 05/63721 ; WO 05/87772; WO 05/87773; WO 06/15866; WO 06/87325; WO 06/87343; WO 07/82098; WO 07/90624).

[00266] The mixtures of active substances can be prepared as compositions comprising besides the active ingredients at least one inert ingredient by usual means, e.g. by the means given for the compositions of compounds of formula I.

[00267] Concerning usual ingredients of such compositions reference is made to the explanations given for the compositions containing compounds of formula I.

[00268] The mixtures of active substances according to the present invention are suitable as fungicides, as are the compounds of formula I. In some embodiments the mixtures and compositions of the present invention are useful for the protection of plants against a broad spectrum of phytopathogenic fungi. In some embodiments, the phytopathogenic fungi are from the classes of the Ascomycetes, Basidiomycetes, Deuteromycetes and Peronosporomycetes (syn. Oomycetes).

[00269] The compounds of formula I and pharmaceutically acceptable salts thereof are also suitable for treating diseases in men and animals, especially as antimycotics, for treating cancer and for treating virus infections. The term "antimycotic", as distinguished from the term "fungicide", refers to a medicament for combating zoopathogenic or humanpathogenic fungi, i.e. for combating fungi in animals, especially in mammals (including humans) and birds.

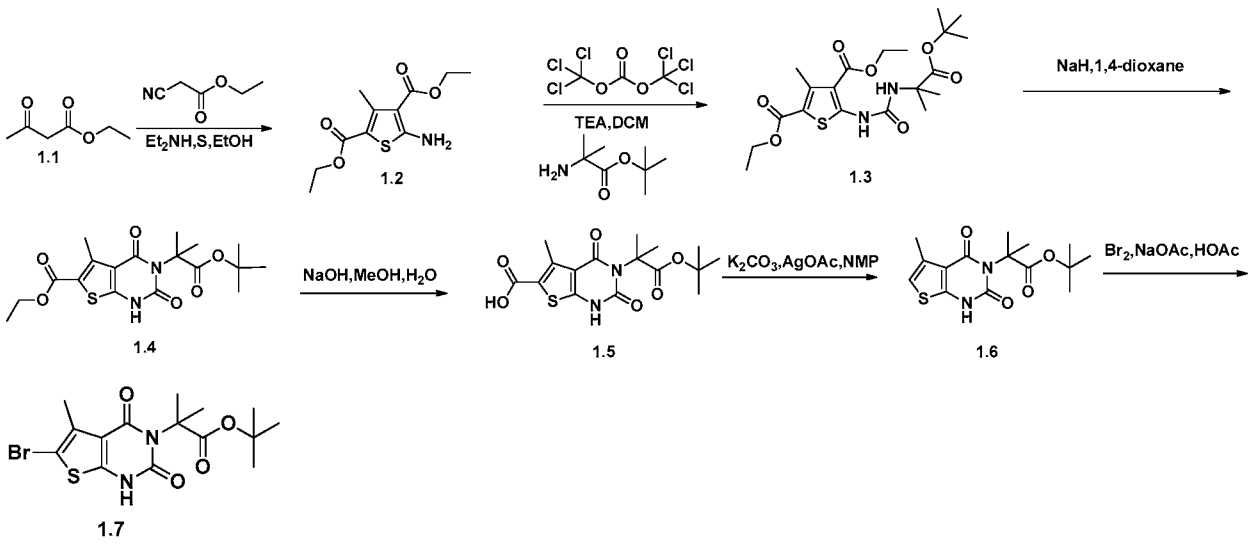
[00270] In some embodiments, the present invention provides a medicament comprising at least one compound of formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

[00271] In some embodiments, the invention relates to the use of a compound of formula I or a pharmaceutically acceptable salt thereof for preparing an antimycotic medicament; i.e. for preparing a medicament for the treatment and/or prophylaxis of infections with humanpathogenic and/or zoopathogenic fungi.

EXEMPLIFICATION

[00272] As depicted in the Examples below, in certain exemplary embodiments, compounds are prepared according to the following general procedures. It will be appreciated that, although the general methods depict the synthesis of certain compounds of the present invention, the following general methods, and other methods known to one of ordinary skill in the art, can be applied to all compounds and subclasses and species of each of these compounds, as described herein.

[00273] **Example 1: Intermediate 1.7.**



[00274] **Synthesis of compound 1.2.** Into a 2000-mL round-bottom flask was placed a solution of ethyl 3-oxobutanoate (320 g, 2.46 mol, 1.00 equiv), sulfur (80 g, 1.00 equiv) and ethyl 2-cyanoacetate (280 g, 2.48 mol, 1.00 equiv) in ethanol (600 mL). This was followed by the addition of morpholine (235 g, 1.00 equiv) dropwise with stirring at 45 °C over 30 min. The resulting solution was stirred for 5 h at 60 °C. The solids were filtered out. The solution was

diluted with 3000 mL of H_2O. The solids were collected by filtration and the filter cake was washed with 1 L of EtOH (30%). Purification afforded 380 g (60%) of 2,4-diethyl 5-amino-3-methylthiophene-2,4-dicarboxylate as a yellow solid.

[00275] **Synthesis of compound 1.3.** Into a 2000-mL 3-necked round-bottom flask, purged and maintained under an inert atmosphere of nitrogen, was placed 2,4-diethyl 5-amino-3-methylthiophene-2,4-dicarboxylate (200 g, 777.28 mmol, 1.00 equiv) and dichloromethane (1000 mL). This was followed by the addition of ditrichloromethyl carbonate (76.9 g, 259.14 mmol, 0.33 equiv) at 0 °C. This was followed by the addition of TEA (314 g, 3.10 mol, 3.99 equiv) dropwise with stirring at 0 °C over 2 hr. The resulting solution was stirred for 3 h at 0 °C. To this was added tert-butyl 2-amino-2-methylpropanoate (152 g, 776.70 mmol, 1.00 equiv) at 0 °C. The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 1 L of water. The resulting mixture was concentrated under vacuum. The crude product was re-crystallized from EA/PE in the ratio of 1:10 to afford 105 g (31%) of **1.3** as a yellow solid.

[00276] **Synthesis of compound 1.4.** Into a 1-L 3-necked round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed **1.3** (42 g, 94.91 mmol, 1.00 equiv) and 1,4-dioxane (400 mL). This was followed by the addition of sodium hydride (5.7 g, 142.50 mmol, 1.50 equiv) at 10 °C. The resulting solution was stirred for 2 h at 110 °C. The reaction was then quenched by the addition of 500 mL of NH_4Cl (sat., aq.). The resulting solution was extracted with 3x200 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The crude product was re-crystallized from EA/PE in the ratio of 1:10. Purification afforded 24.4 g (65%) of **1.4** as a white solid.

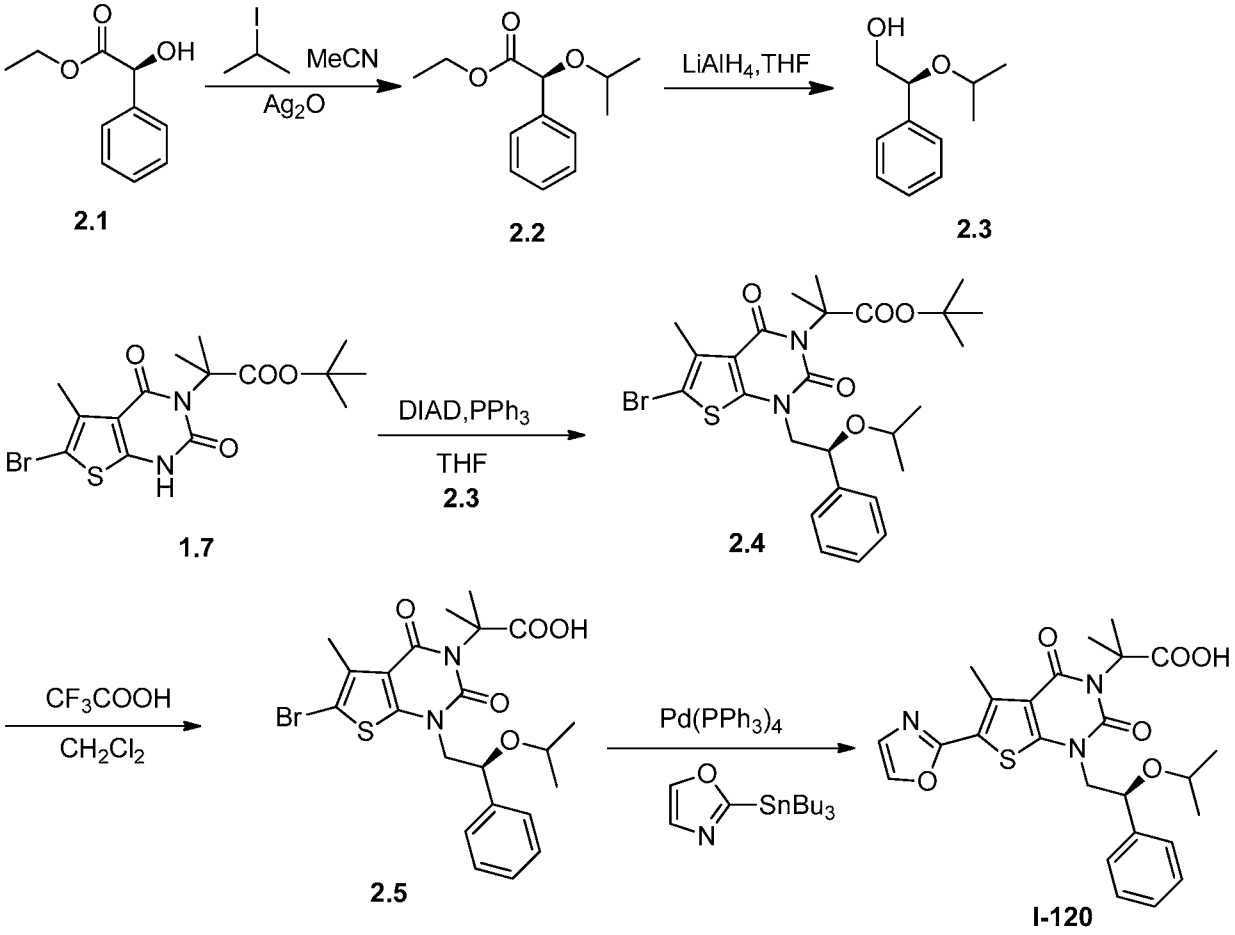
[00277] **Synthesis of compound 1.5.** Into a 500-mL 3-necked round-bottom flask, was placed **1.5** (24.4 g, 61.54 mmol, 1.00 equiv), sodium hydroxide (12.2 g, 305.00 mmol, 4.96 equiv), water (20 mL) and methanol (250 mL). The resulting solution was stirred for 4 h at 50 °C. The resulting mixture was concentrated under vacuum. The pH value of the solution was adjusted to 2 with hydrogen chloride (10%). The resulting solution was extracted with 3x300 mL of ethyl acetate and the organic layers combined, dried over anhydrous sodium sulfate and concentrated under vacuum to afford 19.4 g (86%) of **1.5** as a white solid.

[00278] **Synthesis of compound 1.6.** A 1-L 3-necked round-bottom flask was charged with **1.5** (19.4 g, 52.66 mmol, 1.00 equiv), potassium carbonate (8.7 g, 62.95 mmol, 1.20 equiv),

CH_3COOAg (10.5 g) and NMP (400 mL). The resulting solution was stirred for 2 h at 110 °C. The reaction was then quenched by the addition of 1 L of water. The resulting solution was extracted with 5x200 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:20). Purification afforded 15.3 g (90%) of **1.6** as a white solid.

[00279] Synthesis of compound 1.7. Into a 1000-mL 3-necked round-bottom flask was placed **1.6** (15.3 g, 47.16 mmol, 1.00 equiv), CH_3COONa (8.5 g, 103.66 mmol, 2.20 equiv) and acetic acid (300 mL). This was followed by the addition of Br_2 (8.3 g, 51.94 mmol, 1.10 equiv) dropwise with stirring. The resulting solution was stirred for 1 h at room temperature, concentrated under vacuum and washed with 500 mL of H_2O to afford 17 g (89%) of **1.7** as a white solid.

[00280] Example 2: Synthesis of 2-methyl-2-[5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1-[(2S)-2-phenyl-2-(propan-2-yloxy)ethyl]-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-120).



[00281] **Synthesis of compound 2.2.** A 500-mL round-bottom flask was charged with **2.1** (15 g, 83.24 mmol, 1.00 equiv), prop-1-yne (200 mL), Ag_2O (52 g, 225.11 mmol, 2.70 equiv) and 2-iodopropane (60 g, 352.96 mmol, 4.24 equiv). The resulting solution was stirred overnight at 40 ^oC in an oil bath. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with EA/PE (1:50). Purification afforded 3.2 g (crude) of **2.2** as a yellow oil.

[00282] **Synthesis of compound 2.3.** A 100-mL 3-necked round-bottom flask was charged with tetrahydrofuran (10 mL) and **2.2** (300 mg, 1.35 mmol, 1.00 equiv). This was followed by the addition of $LiAlH_4$ (51 mg, 1.34 mmol, 1.00 equiv) in portions at 0 ^oC. The resulting solution was stirred for 1 h at room temperature. The reaction was then quenched by the addition of 20 mL of NH_4Cl (aq.). The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined, dried over anhydrous magnesium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). Purification afforded 210 mg (86%) of **2.3** as a yellow oil.

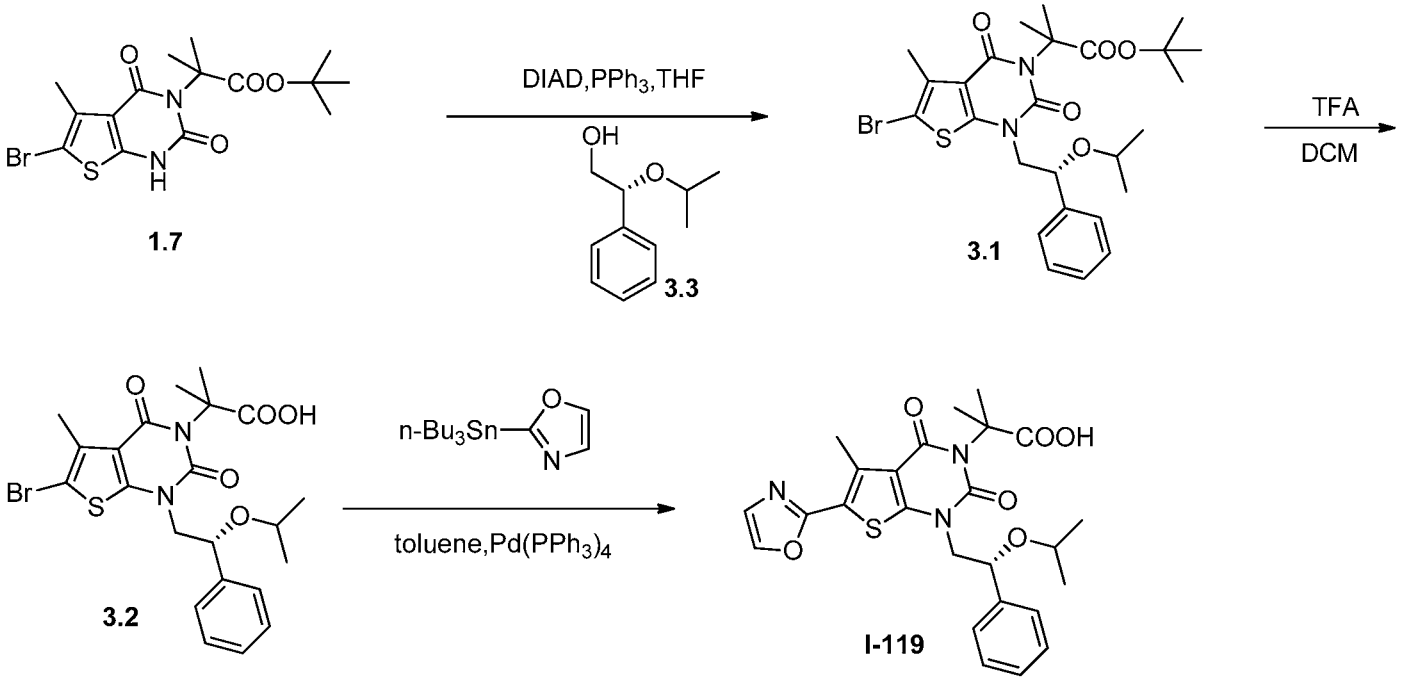
[00283] **Synthesis of compound 2.4.** A 100-mL 3-necked round-bottom flask was charged with tetrahydrofuran (10 mL), **2.3** (500 mg, 1.24 mmol, 1.00 equiv), PPh_3 (650 mg, 2.48 mmol, 2.00 equiv), DIAD (362 mg, 1.79 mmol, 1.44 equiv) and **2.3** (268 mg, 1.49 mmol, 1.20 equiv) under an atmosphere of nitrogen. The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:15). Purification afforded 0.430 g (61%) of **2.4** as a colorless oil.

[00284] **Synthesis of compound 2.5.** A 25-mL round-bottom flask was charged with dichloromethane (5 mL), **2.4** (428 mg, 0.76 mmol, 1.00 equiv) and CF_3COOH (2 mL). The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). Purification afforded 0.282 g (73%) of **2.4** as a colorless oil.

[00285] **Synthesis of compound I-120.** A 100-mL 3-necked round-bottom flask was charged with toluene (10 mL), **2.5** (282 mg, 0.55 mmol, 1.00 equiv), Pd(PPh3)4 (200 mg, 0.17 mmol, 0.31 equiv) and 2-(tripropylstannyl)-1,3-oxazole (238 mg, 0.75 mmol, 1.36 equiv) under an atmosphere of nitrogen. The resulting solution was heated to reflux overnight in an oil bath. The resulting mixture was concentrated under vacuum. The crude product (300 mg) was purified by

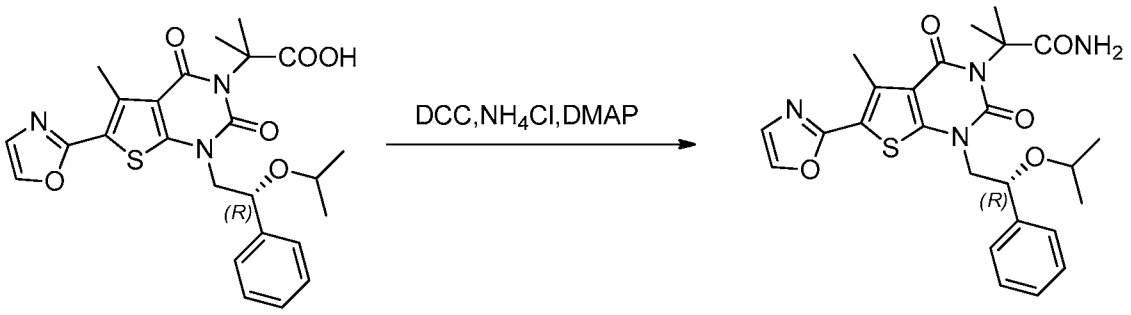
preparative HPLC under the following conditions (SHIMADZU): column: SunFire Prep C18, 19*150 mm 5 μm; mobile phase: water with 0.05% NH_4HCO_3 and CH_3CN (7.0% CH_3CN up to 46.0% in 10 min); detector: 254/220 nm. 0.193 g (70%) of Compound **I-120** were obtained as a white solid. MS (ES): *m/z* 498 $(M+H)^+$. ^1H NMR (CD_3OD, 300 MHz): δ 0.97 (m, 6H), 1.77 (d, J = 6.0 Hz, 6H), 3.04 (s, 3H), 3.46 (m, 1H), 3.82 (m, 1H), 4.13 (m, 1H), 4.88 (m, 1H), 7.24-7.44 (m, 6H), 7.94 (d, *J* = 0.9 Hz, 1H).

[00286] Example 3: Synthesis of 2-methyl-2-[5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1-[(2R)-2-phenyl-2-(propan-2-yloxy)ethyl]-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-119).



[00287] Compound **I-119** was synthesized in a manner analogous to Example 2 except that (2R)-2-phenyl-2-(propan-2-yloxy)ethan-1-ol was used rather than (2S)-2-phenyl-2-(propan-2-yloxy)ethan-1-ol. Compound **I-119** was obtained in 11% overall yield as a yellow solid. MS (ES): *m/z* 498 $(M+H)^+$. ^1H NMR (CD_3OD, 300 MHz): δ 0.97 (d, *J* = 6.3 Hz, 3H), 0.99 (d, *J* = 6.3 Hz, 3H), 1.77 (d, *J* = 6.3 Hz, 6H), 2.77 (s, 3H), 3.50 (m, 1H), 3.81 (m, 1H), 4.13 (m, 1H), 4.89 (m, 1H), 7.24-7.45 (m, 6H), 7.94 (d, *J* = 0.9 Hz, 1H).

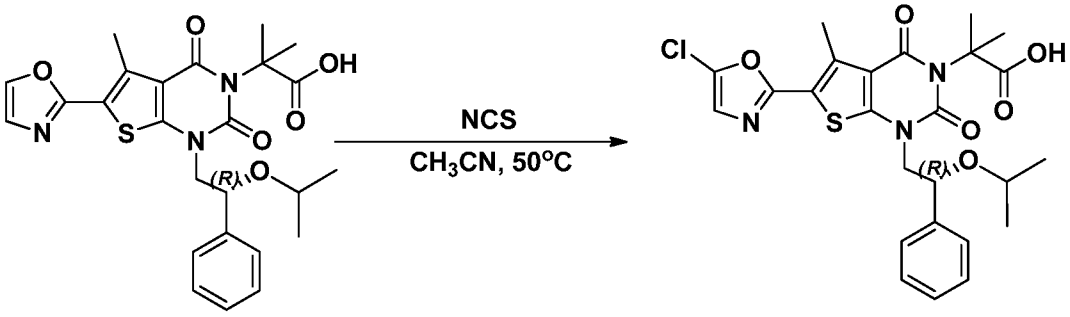
[00288] Example 4. Synthesis of 2-methyl-2-[5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1-[(2R)-2-phenyl-2-(propan-2-yloxy)ethyl]-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanamide (I-121).



I-119 I-121

[00289] A 25-mL round-bottom flask was charged with dichloromethane (10 mL), Compound **I-119** (70 mg, 0.14 mmol, 1.00 equiv), DCC (39 mg, 0.19 mmol, 1.34 equiv), 4-dimethylaminopyridine (19 mg, 0.16 mmol, 1.11 equiv) and NH_4Cl (20 mg, 0.37 mmol, 2.66 equiv). The resulting solution was stirred overnight at 40 °C in an oil bath. The reaction was then quenched by the addition of 10 mL of water. The resulting solution was extracted with 5x20 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was purified by preparative TLC (DCM:MeOH = 15:1). The product (50 mg) thus obtained was repurified by preparative HPLC under the following conditions (SHIMADZU): column: SunFire Prep C18, 19*150 mm 5 μm; mobile phase: water with 0.05% NH_4HCO_3 and CH_3CN (6.0% CH_3CN up to 48.0% in 13 min); detector: 254/220 nm. 0.030 g (43%) of Compound **I-121** were obtained as a white solid. MS (ES): *m/z* 497 $(M+H)^+$. ^1H NMR (CD_3OD, 300 MHz): δ 0.90 (m, 6H), 1.79 (d, *J* = 5.1 Hz, 6H), 2.77 (s, 3H), 3.54 (m, 1H), 3.81 (m, 1H), 4.11(m, 1H), 4.90 (m, 1H), 7.24-7.44 (m, 6H), 7.94 (d, *J* = 0.9 Hz, 1H).

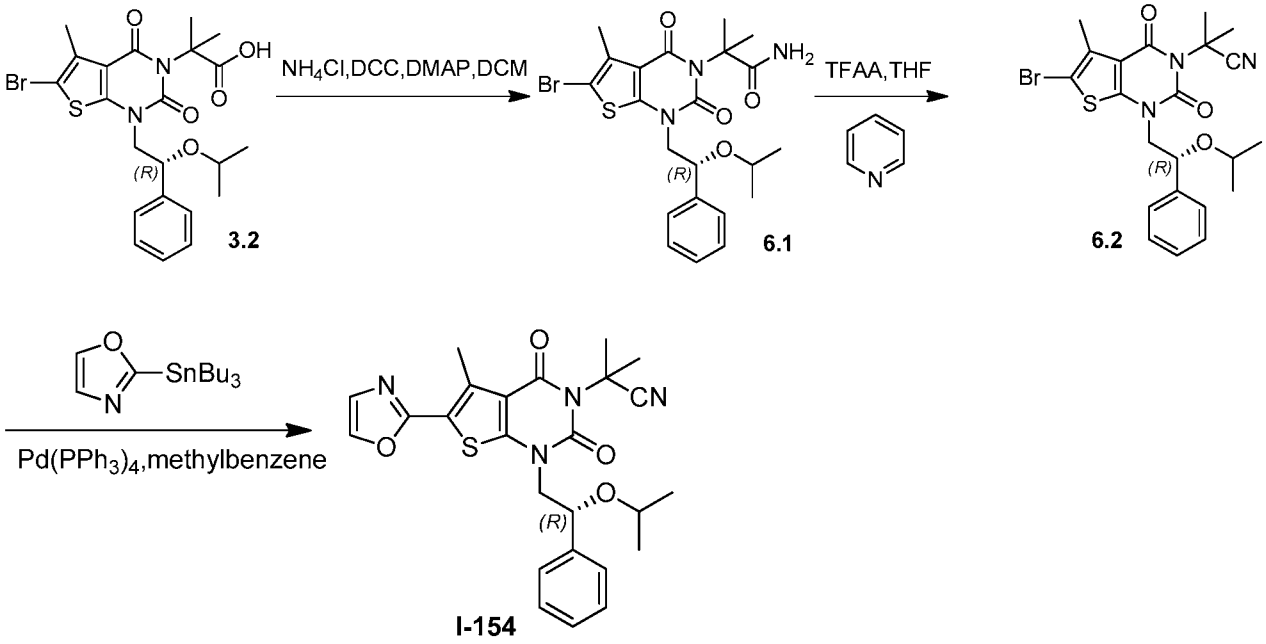
[00290] Example 5: Synthesis of 2-[6-(5-chloro-1,3-oxazol-2-yl)-5-methyl-2,4-dioxo-1-[(2R)-2-phenyl-2-(propan-2-yloxy)ethyl]-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-156).



I-119 I-156

[00291] Into a 50-mL round-bottom flask protected by nitrogen was placed CH_3CN (10 mL), Compound **I-119** (60 mg, 0.12 mmol, 1.00 equiv) and NCS (32 mg, 0.24 mmol, 1.99 equiv). The resulting solution was stirred for 3 days at 50 °C in an oil bath and monitored by LCMS. The resulting mixture was concentrated under vacuum. The crude product (60 mg) was purified by preparative HPLC under the following conditions (Waters): column: Xbridge Prep C18, 5 μm, 19*50mm; mobile phase: water with 50 mmol NH_4HCO_3 and CH_3CN (10% CH_3CN up to 35% in 10 min, up to 95% in 1.5 min, down to 10% in 1.5 min); detector: UV 254/220 nm. 0.010 g (16%) of **I-156** were obtained as a white solid. ^1H NMR (CD_3OD, 400 MHz): δ 1.00 (dd, 6H), 1.82 (d, J = 8.0 Hz, 6H), 2.79 (s, 3H), 3.54 (m, 1H), 3.85 (dd, J = 1H), 4.18 (dd, 1H), 4.93 (dd, 1H), 7.16 (s, 1H), 7.34 (t, J = 7.2 Hz, 1H), 7.41 (t, J = 7.6 Hz, 2H), 7.47 (d, J = 7.2 Hz).

[00292] Example 6: Synthesis of 2-methyl-2-[5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1-[(2R)-2-phenyl-2-(propan-2-yloxy)ethyl]-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanenitrile (I-154).



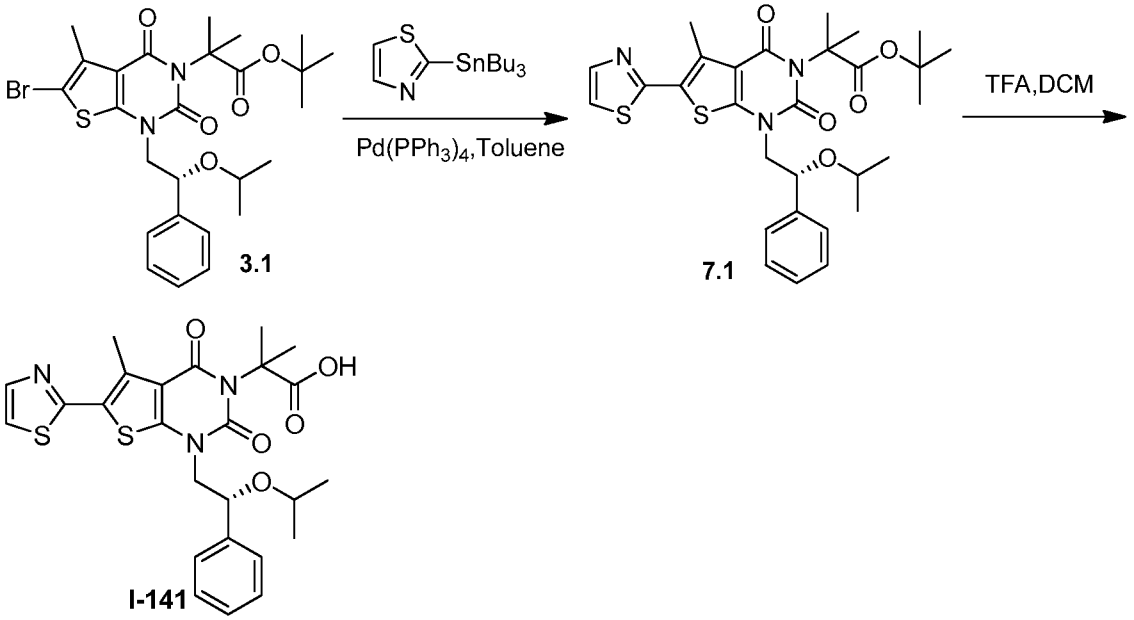
[00293] **Synthesis of compound 6.1.** Compound **6.1** was prepared in a manner analogous to Compound **I-121** (Example 4). Isolated 100 mg (42%) of **6.1** as a white solid.

[00294] **Synthesis of compound 6.2.** A 25-mL round-bottom flask was charged with **6.1** (100 mg, 0.20 mmol, 1.00 equiv), tetrahydrofuran (5 mL) and pyridine (78 mg, 0.99 mmol, 5.01 equiv). This was followed by the addition of TFAA (103 mg, 0.49 mmol, 2.49 equiv) dropwise with stirring at 0 °C. The resulting solution was stirred for 3 h at room temperature and then

concentrated under vacuum. The residue was purified by preparative TLC with ethyl acetate/petroleum ether (1:3). Purification afforded 90 mg (93%) of **6.2** as a white solid.

[00295] Synthesis of Compound I-154. Into a 25-mL round-bottom flask was placed **6.2** (100 mg, 0.20 mmol, 1.00 equiv), $Pd(PPh_3)_4$ (60 mg, 0.05 mmol, 0.26 equiv), 2-(tributylstannyl)-1,3-oxazole (153 mg, 0.43 mmol, 2.17 equiv) and methylbenzene (5 mL). The resulting solution was stirred overnight at 110 °C and then concentrated under vacuum. The residue was purified by preparative TLC with ethyl acetate/petroleum ether (1:2). Purification afforded 5.2 mg (6%) of Compound **I-154**. ^1H NMR (300 MHz, CD_3OD): δ 1.00-1.06 (m, 6H), 2.09-2.10 (d, 6H), 2.84-2.89 (s, 3H), 3.49-3.57 (m, 1H), 3.89-3.96 (m, 1H), 4.18-4.25 (m, 1H) , 4.94-4.98 (m, 1H), 7.30-7.32 (s, 1H), 7.34-7.49(m, 5H), 8.01(s, 1H). MS (ES): *m/z* 479 $(M+H)^+$.

[00296] Example 7: Synthesis of 2-methyl-2-[5-methyl-2,4-dioxo-1-[(2R)-2-phenyl-2-(propan-2-yloxy)ethyl]-6-(1,3-thiazol-2-yl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-141).

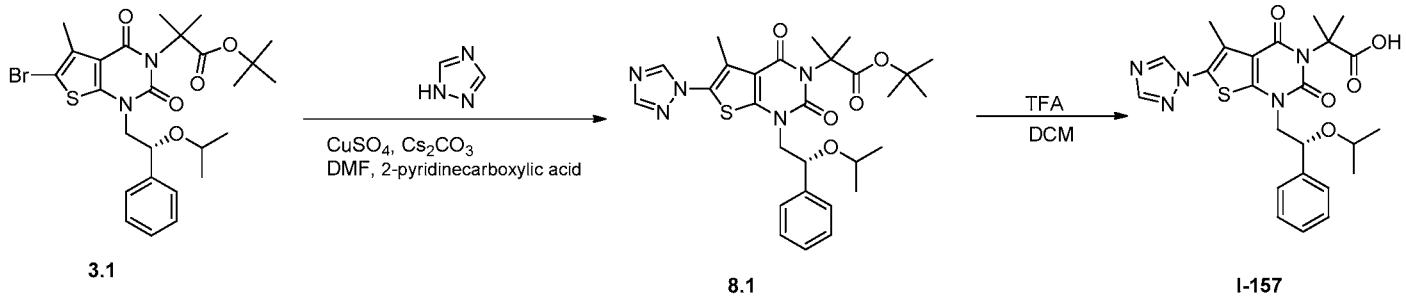


[00297] Synthesis of compound 7.1. To a 25-mL round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was added **3.1** (210 mg, 0.37 mmol, 1.00 equiv), 2-(tributylstannyl)-1,3-thiazole (208 mg, 0.56 mmol, 1.50 equiv), methylbenzene (5 mL) and $Pd(PPh_3)_4$ (200 mg, 0.17 mmol, 0.47 equiv). The resulting solution was stirred overnight at 110 °C. The reaction mixture was cooled to room temperature. The resulting mixture was

concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:20). Purification afforded 137 mg (65%) of **7.1** as a white solid.

[00298] Synthesis of Compound I-141. A 10-mL round-bottom flask was charged with compound **7.1** (137 mg, 0.24 mmol, 1.00 equiv), trifluoroacetic acid (2 mL) and dichloromethane (3 mL). The resulting solution was stirred overnight at room temperature and then concentrated under vacuum. The crude product (130 mg) was purified by preparative HPLC under the following conditions (SHIMADZU): column: Xbridge Prep Phenyl 5 μm, 19*150 mm; mobile phase: water (0.05% NH_4HCO_3) and CH_3CN (6.0% CH_3CN up to 50.0% in 11.5 min); detector: 220/254 nm. 43.9 mg (36%) of Compound **I-141** were obtained as a white solid. MS (ES): *m/z* 514 $(M+H)^+$. ^1H NMR (CD_3OD, 400 MHz): δ 0.99-1.05 (m, 6H), 1.82-1.84 (d, 6H), 2.76 (s, 3H), 3.49-3.55 (m, 1H), 3.85-3.89 (m, 1H), 4.14-4.19 (m, 1H), 4.92-4.95 (m, 1H), 7.31-7.35 (t, 1H), 7.39-7.43 (t, 2H), 7.47-7.49 (d, 2H), 7.66-7.66 (d, 1H), 7.83-7.84 (d, 1H).

[00299] Example 8: Synthesis of 2-methyl-2-[5-methyl-2,4-dioxo-1-[(2R)-2-phenyl-2-(propan-2-yloxy)ethyl]-6-(1H-1,2,4-triazol-1-yl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-157).

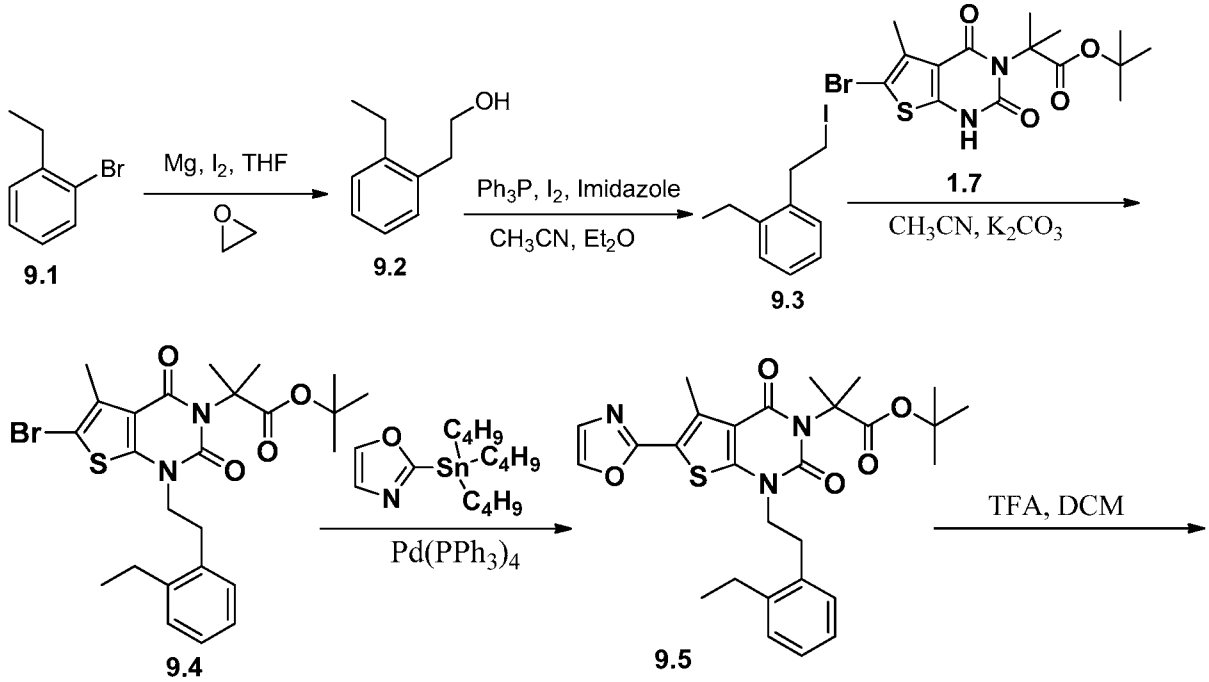


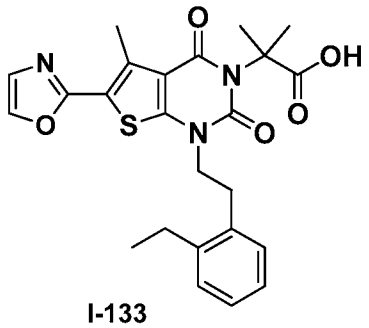
3.1 8.1 I-157

[00300] Synthesis of compound 8.1. An 8-mL sealed tube was charged with 1H-1,2,4-triazole (100 mg, 1.45 mmol, 8.19 equiv), **3.1** (100 mg, 0.18 mmol, 1.00 equiv), pyridine-2-carboxylic acid (70 mg, 0.57 mmol, 3.22 equiv), $CuSO_4$ (5 mL), N,N-dimethylformamide (100 mg, 1.37 mmol, 7.74 equiv) and Cs_2CO_3 (70 mg, 3.22 equiv). The reaction mixture was irradiated with microwave radiation for 30 min at 170 °C. The reaction was then quenched by the addition of 20 mL of NH_4Cl (sat.). The resulting solution was extracted with 2x20 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). Purification afforded 30 mg (31%) of **8.1** as a white solid.

[00301] **Synthesis of compound I-157.** A 50-mL round-bottom flask was charged with **8.1** (57 mg, 0.10 mmol, 1.00 equiv), dichloromethane (10 mL) and trifluoroacetic acid (2 mL). The resulting solution was stirred overnight at 30 °C. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (50:1). The crude product (60 mg) was purified by preparative HPLC under the following conditions (Waters): column: SunFire Prep C18, 19*150 mm 5 μm; mobile phase: water (50 mM NH_4HCO_3) and CH_3CN (5.0% CH_3CN up to 50.0% in 10 min, up to 95.0% in 2 min, down to 5.0% in 2 min); detector: UV 254/220 nm. Purification afforded 9.9 mg (19%) of Compound **I-157** as a white solid. ^1H NMR (CD_3OD, 400 MHz): 1.06 (m, 6H), 1.82 (d, 6H), 2.35 (s, 3H), 3.51 (m, 1H), 3.78 (m, 1H), 4.17 (m, 1H), 4.91 (m, 1H), 7.42 (m, 5H), 8.25 (s, 1H), 8.86 (s, 1H). MS (ES): 498 *m/z* $(M+H)^+$.

[00302] **Example 9: Synthesis of 2-[1-[2-(2-ethylphenyl)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-133).**





I-133

[00303] **Synthesis of compound 9.2.** Into a 250-mL round-bottom flask protected by N_2 was placed tetrahydrofuran (100 mL), Mg (1.0 g, 41.67 mmol, 2.14 equiv) and I_2 (0.010 g). Then a solution of 1-bromo-2-ethylbenzene (3.6 g, 19.45 mmol, 1.00 equiv) in THF (15 mL) was added dropwise. The resulting mixture was heated to reflux for 1 h. Then it was cooled to 0 °C and oxirane (50 mL) was added. The resulting solution was stirred at room temperature overnight. The reaction was then quenched by the addition of 20 mL of NH_4Cl (aq.). The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). Purification afforded 1.83 g (63%) of 2-(2-ethylphenyl)ethan-1-ol as a colorless oil.

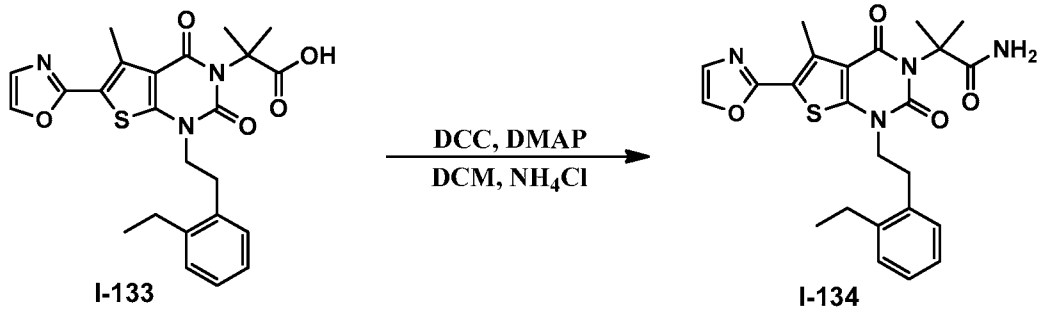
[00304] **Synthesis of compound 9.3.** Into a 50-mL round-bottom flask was placed ether (10 mL), CH_3CN (5 mL) and 2-(2-ethylphenyl)ethan-1-ol (900 mg, 5.99 mmol, 1.00 equiv). Then imidazole (570 mg, 8.38 mmol, 1.40 equiv), PPh_3 (2.20 g, 8.39 mmol, 1.40 equiv) and I_2 (1.98 g, 7.80 mmol, 1.30 equiv) were added at 0 °C. The resulting solution was stirred for 6 h at room temperature. The reaction was then quenched by the addition of 10 mL of saturated Na_2SO_3 solution. The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined, dried over Na_2SO_4 and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:20). Purification afforded 1.16 g (74%) of 1-ethyl-2-(2-iodoethyl)benzene as a colorless oil.

[00305] **Synthesis of compound 9.4.** A 50-mL round-bottom flask was charged with **9.3** (200 mg, 0.50 mmol, 1.00 equiv), potassium carbonate (205 mg, 1.48 mmol, 2.99 equiv), acetonitrile (20 mL) and 1-ethyl-2-(2-iodoethyl)benzene (258 mg, 0.99 mmol, 2.00 equiv). The resulting solution was heated to reflux overnight in an oil bath. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:50). Purification afforded 220 mg (83%) of compound **9.4** as a white solid.

[00306] **Synthesis of compound 9.5.** A 50-mL round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was charged with **9.4** (220 mg, 0.41 mmol, 1.00 equiv), toluene (20 mL), 2-(tributylstannyl)-1,3-oxazole (280 mg, 0.78 mmol, 1.90 equiv) and tetrakis(triphenylphosphane) palladium (67 mg, 0.06 mmol, 0.14 equiv). The resulting solution was stirred overnight at 110 °C in an oil bath. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:25). Purification afforded 180 mg (84%) of **9.5** as a white solid.

[00307] **Synthesis of Compound I-133**. Into a 50-mL round-bottom flask was placed compound **9.5** (180 mg, 0.34 mmol, 1.00 equiv), dichloromethane (10 mL) and trifluoroacetic acid (3 mL). The resulting solution was stirred for 3 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:2). Purification afforded 130 mg (81%) of Compound **I-133** as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.19 (t, J =7.5, 3H), 1.68 (s, 6H), 2.50 (q, J = 1.8, 2H), 2.74 (s, 3H), 3.03 (t, J = 7.8, 2H), 4.04 (t, J = 7.8, 2H), 7.10-7.21 (m, 4H), 7.38 (s, 1H), 8.23 (s, 1H). MS (ES): *m/z* 468 $(M+H)^+$, 509 $(M+CH_3CN)^+$.

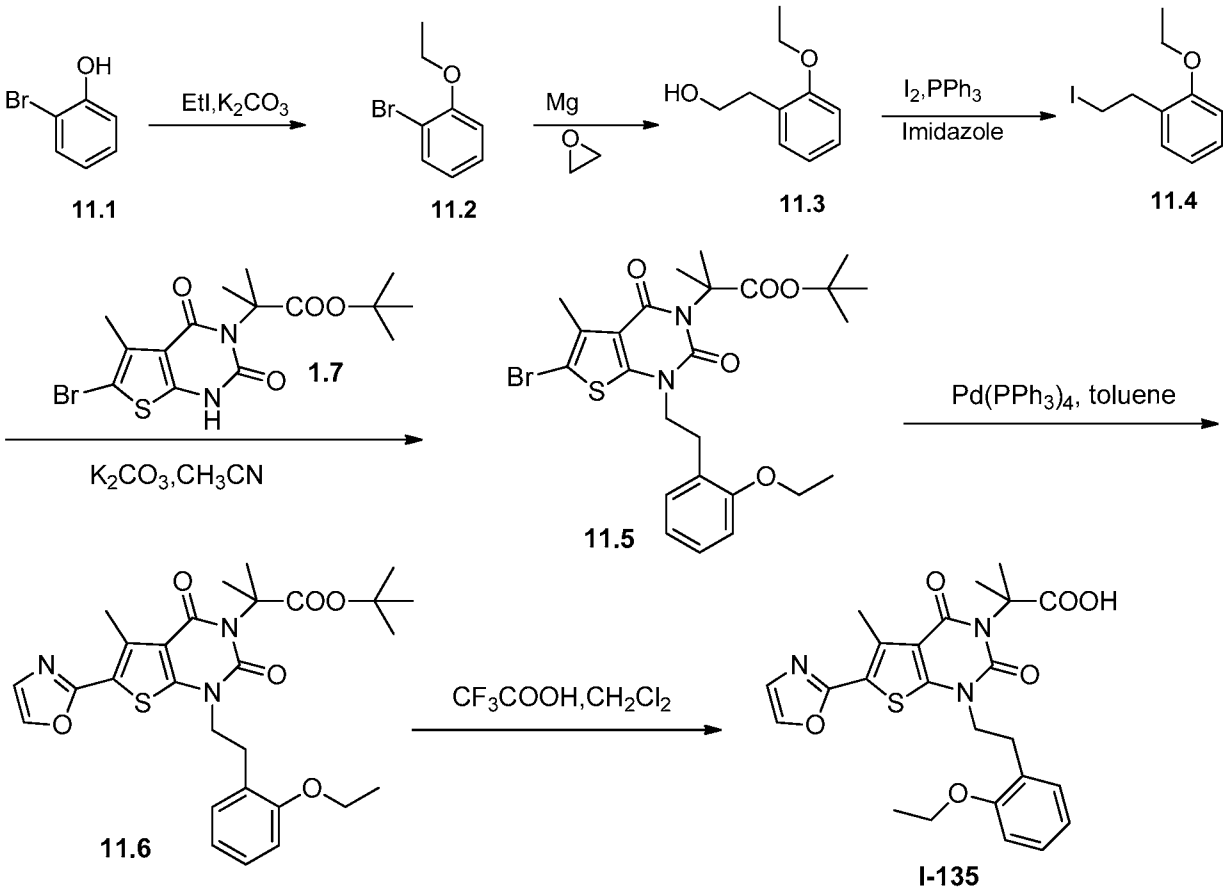
[00308] **Example 10: Synthesis of 2-[1-[2-(2-ethylphenyl)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanamide (I-134).**



I-133 I-134

[00309] Compound **I-134** was prepared from **I-133** in a manner analogous to Compound **I-121** (Example 4). Isolated 37.4 mg (42%) of Compound **I-134** as a white solid. MS (ES): *m/z* 467 $(M+H)^+$. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.20 (t, J = 7.8 Hz ,3H), 1.66 (s, 6H), 2.67-2.74 (m, 5H), 3.01 (t, J = 7.2 Hz, 2H), 4.00 (t, J = 7.2 Hz, 2H), 7.14-7.20 (m, 4H), 7.38 (s,1H), 8.22 (s, 1H).

[00310] **Example 11: Synthesis of 2-[1-[2-(2-ethoxyphenyl)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-135).**



Synthesis of compound 11.2. Into a 500-mL round-bottom flask was placed CH_3COCH_3 (200 mL), 2-bromophenol (10.38 g, 60.00 mmol, 1.00 equiv), iodoethane (28.08 g, 180.04 mmol, 3.00 equiv) and potassium carbonate (33.12 g, 239.64 mmol, 3.99 equiv). The resulting solution was heated to reflux overnight in an oil bath. The solids were filtered out. The filtrate was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:100). Purification afforded 11.48 g (95%) of 1-bromo-2-ethoxybenzene as a colorless oil.

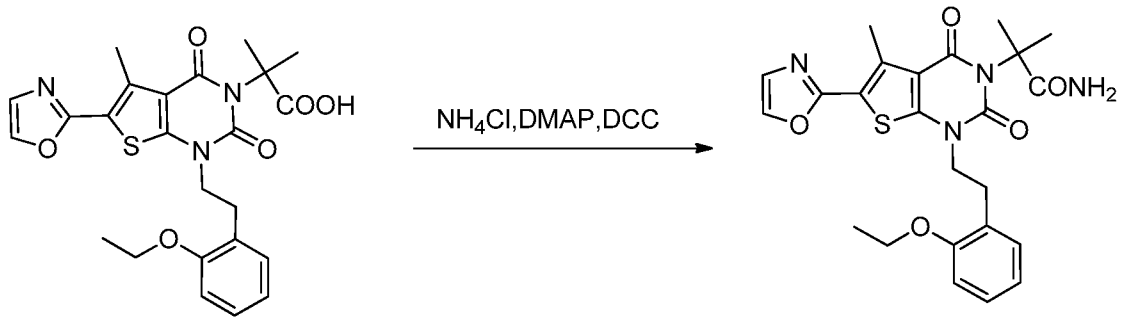
[00311] Synthesis of compound 11.3. Into a 250-mL 3-necked round-bottom flask, maintained with an inert atmosphere of nitrogen, was placed Mg (1.0 g, 41.67 mmol, 2.09 equiv) and I_2 (10 mg). Then a solution of 1-bromo-2-ethoxybenzene (4.0 g, 19.89 mmol, 1.00 equiv) in 25 mL THF was added dropwise and the resulting mixture was heated to reflux for 0.5 hr. After the reaction was complete, the resulting mixture was cooled to 0 °C and then oxirane (50 mL) was added in one portion. The reaction mixture was stirred overnight at room temperature. The reaction was then quenched by the addition of 50 mL of NH_4Cl (aq.) and extracted with 3x50 mL of ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate and

concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). Purification afforded 2.14 g (65%) of 2-(2-ethoxyphenyl)ethan-1-ol as a yellow oil.

[00312] Synthesis of compound 11.4. Into a 50-mL round-bottom flask was placed dichloromethane (20 mL) and 2-(2-ethoxyphenyl)ethan-1-ol (1.33 g, 8.00 mmol, 1.00 equiv). The solution was cooled to 0 °C in a water/ice bath. Then PPh_3 (2.72 g, 10.37 mmol, 1.30 equiv), imidazole (707 mg, 10.40 mmol, 1.30 equiv) and I_2 (2.44 g, 9.61 mmol, 1.20 equiv) were added. The resulting solution was stirred at room temperature overnight. The reaction was then quenched by the addition of 50 mL of $NaHSO_3$ (aq.). The organic layer was separated and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (0:100). Purification afforded 1.34 g (61%) of 1-ethoxy-2-(2-iodoethyl)benzene as a colorless oil.

Synthesis of Compound I-135. Compound **I-135** was prepared from **11.4** and **1.7** in a manner analogous to Example 9. Isolated a white solid in 50% overall yield for the two steps. MS (ES): *m/z* 484 $(M+H)^+$. ^1H NMR (DMSO-d_6, 300 MHz): δ 1.37 (t, *J* = 7.2 Hz, 3H), 1.64 (s, 6H), 2.73 (s, 3H), 3.00 (t, *J* = 7.2 Hz, 2H), 4.05 (m, 4H), 6.84 (m, 1H), 6.92 (m, 1H) , 7.16 (m, 2H), 7.38 (d, *J* = 0.6 Hz, 1H), 8.22 (d, *J* = 0.6 Hz, 1H).

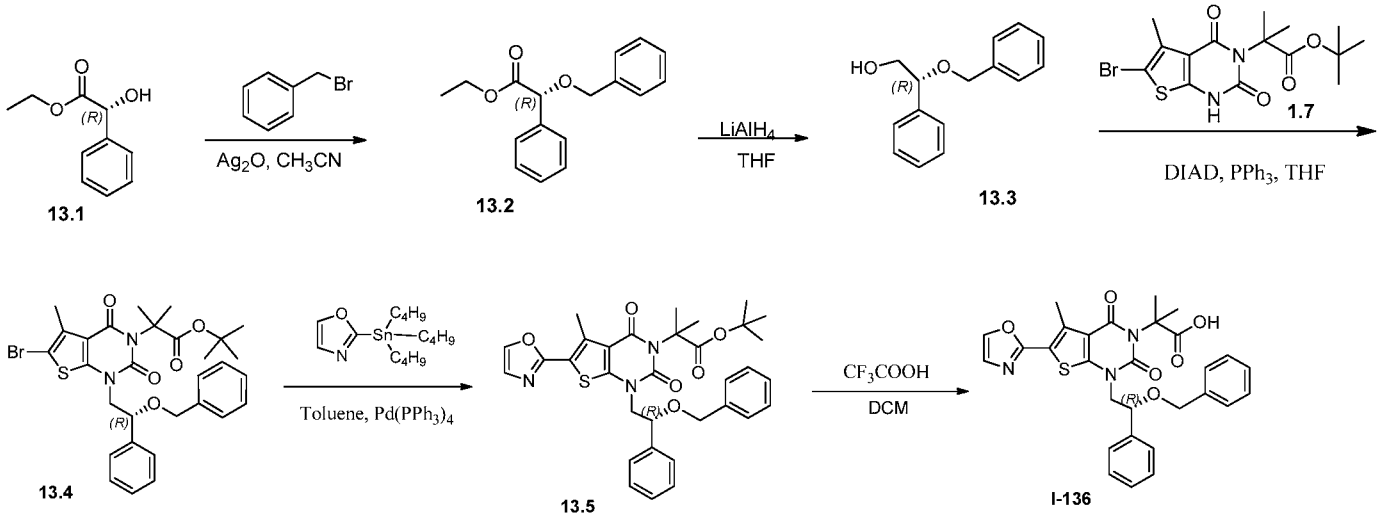
[00313] Example 12: Synthesis of 2-[1-[2-(2-ethoxyphenyl)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanamide (I-139).



I-135 I-139

Compound I-139 was prepared from Compound **I-135** in a manner analogous to Example 10. Isolated a white solid in 67% yield. MS (ES): *m/z* 505 $(M+Na)^+$. ^1H NMR (DMSO-d_6, 300 MHz): δ 1.41 (t, *J* = 7.2 Hz, 3H), 1.64 (s, 6H), 2.74 (s, 3H), 2.98 (t, *J* = 7.2 Hz, 2H), 4.05 (m, 4H), 6.65 (s, 1H), 6.86 (t, *J* = 7.2 Hz, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 7.11 (m, 2H), 7.38 (s, 1H), 8.22 (s, 1H).

[00314] Example 13: Synthesis of 2-[1-[(2R)-2-(benzyloxy)-2-phenylethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-136).



[00315] Synthesis of compound 13.2. Into a 500-mL round-bottom flask was placed a solution of **13.1** (5.2 g, 28.86 mmol, 1.00 equiv) in CH_3CN (250 mL), (bromomethyl)benzene (14.7 g, 85.95 mmol, 2.98 equiv), Ag_2O (10 g, 43.29 mmol, 1.50 equiv). The resulting solution was stirred overnight at 40 °C in an oil bath. The solids were filtered out. The filtrate was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). Purification 6.38 g (crude) of **13.2** as a yellow oil.

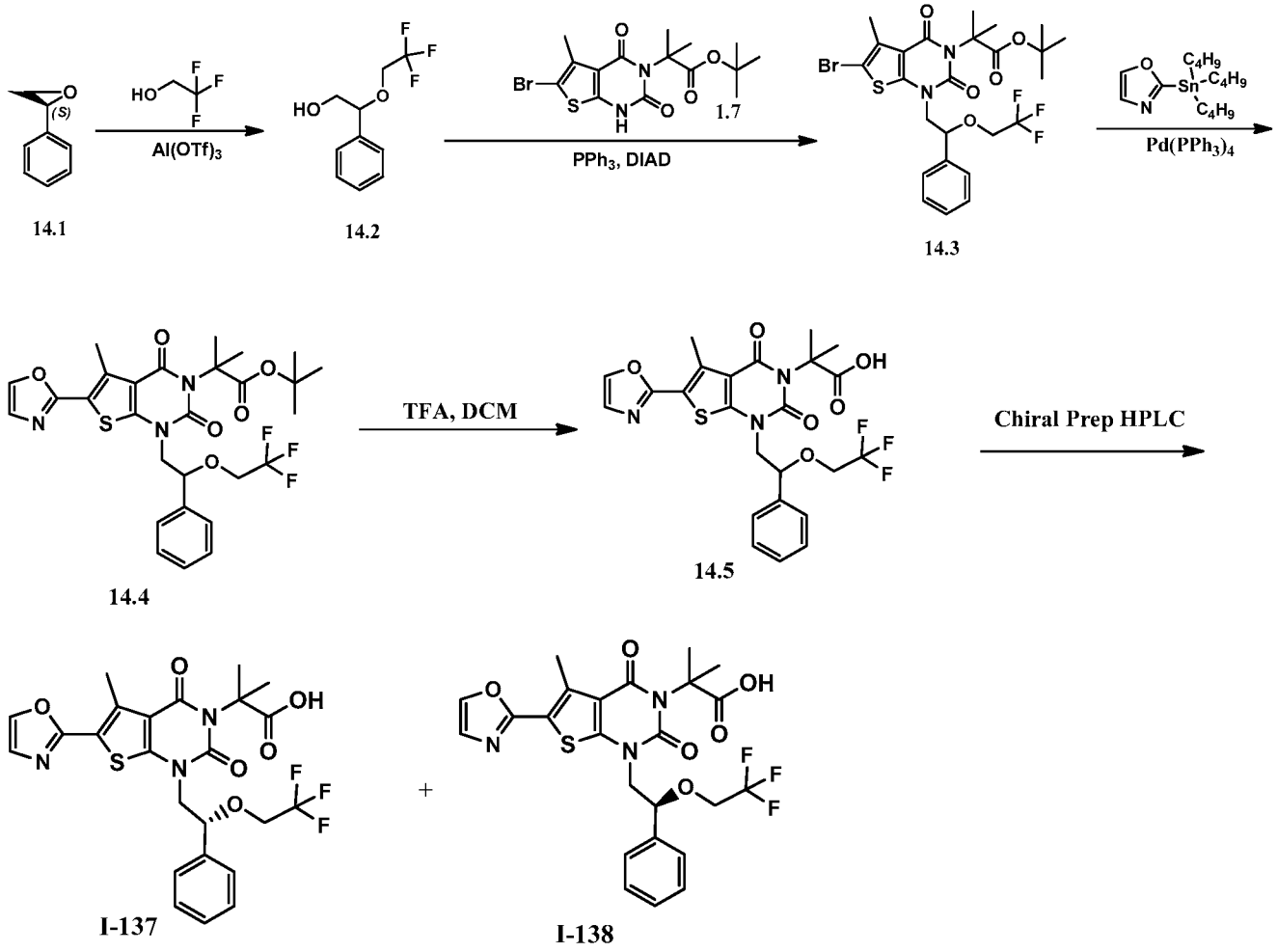
[00316] Synthesis of compound 13.3. Into a 500-mL round-bottom flask was placed tetrahydrofuran (200 mL) and **13.2** (6.38 g, 23.60 mmol, 1.00 equiv). Then LiAlH (898 mg, 23.66 mmol, 1.00 equiv) was added at 0 °C, slowly. The resulting solution was stirred for 2 h at 0 °C in an ice/salt bath. The reaction was then quenched by the addition of 2 mL of NH_4Cl (aq.). The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). Purification afforded 1.80 g (33%) of **13.3** as a yellow oil.

[00317] Synthesis of compound 13.4. Into a 100-mL 3-necked round-bottom flask maintained with an inert atmosphere of nitrogen was placed tetrahydrofuran (10 mL), intermediate **1.7** (175 mg, 0.43 mmol, 1.00 equiv), DIAD (133 mg, 0.66 mmol, 1.52 equiv), PPh_3 (173 mg, 0.66 mmol, 1.52 equiv) and **13.3** (150 mg, 0.66 mmol, 1.51 equiv). The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated

under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). Purification afforded 0.422 g (crude) of compound **13.4** as a yellow oil.

[00318] Synthesis of Compound I-136. Compound **I-136** was prepared from **13.4** and 2-(tributylstannyl)-1,3-oxazole in a manner analogous to Example 9. Isolated a white solid in 24% yield for the two steps. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.64 (s, 6H), 2.76 (s, 3H), 4.10 (m, 2H), 4.18 (d, J = 12.9 Hz, 1H), 4.46 (d, J = 12.9 Hz, 1H), 4.80 (t, J = 6.0 Hz, 1H), 7.08 (d, J = 2.1 Hz, 2H), 7.18 (t, J = 3.0 Hz, 3H), 7.42 (m, 6H), 8.24 (d, J = 0.6 Hz, 1H).

[00319] Example 14: Synthesis of 2-methyl-2-[5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1-[2-phenyl-2-(2,2,2-trifluoroethoxy)ethyl]-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-137) and Example 15: (S)-2-methyl-2-(5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1-(2-phenyl-2-(2,2,2-trifluoroethoxy)ethyl)-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)propanoic acid (I-138).



[00320] **Synthesis of compound 14.2.** Into a 25-mL round-bottom flask was placed (2S)-2-phenyloxirane (1 g, 8.32 mmol, 1.00 equiv), 2,2,2-trifluoroethan-1-ol (5 mL) and bis[(trifluoromethane)sulfonyloxy]alumanyl trifluoromethanesulfonate (197 mg, 0.42 mmol, 0.05 equiv). The resulting solution was stirred for 2 h at room temperature. The mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:20). Purification afforded 410 mg (22%) of 2-phenyl-2-(2,2,2-trifluoroethoxy)ethan-1-ol as a colorless oil.

[00321] **Synthesis of compound 14.3.** Into a 25-mL round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed a solution of **1.7** (300 mg, 0.74 mmol, 1.00 equiv), PPh_3 (390 mg, 1.49 mmol, 2.00 equiv), 2-phenyl-2-(2,2,2-trifluoroethoxy)ethan-1-ol (310 mg, 1.41 mmol, 1.89 equiv), DIAD (300 mg, 1.48 mmol, 1.99 equiv) in tetrahydrofuran (10 mL). The solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). Purification afforded 260 mg (58%) of **14.3** as a white solid.

[00322] **Synthesis of compound 14.4.** Into a 50-mL round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed a solution of **14.3** (260 mg, 0.43 mmol, 1.00 equiv), $Pd(PPh_3)_4$ (74 mg, 0.06 mmol, 0.14 equiv) and 2-(tributylstannyl)-1,3-oxazole (231 mg, 0.65 mmol, 1.43 equiv) in toluene (10 mL). The solution was stirred overnight at 110 °C in an oil bath. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). Purification afforded 150 mg (59%) of **14.4** as a white solid.

[00323] **Synthesis of compound 14.5.** Into a 50-mL round-bottom flask was placed **14.4** (150 mg, 0.25 mmol, 1.00 equiv), dichloromethane (10 mL) and trifluoroacetic acid (2 mL). The resulting solution was stirred for 4 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:1). Purification afforded 70 mg (52%) of **14.5** as a white solid.

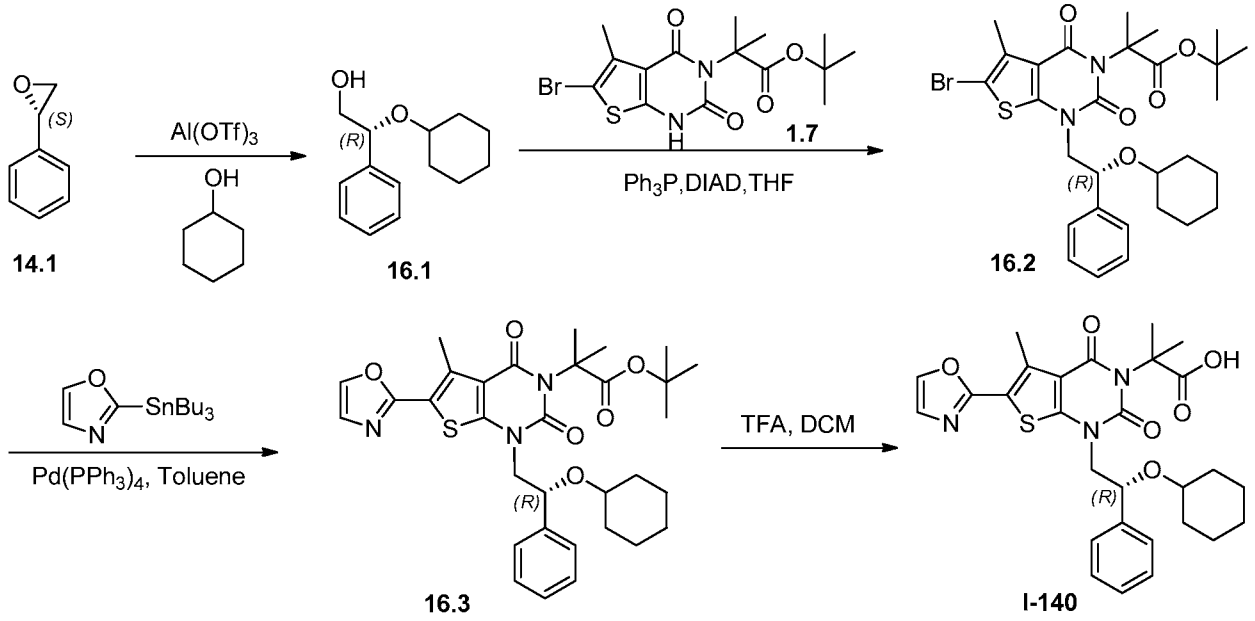
[00324] **Synthesis of Compounds I-137 and I-138.** The enantiomers of the product of the previous step (64 mg) were purified by chiral preparative HPLC under the following conditions (Gilson Gx 281): column: Chiralpak IC, 2*25 cm, 5 μm; mobile phase: hexanes and ethanol

(hold at 15.0% ethanol in 25 min); detector: 220/254 nm. 6.8 mg (off-white solid) of Compound **I-137** and 20 mg (off-white solid) of Compound **I-138** were obtained.

Analytical data for Compound I-137: MS (ES): *m/z* 538 $(M+H)^+$, 579 $(M+ CH_3CN)^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.82 (s, 6H), 2.82 (s, 3H), 3.84 (m, 2H), 4.09 (dd, *J* = 10.8, 6.9, 1H), 4.23 (dd, *J* = 11.1, 2.7, 1H) , 5.05 (m,1H), 7.29 (s, 1H), 7.38-7.50 (m, 5H), 7.99 (s, 1H).

Analytical data for Compound I-138: MS (ES): *m/z* 538 $(M+H)^+$, 560 $(M+ Na)^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.82 (s, 6H), 2.82 (s, 3H), 3.84 (m, 2H), 4.09 (dd, *J* = 10.8, 6.9, 1H), 4.23 (dd, *J* = 11.1, 2.7, 1H) , 5.05 (m, 1H), 7.29 (s, 1H), 7.38-7.50 (m, 5H), 7.99 (s, 1H).

[00325] Example 16: Synthesis of 2-[1-[(2R)-2-(cyclohexyloxy)-2-phenylethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-140).

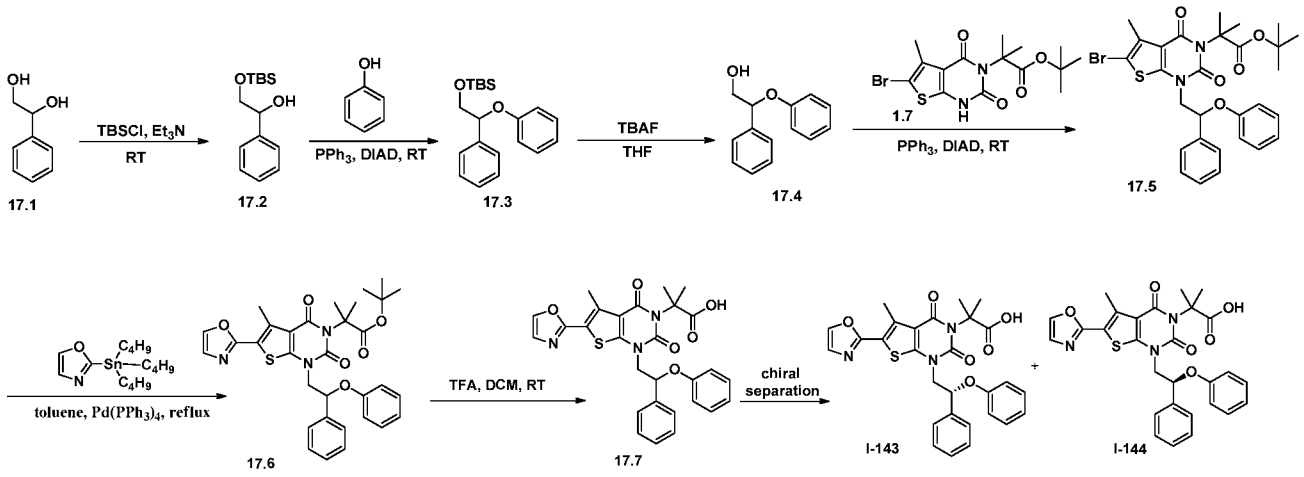


[00326] Synthesis of compound 16.1. Into a 50-mL round-bottom flask, was placed $Al(OTf)_3$ (237 mg, 0.50 mmol, 0.05 equiv), cyclohexanol (7 mL). This was followed by the addition of (2S)-2-phenyloxirane (1.2 g, 9.99 mmol, 1.00 equiv) dropwise with stirring. The resulting solution was stirred for 3 h at room temperature. The reaction was then quenched by the addition of 20 mL of water. The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined. The resulting mixture was washed with water. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl

acetate/petroleum ether (1:50). This resulted in 1 g (45%) of (2R)-2-(cyclohexyloxy)-2-phenylethan-1-ol as a yellow solid.

[00327] **Synthesis of Compound I-140**. Compound **I-140** was prepared, in a manner analogous to **14.5**, from **16.1** and **1.7**. Isolated a white semi-solid in 16% yield from **1.7**. MS: (ES): *m/z* 538 $(M+H)^+$, 579 $(M+CH_3CN)^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.17-1.61 (m, 10H), 1.84 (d, *J* = 6.8, 6H), 2.86 (s, 3H), 3.21-3.29 (m, 1H), 3.80-3.88 (m, 1H), 4.22-4.27 (m, 1H), 4.97-5.00 (m, 1H), 7.30 (s, 1H), 7.33-7.50 (m, 5H), 8.00 (s, 1H).

[00328] **Example 17: Synthesis of 2-methyl-2-[5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1-[(2S)-2-phenoxy-2-phenylethyl]-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-143) and Example 18: Synthesis of 2-methyl-2-[5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1-[(2S)-2-phenoxy-2-phenylethyl]-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-144).**



[00329] **Synthesis of compound 17.2.** Into a 250-mL 3-necked round-bottom flask was placed a solution of 1-phenylethane-1,2-diol (10 g, 72.38 mmol, 1.00 equiv), TBSCl (22 g, 145.97 mmol, 2.00 equiv) and triethylamine (14.7 g, 145.27 mmol, 2.00 equiv) in tetrahydrofuran (100 mL). The solution was stirred overnight at room temperature. The next day it was diluted with 150 mL of H_2O and the mixture was extracted with 3x80 mL of ethyl acetate. The organic layers were combined, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1/10). Purification afforded 17 g (93%) of 2-[(tert-butyldimethylsilyl)oxy]-1-phenylethan-1-ol as a white oil.

[00330] Synthesis of compound 17.3. Into a 100-mL round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed **17.2** (20 mg, 0.08 mmol, 1.00 equiv), phenol (15 mg, 0.16 mmol, 2.00 equiv), tetrahydrofuran (3 mL), DIAD (32 mg, 0.16 mmol, 2.00 equiv) and PPh_3 (41 mg, 0.16 mmol, 2.00 equiv). The resulting solution was stirred for 2 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). This resulted in 15 mg (58%) of tert-butyldimethyl(2-phenoxy-2-phenylethoxy)silane as a white solid.

[00331] Synthesis of compound 17.4. Into a 50-mL round-bottom flask, was placed a solution of **17.3** (1.16 g, 3.53 mmol, 1.00 equiv) in tetrahydrofuran (10 mL). Then TBAF (1.8 g, 6.88 mmol, 2.00 equiv) was added at 0 °C. The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 30 mL of water. The resulting solution was extracted with 3x20 mL of ethyl acetate and the organic layers were combined, dried and concentrated under vacuum. The residue was applied onto a silica gel column with PE/EA (10/1). Purification afforded 480 mg (63%) of **17.4** as a white solid.

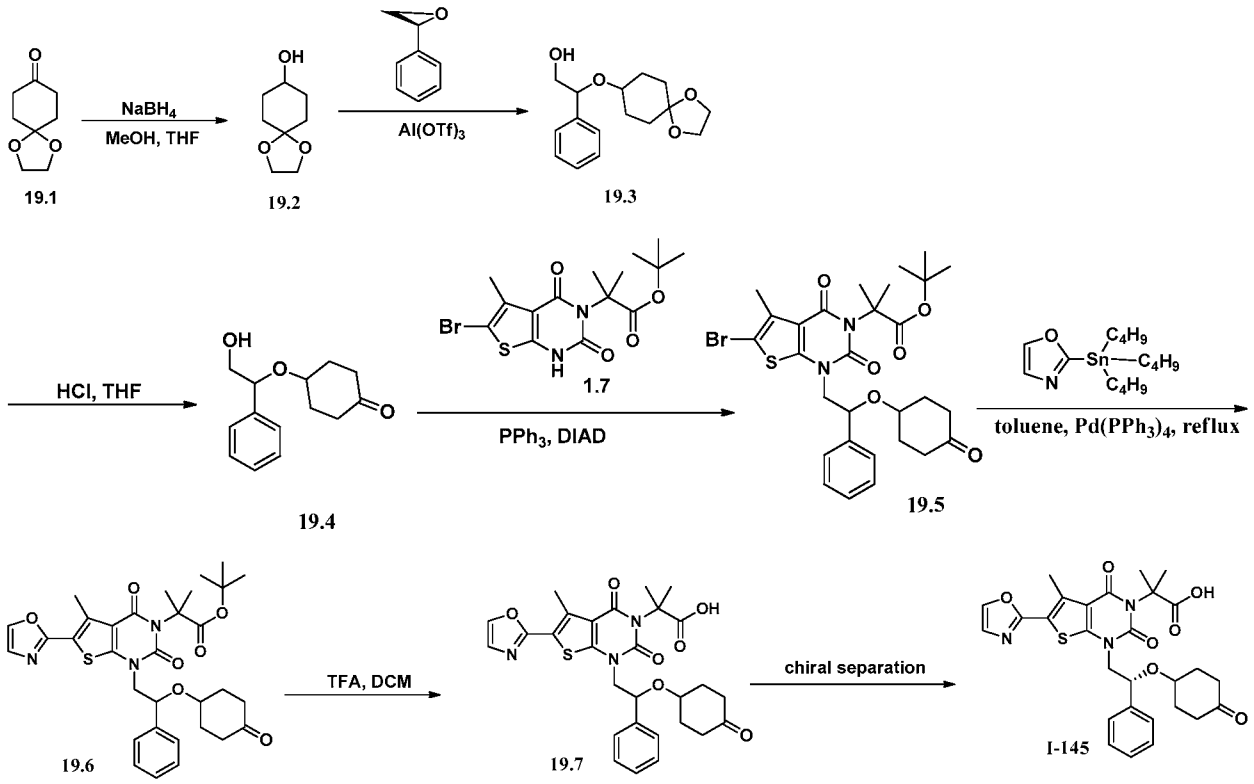
[00332] Synthesis of compound 17.7. Compound **17.7** was prepared, in a manner analogous with **14.5**, from **17.4** and **1.7.** Isolated the crude product in 32% yield for the three steps.

[00333] Synthesis of Compounds I-143 and I-144. The crude product (110 mg) was purified by chiral preparative HPLC under the following conditions (Gilson Gx 281): column: Chiralpak IC, 2*25 cm, 5 μm; mobile phase: hexanes (0.1% TFA) and ethanol (hold at 15.0% ethanol over 5 min); detector: UV 220/254 nm. This purification afforded 6.6 mg (9%) of Compound **I-143** as a white solid and 15.9 mg (21%) of Compound **I-144** as a white solid.

Analytical data for Compound I-143: MS (ES): *m/z* 532 $(M+H)^+$. ^1H NMR (CD_3OD, 400 MHz): 1.79 (s, 6H), 2.71 (s, 3H), 4.22 (m, 1H), 4.39 (d, 2H), 5.71 (m, 1H), 6.83 (m, 3H), 7.12 (t, 2H), 7.31 (m, 2H), 7.38 (t, 2H), 7.51 (d, 2H), 8.01 (s, 1H).

Analytical data for Compound I-144: MS (ES): *m/z* 532 $(M+H)^+$. ^1H NMR (CD_3OD, 400 MHz): 1.79 (s, 6H), 2.71 (s, 3H), 4.22 (m, 1H), 4.39 (d, 1H), 5.71 (m, 1H), 6.83 (m, 3H), 7.12 (t, 2H), 7.31 (m, 2H), 7.38 (t, 2H), 7.51 (d, 2H), 8.01 (s, 1H).

[00334] Example 19: Synthesis of (R)-2-methyl-2-(5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1-(2-((4-oxocyclohexyl)oxy)-2-phenylethyl)-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)propanoic acid (I-145).



[00335] **Synthesis of compound 19.2.** Into a 500-mL 3-necked round-bottom flask was placed 1,4-dioxaspiro[4.5]decan-8-one (20 g, 128.06 mmol, 1.00 equiv), methanol (250 mL) and $NaBH_4$ (7.3 g, 198.23 mmol, 1.55 equiv). The resulting solution was stirred for 2 h at room temperature. The reaction was then quenched by the addition of 150 mL of NH_4Cl (sat., aq.). The resulting solution was extracted with 2x300 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). Purification afforded 19.6 g (97%) of 1,4-dioxaspiro[4.5]decan-8-ol as a colorless oil.

[00336] **Synthesis of compound 19.3.** Into a 50-mL round-bottom flask, was placed 1,4-dioxaspiro[4.5]decan-8-ol (10 g, 63.21 mmol, 3.80 equiv), (2S)-2-phenyloxirane (2 g, 16.65 mmol, 1.00 equiv) and $Al(OTf)_3$ (197 mg, 0.42 mmol, 0.02 equiv). The resulting solution was stirred for 2 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). Purification afforded 2.7 g (crude) of **19.3** as a colorless oil.

[00337] **Synthesis of compound 19.4.** Into a 50-mL round-bottom flask was placed **19.3** (2.7 g, 9.70 mmol, 1.00 equiv), tetrahydrofuran (15 mL) and hydrogen chloride (18%) (15 mL). The resulting solution was stirred overnight at 70 °C. The reaction was then quenched by the addition

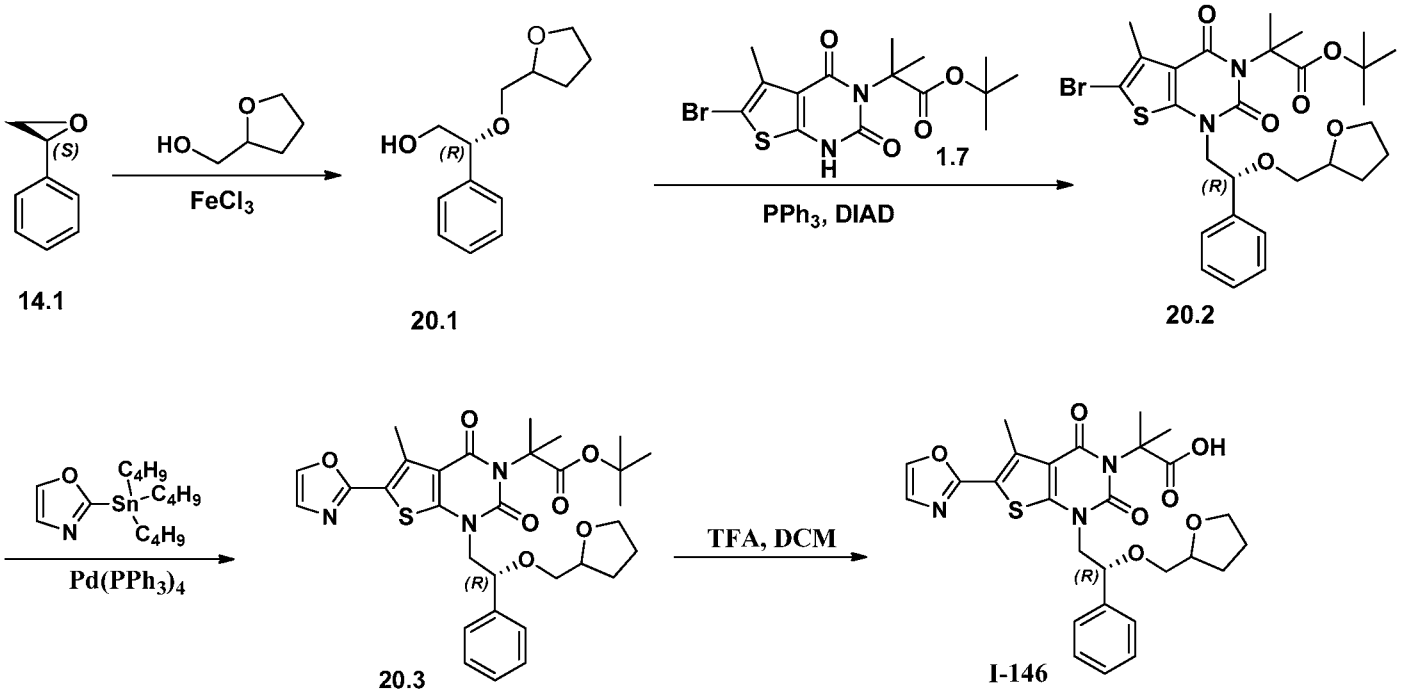
of 30 mL of sodium carbonate (aq.). The resulting solution was extracted with 2x50 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). Purification afforded 1.6 g (70%) of **19.4** as a colorless oil.

[00338] Synthesis of compound 19.7. Compound **19.7** was prepared, in a manner analogous to **14.5**, from **19.4** and **1.7**. Isolated a light yellow solid in 21% yield for the three steps.

[00339] Synthesis of Compound I-145. The crude product (58 mg) was purified by chiral preparative HPLC under the following conditions (Gilson Gx 281): column: Chiralpak IC, 2*25 cm, 5 μm; mobile phase: hexanes and ethanol (hold at 25.0% ethanol for 25 min); detector: UV 220/254 nm. 20.1 mg of a white solid product were obtained. MS (ES): *m/z* 552 $(M+H)^+$.

^{1}H NMR (300 MHz, CD_3OD): δ 1.25 (m, 1H), 1.55 (m, 7H), 1.82 (s, 3H), 1.85 (s, 3H), 2.83 (s, 3H), 3.33 (m, 1H), 3.78 (m, 1H), 4.29 (m, 1H), 4.92 (m,1H), 7.29 (s, 1H), 7.33-7.51 (m, 5H), 7.99 (s, 1H).

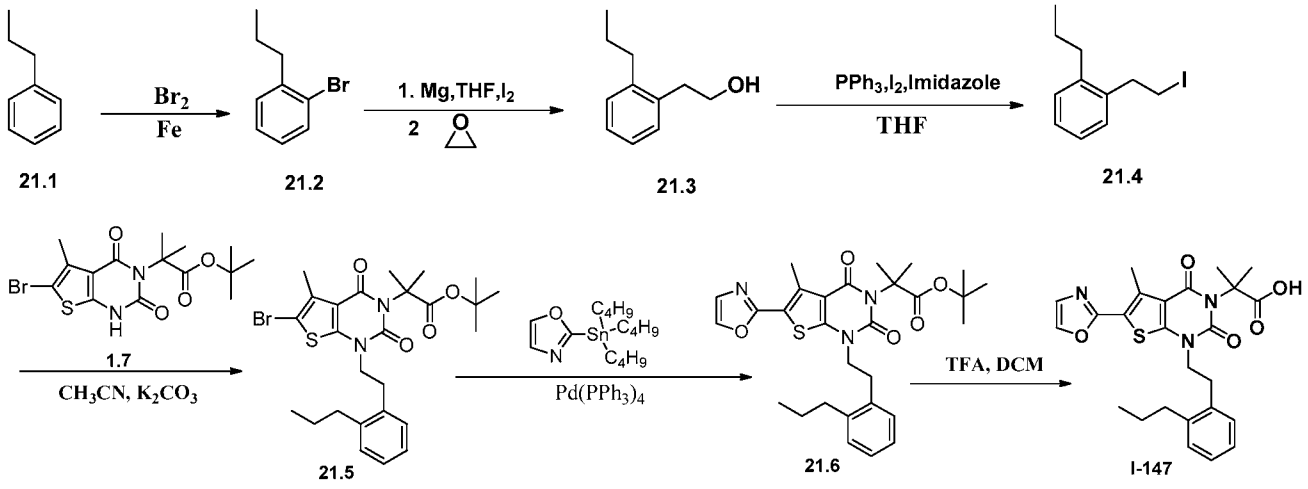
[00340] Example 20: Synthesis of 2-methyl-2-[5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1-[(2R)-2-(oxolan-2-ylmethoxy)-2-phenylethyl]-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-146).



[00341] Synthesis of compound 20.1. Into a 50-mL round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed (2R)-2-phenyloxirane (1 g, 8.32 mmol, 1.00 equiv), oxolan-2-ylmethanol (5 mL) and $FeCl_3$ (68 mg, 0.42 mmol, 0.05 equiv). The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 20 mL of water. The resulting solution was extracted with 3x10 mL of ethyl acetate, and the organic layers were combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1/10). Purification afforded 360 mg (19%) of **20.1** as a white oil.

[00342] Synthesis of Compound I-146. Compound **I-146** was prepared, in a manner analogous to **14.5**, from **20.1** and **1.7**. MS (ES): *m/z* 562 $(M+Na)^+$. ^1H NMR (CD_3OD, 300 MHz): δ 7.99 (s, 1H), 7.48-7.29 (m, 6H), 4.93-4.92 (m, 1H), 4.25-4.19 (m, 1H), 3.99-3.85 (m, 2H), 3.70-3.61 (m, 2H), 3.59-3.41 (m, 1H), 3.32-3.13 (m, 1H), 2.81 (s, 3H), 1.85 (s, 6H), 1.82-1.70 (m, 3H), 1.68-1.47 (m, 1H).

[00343] Example 21: Synthesis of 2-methyl-2-[5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1-[2-(2-propylphenyl)ethyl]-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-147).



[00344] Synthesis of compound 21.2. Into a 250-mL round-bottom flask was placed propylbenzene (20 g, 166.40 mmol, 1.00 equiv) and Fe (10 g, 178.57 mmol, 1.07 equiv). This was followed by the addition of Br_2 (26.6 g, 166.45 mmol, 1.00 equiv) dropwise with stirring. The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 100 mL of $NaHSO_3$ (aq.). The mixture was extracted with 3x100 mL

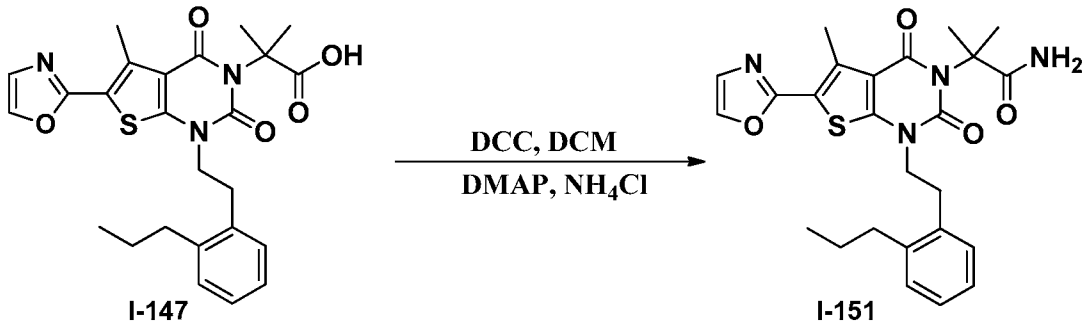
of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. Purification afforded 29.4 g (crude) of 1-bromo-2-propylbenzene as a yellow oil.

[00345] Synthesis of compound 21.3. Into a 250-mL 3-necked round-bottom flask, maintained with a nitrogen atmosphere, was placed I_2 (10 mg, 0.04 mmol) and Mg (500 mg, 20.83 mmol, 2.07 equiv). Then 1-bromo-2-propylbenzene (2.0 g, 10.05 mmol, 1.00 equiv) dissolved in tetrahydrofuran (50 mL) was added dropwise into the flask and the mixture was heated to reflux. After the reaction was complete the resulting mixture was cooled to 0 °C and then oxirane (50 mL) was added in one portion. The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 5 mL of NH_4Cl (aq.). The solids were filtered out. The filtrate was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). Purification afforded 0.24 g (15%) of 2-(2-propylphenyl)ethan-1-ol as a colorless oil.

[00346] Synthesis of compound 21.4. Into a 50-mL round-bottom flask was placed 2-(2-propylphenyl)ethan-1-ol (240 mg, 1.46 mmol, 1.00 equiv), PPh_3 (498 mg, 1.90 mmol, 1.30 equiv), I_2 (446 mg), imidazole (129 mg) and dichloromethane (20 mL). The resulting solution was stirred for 16 h at 30 °C. The reaction was then quenched by the addition of 100 mL of $NaHSO_3$ (aq.). The resulting solution was extracted with 2x50 mL of dichloromethane and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:100). Purification afforded 200 mg (50%) of 1-(2-iodoethyl)-2-propylbenzene as a colorless oil.

[00347] Synthesis of compound I-147. Compound **I-147** was prepared from **21.4** and **1.7** in a manner analogous to Example 9. Isolated a white solid in 45% yield for the three steps. MS (ES): *m/z* 538 $(M+H)^+$. ^1H NMR (CD_3OD, 300 MHz): 1.30 (t, 3H), 1.70-1.80 (m, 2H), 1.95 (s, 6H), 2.74 (t, 2H), 2.8 (s, 3H), 3.13 (t, 2H), 4.13 (t, 2H), 7.10-7.15 (m, 4H), 7.28 (s, 1H), 7.97 (s, 1H).

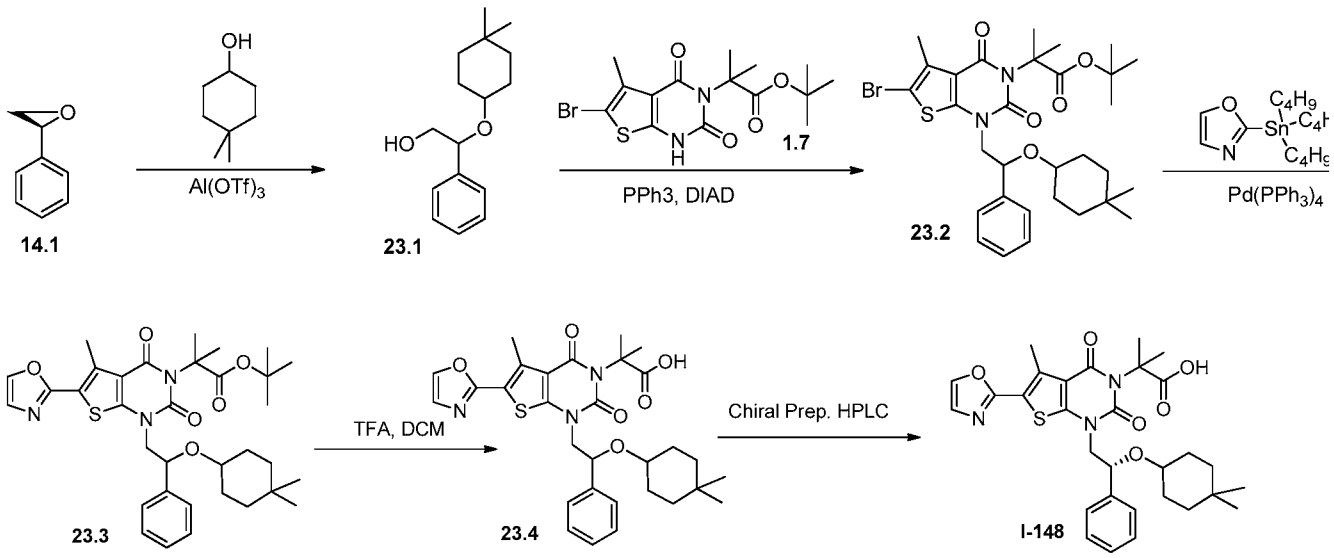
[00348] Example 22. Synthesis of 2-methyl-2-[5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1-[2-(2-propylphenyl)ethyl]-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanamide (I-151).



I-147 I-151

[00349] **Compound I-151** was prepared in a manner analogous to Compound **I-121** (Example 4). Isolated a white solid in 11% yield. MS (ES): *m/z* 464 $(M\text{-}NH_2)^+$. ^1H (CD_3OD, 400 MHz): 1.05 (t, 3H), 1.65 (m, 2H), 1.83 (s, 6H), 2.74 (t, 2H), 2.81 (s, 3H), 3.11 (t, 3H), 4.11 (t, 2H), 7.19 (ArH, 4H), 7.28 (s, 1H), 7.98 (s, 1H).

[00350] **Example 23. Synthesis of 2-[1-[(2R)-2-[(4,4-dimethylcyclohexyl)oxy]-2-phenylethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-148).**



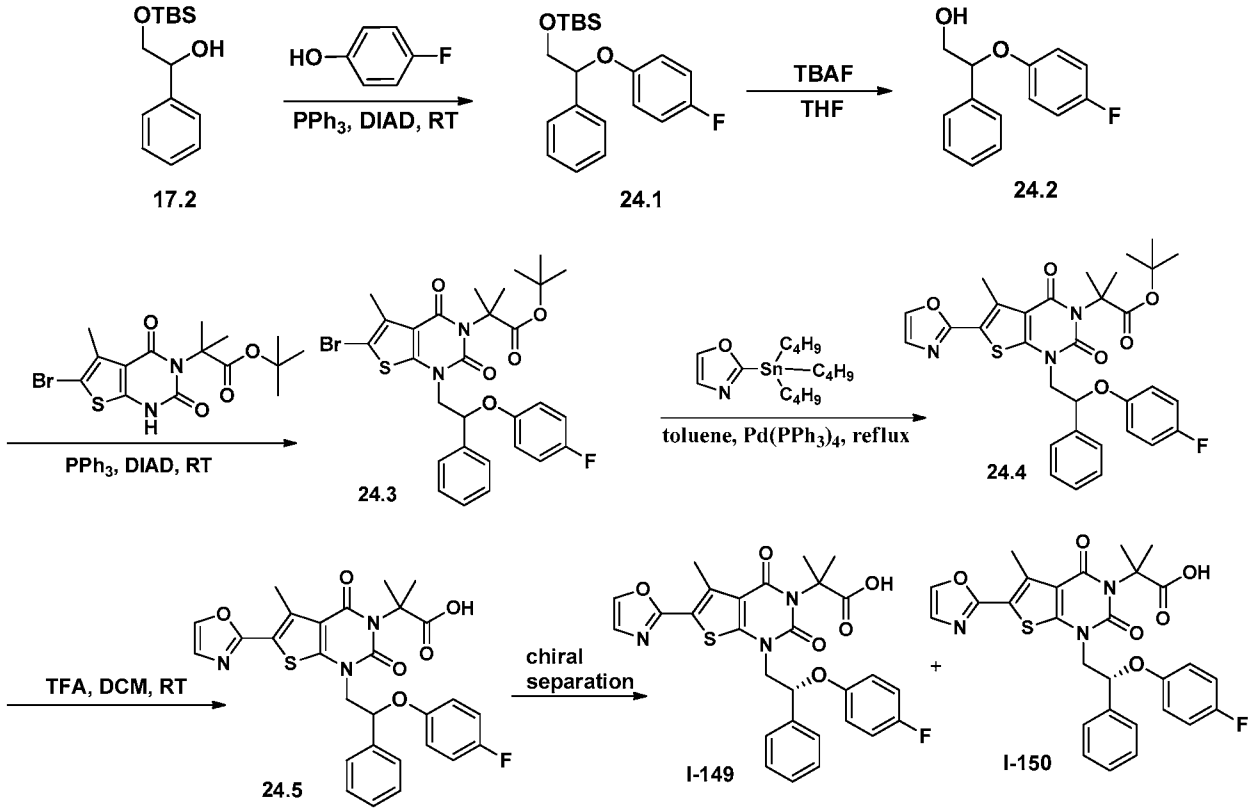
14.1 23.1 1.7 23.2 23.3 23.4 I-148

[00351] **Synthesis of compound 23.4.** Compound **23.4** was prepared in a manner analogous to compound **14.5**, substituting 4,4-dimethylcyclohexanol for 2,2,2-trifluoroethan-1-ol. Isolated a white solid in 34% yield from **1.7**.

[00352] **Purification of Compound I-148.** Crude **23.4** was purified by chiral preparative HPLC under the following conditions (Gilson Gx 281): column: Chiralpak IC, 2*25 cm, 5 μm; mobile phase: hexanes (0.1% TFA) and ethanol (0.1% TFA) (hold at 5.0% ethanol (0.1%TFA) for 8 min); detector: UV 220/254 nm. Purification afforded 73 mg (36.5%) of Compound **I-148**

as a white solid. MS (ES): *m/z* 566 $(M+H)^+$. ^1H NMR (CD_3OD, 400 MHz): 0.62 (s, 3H), 0.83 (s, 3H), 1.02 (m, 3H), 1.24 (m, 1H), 1.51 (m, 4H), 1.81 (d, 6H), 2.82 (s, 3H), 3.31 (s, 1H), 3.75 (m, 1H), 4.31 (d, 1H), 4.96 (d, 1H), 7.31 (s, 1H), 7.41 (m, 3H), 7.55 (d, 2H), 8.01 (s, 1H).

[00353] Example 24: Synthesis of (R)-2-(1-(2-(4-fluorophenoxy)-2-phenylethyl)-5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)-2-methylpropanoic acid (I-149) and Example 25: Synthesis of (S)-2-(1-(2-(4-fluorophenoxy)-2-phenylethyl)-5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)-2-methylpropanoic acid (I-150).



[00354] Synthesis of compound 24.2. 2-(4-fluorophenoxy)-2-phenylethan-1-ol (**24.2**) was prepared in a manner analogous to compound **17.4**, substituting 4-fluorophenol for phenol. Isolated a colorless oil in *ca.* 31% yield (crude).

[00355] Synthesis of compound 24.5. 24.5 was prepared in a manner analogous to compound **14.5**. Isolated a white solid in 28% yield from **1.7**.

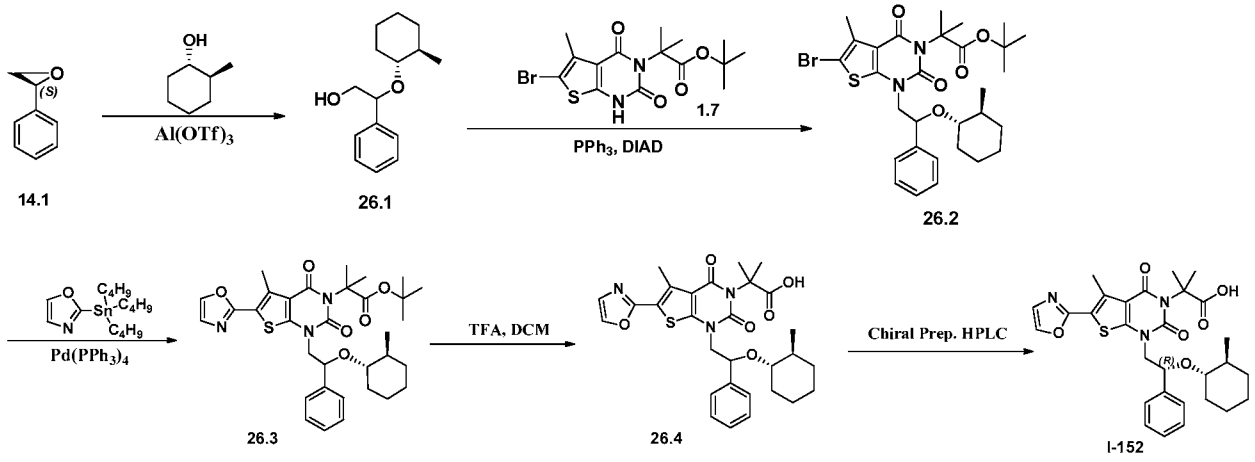
[00356] Purification of Compound I-149 and Compound I-150. The enantiomers of **24.5** (140 mg) were separated by chiral preparative HPLC under the following conditions (Gilson Gx

281): Column: Chiralpak IC, 2*25 cm, 5 μm; mobile phase: hexanes (0.1%TFA) and ethanol (hold at 15.0% ethanol for 30 min; detector: UV 220/254 nm. 48.1 mg of a white solid product were obtained.

Analytical data for Compound I-149: MS (ES): *m/z* 550 $(M+H)^+$, 591 $(M+CH_3CN)^+$. ^1H NMR (300 MHz, CD_3OD): 1.79 (s, 6H), 278 (s, 3H), 4.20 (dd, *J* = 14.7, 8.7, 1H), 4.36 (dd, *J* = 14.7, 3.9, 1H), 5.65 (m, 1H) , 6.77-6.89 (m, 4H), 7.29-7.53 (m, 6H) , 7.99 (s, 1H).

Analytical data for Compound I-150: MS (ES): *m/z* 550 $(M+H)^+$, 591 $(M+ CH_3CN)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.79 (s, 6H), 28 (s, 3H), 4.20 (dd, *J* = 14.7,8.7, 1H), 4.36 (dd, *J* = 14.7, 3.9, 1H), 5.65 (m, 1H) , 6.77-6.89 (m, 4H), 7.29-7.53 (m, 6H) , 7.99 (s, 1H).

[00357] Example 26: Synthesis of 2-methyl-2-[5-methyl-1-[(2R)-2-[[(1S,2S)-2-methylcyclohexyl]oxy]-2-phenylethyl]-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-152).



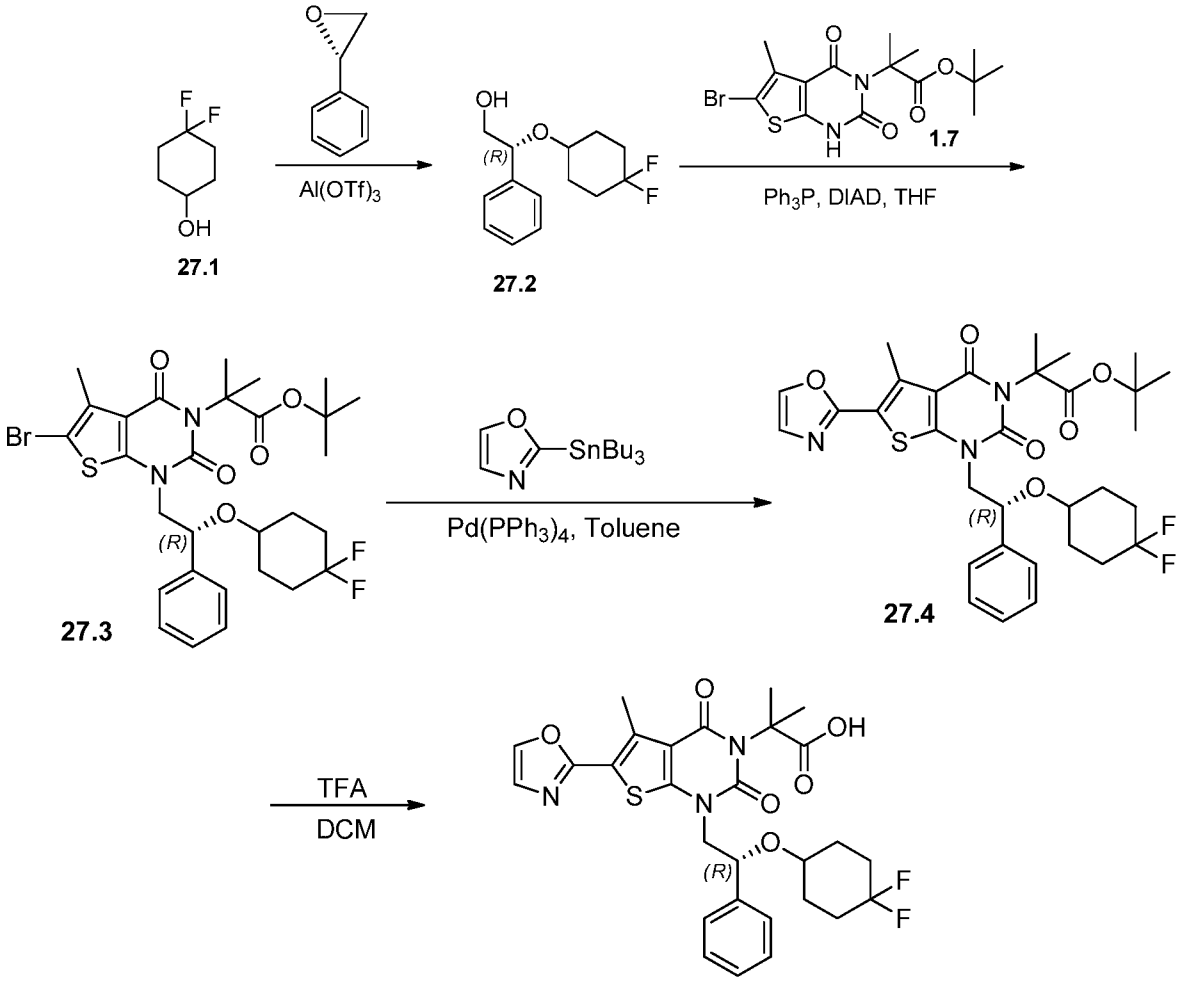
[00358] Synthesis of compound 26.1. 26.1 was prepared in a manner analogous to **14.2**, substituting methylcyclohexan-1-ol for 2,2,2-trifluoroethan-1-ol. Isolated a colorless oil in 18% yield.

[00359] Synthesis of compound 26.4. 26.4 was prepared in a manner analogous to **14.5**. Isolated a white solid in *ca.* 34% yield from **1.7**.

[00360] Purification of Compound I-152. The enantiomers of **26.4** (110 mg) were separated by chiral preparative HPLC under the following conditions (Gilson Gx 281): Column: Chiralpak IC, 2*25 cm, 5 μm; mobile phase: hexanes (0.2%TEA) and ethanol (0.2%TEA) (hold at 2.0% ethanol (0.2% TEA) for 20 min); detector: UV 220/254 nm. Purification afforded 58.7 mg (53%) of Compound **I-152** as a white solid. MS (ES): *m/z* 552 $(M+H)^+$, 615 $(M+Na+CH_3CN)^+$. ^1H

NMR (300 MHz, CD_3OD): δ 0.76 (d, *J* = 6.3, 2H), 0.86 (d, *J* = 6.6 2H), 1.07 (m, 2H), 1.50 (m, 5H), 1.81 (s, 6H), 2.00 (d, *J* = 14.1, 1H), 2.80 (m, 4H), 3.91 (m, 1H), 4.17 (m, 1H) , 5.09 (m, 1H), 7.29-7.49 (m, 6H), 8.00 (s, 1H).

[00361] Example 27: Synthesis of 2-[1-[(2R)-2-[(4,4-difluorocyclohexyl)oxy]-2-phenylethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-155).

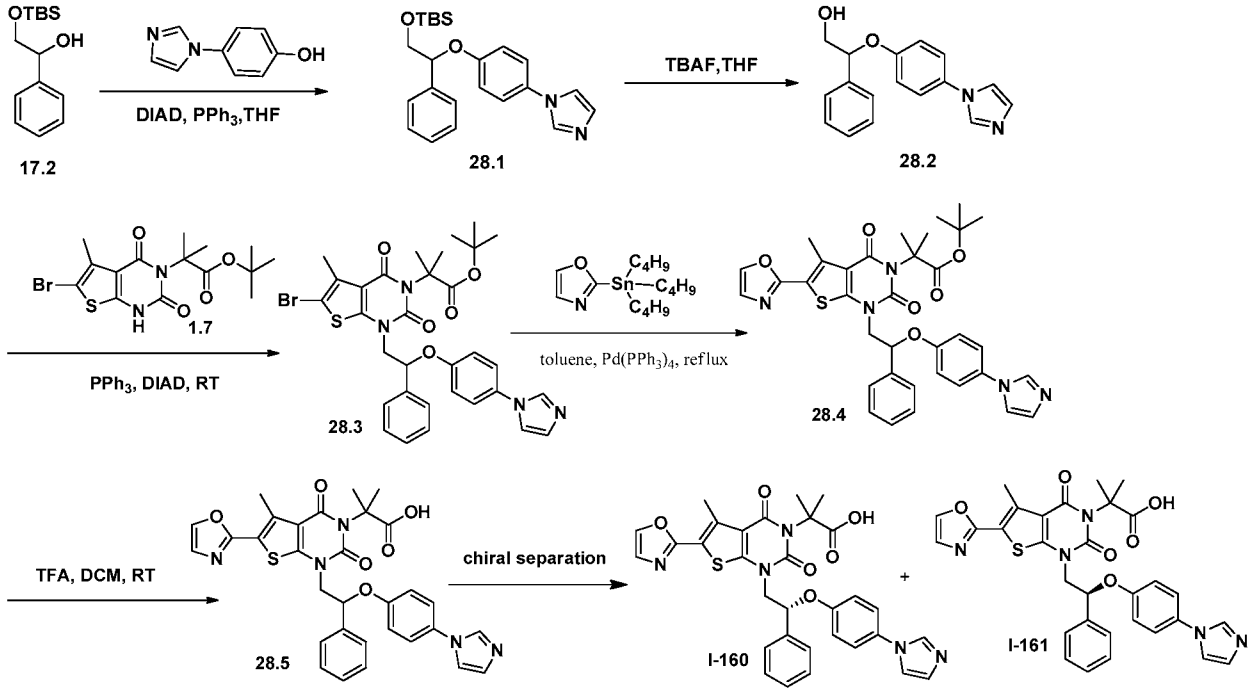


[00362] Synthesis of compound 27.2. Compound **27.2** was prepared in a manner analogous to **14.2**, substituting 4,4-difluorocyclohexan-1-ol for 2,2,2-trifluoroethan-1-ol. Isolated a yellow oil in 18% yield.

[00363] Synthesis of Compound I-155. Compound **I-155** was prepared in a manner analogous to compound **14.5**. Isolated a colorless oil in 2% overall yield from **1.7**. MS (ES): *m/z* 574 $(M+H)^+$, 596 $(M+Na)^+$, 637 $(M+Na+CH_3CN)^+$. ^1H NMR (400 MHz, CD_3CN): δ 1.54-1.74

(m, 8H), 1.77 (d, 6H), 2.78 (s, 3H), 3.43 (s, 1H), 3.78-3.84 (m, 1H), 4.21-4.25 (m, 1H), 4.91-4.95 (m, 1H), 7.27 (s, 1H), 7.37-7.52 (m, 5H), 7.90 (s, 1H).

[00364] Example 28: Synthesis of 2-[1-[(2R)-2-[4-(1H-imidazol-1-yl)phenoxy]-2-phenylethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-160) and Example 29: Synthesis of 2-[1-[(2S)-2-[4-(1H-imidazol-1-yl)phenoxy]-2-phenylethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-161).



[00365] Synthesis of compound 28.2. 2-[4-(1H-imidazol-1-yl)phenoxy]-2-phenylethan-1-ol (**28.2**) was prepared in a manner analogous to **17.4**, substituting 4-(1H-imidazol-1-yl)phenol for phenol. Isolated a white solid in 25% yield from **17.2**.

[00366] Synthesis of compound 28.5. Compound **28.5** was prepared in a manner analogous to **14.5**, substituting **28.2** for **14.2**. Isolated a white solid in *ca.* 32% yield from **1.7**.

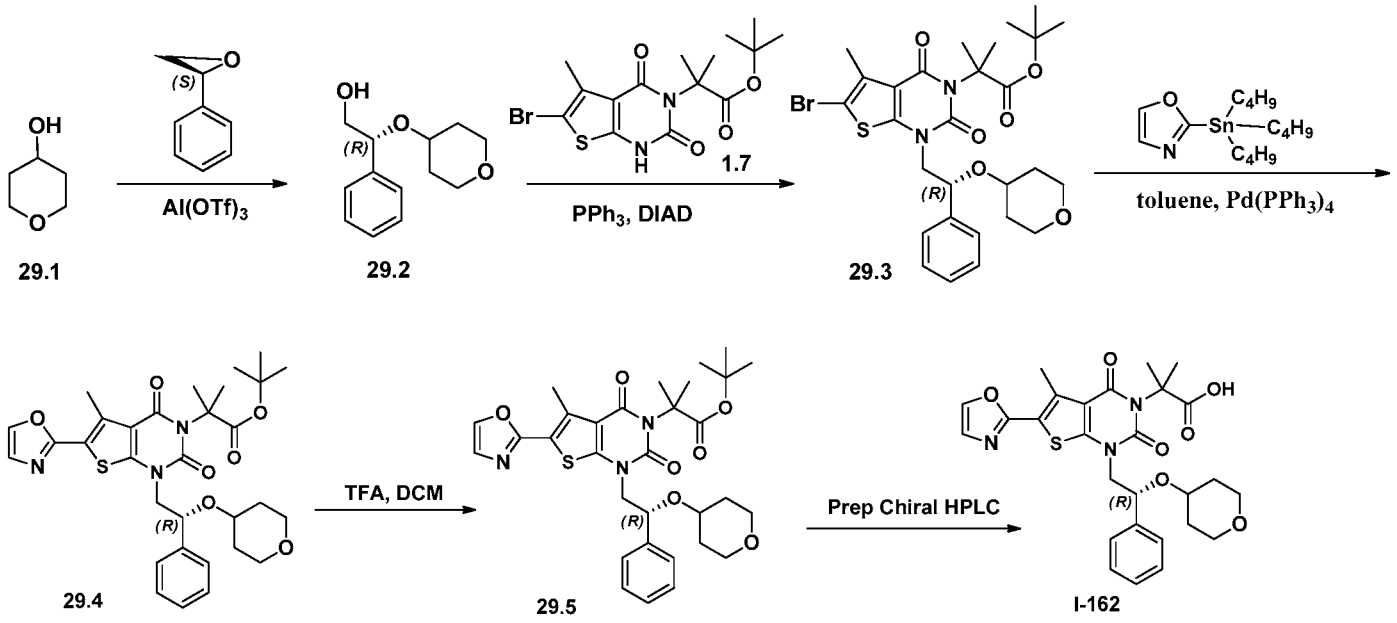
[00367] Purification of Compounds I-160 and I-161. The enantiomers of **28.5** (148 mg, 0.25 mmol) were separated by chiral preparative HPLC under the following conditions (Gilson Gx 281): Column: Chiralpak IC, 2*25 cm, 5 μm; mobile phase: hexanes (0.1%TFA) and ethanol (0.1%TFA) (hold at 30% ethanol for 70 min); detector: 220/254nm. The fraction with a retention time of 49.5 min was collected and concentrated *in vacuo* to afford 0.019 g (26%) of **I-160** as a

white solid. The fraction with a retention time of 42.0 min was collected and concentrated *in vacuo* to afford 0.023 g of **I-161** as a white solid.

Analytical data for Compound I-160: MS (ES): *m/z* 598 $(M+H)^+$. ^1H NMR (CD_3OD, 300 MHz): δ 1.76 (s, 6H), 2.75 (s, 3H), 4.22 (m, 1H), 4.45 (m, 1H), 5.80 (d, *J* = 11.1 Hz, 1H), 7.05 (d, *J* = 8.7 Hz, 2H), 7.44 (m, 8H), 7.64 (s, 1H), 7.84 (s, 1H), 7.98 (s, 1H), 9.17 (s, 1H).

Analytical data for Compound I-161: MS (ES): *m/z* 598 $(M+H)^+$. ^1H NMR (CD_3OD, 300 MHz): δ 1.76 (d, *J* = 1.8 Hz, 6H), 2.74 (s, 3H), 4.26 (dd, *J* = 9.0 Hz, 15.0 Hz, 1H), 4.44 (dd, *J* = 3.9 Hz, 14.7 Hz, 1H), 5.81 (dd, *J* = 3.6 Hz, 8.4 Hz, 1H), 7.06 (m, 2H), 7.27-7.52 (m, 8H), 7.68 (s, 1H), 7.80 (s, 1H), 7.97 (d, *J* = 0.6 Hz, 1H), 9.18 (s, 1H).

[00368] Example 29: Synthesis of 2-methyl-2-[5-methyl-1-[(2R)-2-(oxan-4-yloxy)-2-phenylethyl]-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-162).



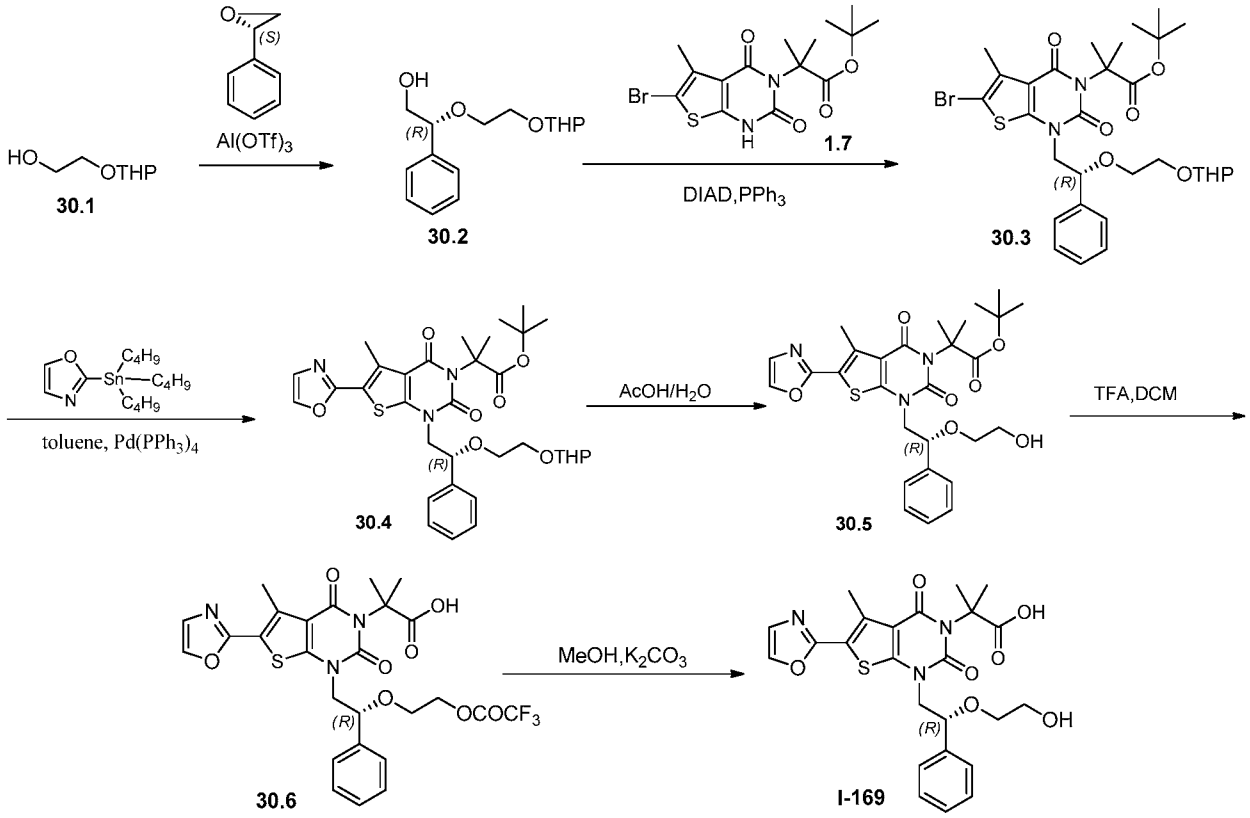
[00369] Synthesis of compound 29.2. (2R)-2-(oxan-4-yloxy)-2-phenylethan-1-ol (**29.2**) was prepared in a manner analogous to **14.2**, substituting oxan-4-ol for 2,2,2-trifluoroethan-1-ol. Isolated a colorless oil in 21% yield.

[00370] Synthesis of compound 29.5. 29.5 was prepared in a manner analogous to **14.5**, substituting **29.2** for **14.2**. Isolated a white solid in 80% yield from **1.7**.

[00371] Purification of Compound I-162. 29.5 (150 mg, 0.28 mmol, 1.00 equiv) was repurified by chiral preparative HPLC under the following conditions (Gilson Gx 281): column: Chiralpak IC, 2*25 cm, 5 μm; mobile phase: hexanes (0.1% TFA) and ethanol (with 0.1% TFA;

hold at 30% ethanol in 13 min); detector: 220/254 nm. The fraction with a retention time of 8.5 min was collected. This fraction afforded 0.050 g of **I-162** as a white solid. MS (ES): *m/z* 540 $(M+H)^+$. ^1H NMR (DMSO-d_6, 400 MHz): δ 1.20 (m, 2H), 1.70 (m, 8H), 2.80 (s, 3H), 3.21-3.50 (m, 5H), 3.82 (s, 1H), 4.17 (d, J = 13.6 Hz, 1H), 4.91 (d, J = 6.8 Hz, 1H), 7.40 (m, 6H), 8.24 (s, 1H), 12.44 (s, 1H).

[00372] Example 30: 2-[1-[(2R)-2-(2-hydroxyethoxy)-2-phenylethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-169).



[00373] Synthesis of compound 30.2. Compound **30.2** was prepared from 2-((tetrahydro-2H-pyran-2-yl)oxy)ethanol in a manner analogous to the synthesis of compound **14.2**. Isolated a colorless oil in 5% yield.

[00374] Synthesis of compound 30.4. Compound **30.4** was prepared in a manner analogous to compound **14.4**. Isolated a yellow solid in 40% overall yield from compounds **30.2** and **1.7**.

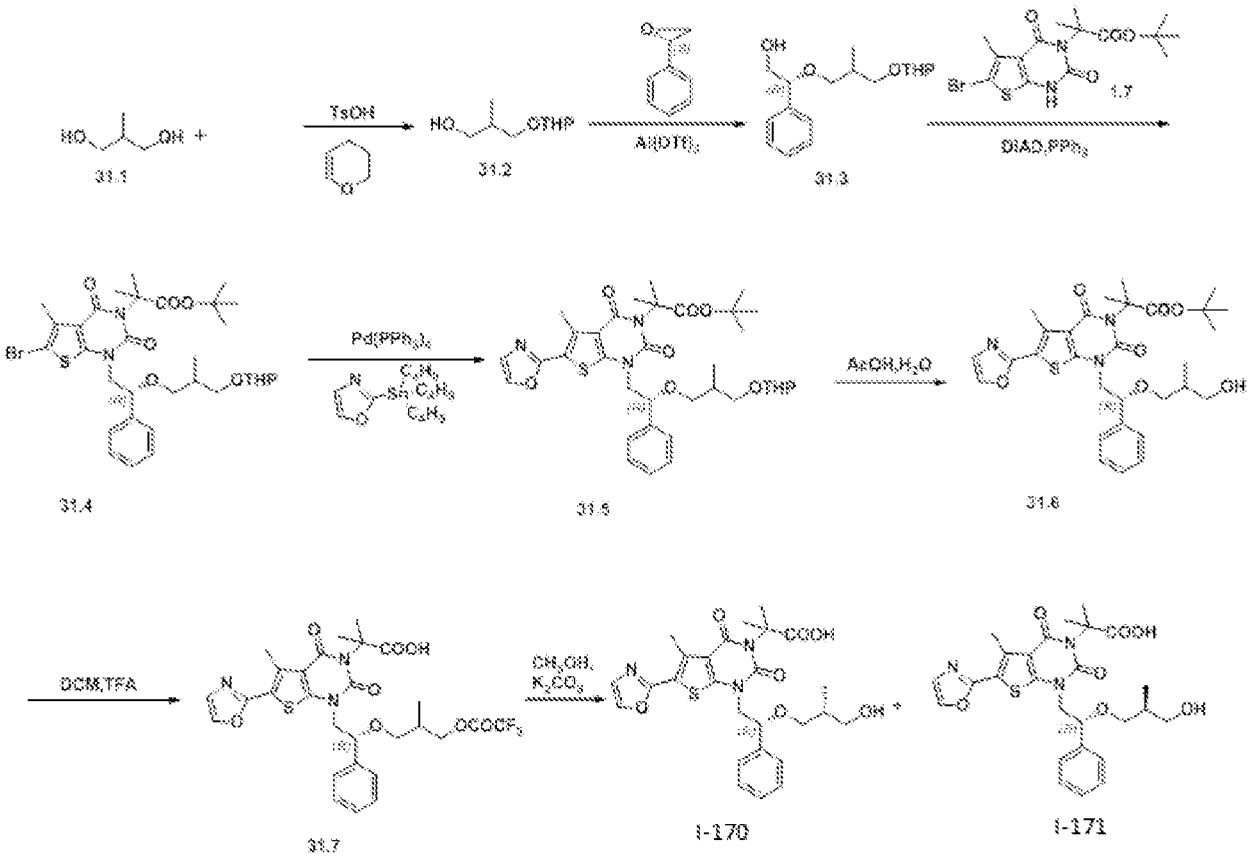
[00375] Synthesis of compound 30.5. Into a 25-mL round-bottom flask was placed **30.4** (150 mg, 0.27 mmol, 1.00 equiv), AcOH (4 mL) and water (1 mL). The resulting solution was stirred overnight at 35 °C in an oil bath. The resulting mixture was concentrated under vacuum. The

residue was applied onto a silica gel column with PE/EA (2:1). The crude product (100 mg) was purified by chiral preparative HPLC under the following conditions (Gilson Gx 281): Column: CHIRALPAK AD-H SFC, 5*25cm, 5 μm; mobile phase: hexanes (0.2%TEA and ethanol (0.2%TEA) (hold at 10% ethanol (0.2%TEA) for 17 min); detector: UV 220/254 nm. The fraction with a retention time of 12.9 min was collected. Concentration afforded 25 mg (17%) of **30.5** as a white solid.

[00376] Synthesis of compound 30.6. Into a 25-mL round-bottom flask was placed dichloromethane (5 mL), **30.5** (20 mg, 0.04 mmol, 1.00 equiv) and CF_3COOH (1.5 mL). The resulting solution was stirred for 4 h at room temperature. The resulting mixture was concentrated under vacuum. Purification afforded 0.020 g (crude) of **30.6** as a colorless oil.

[00377] Synthesis of Compound I-169. Into a 25-mL round-bottom flask was placed methanol (5 mL), **30.6** (20 mg, 0.03 mmol, 1.00 equiv) and potassium carbonate (30 mg, 0.22 mmol, 6.46 equiv). The solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The crude product (30 mg) was purified by preparative HPLC under the following conditions (Waters): Column: SunFire Prep C18, 19*150 mm 5 μm; mobile phase: water (50 mM NH_4CO_3) and CH_3CN (5.0% CH_3CN up to 45.0% in 10 min, up to 95.0% in 2 min, down to 5.0% in 2 min); detector: UV 254/220 nm. This procedure afforded 0.013 g (77%) of Compound **I-169** as a white solid. MS (ES): *m/z* 500 $(M+H)^+$. ^1H NMR (CD_3OD, 400 MHz): δ 1.80 (s, 6H), 2.80 (s, 3H), 3.39-3.49 (m, 3H), 3.59 (q, *J* = 6.0 Hz, 2H), 4.03 (t, *J* = 8.8 Hz, 1H), 4.15 (m, 1H), 7.27 (s, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 6.8 Hz, 2H), 7.48 (d, *J* = 7.2 Hz, 2H), 7.97 (s, 1H).

[00378] Example 31: Synthesis of 2-(1-((R)-2-((R)-3-hydroxy-2-methylpropoxy)-2-phenylethyl)-5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)-2-methylpropanoic acid (I-170) and Example 32: Synthesis of 2-(1-((R)-2-((S)-3-hydroxy-2-methylpropoxy)-2-phenylethyl)-5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)-2-methylpropanoic acid (I-171).



[00379] **Synthesis of compound 31.2.** Into a 50-mL 3-necked round-bottom flask was placed 2-methylpropane-1,3-diol (20 g, 221.92 mmol, 1.00 equiv) and 4-methylbenzene-1-sulfonic acid (11 mg, 0.06 mmol). Then 3,4-dihydro-2H-pyran (5 g, 59.44 mmol, 0.27 equiv) was added at 0 °C. The resulting solution was stirred for 3 h at room temperature. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:20). Purification afforded 6.9 g (18%) of 2-methyl-3-(oxan-2-yloxy)propan-1-ol as a light yellow liquid.

[00380] **Synthesis of compound 31.3.** Compound **31.3** was prepared from **31.2** in a manner analogous to the synthesis of compound **14.2**. Isolated a colorless oil in 5% yield.

[00381] **Synthesis of compound 31.7.** Compound **31.7** was prepared in a manner analogous to compound **30.6.** Isolated a colorless oil in 30% overall yield from **31.3** and **1.7**.

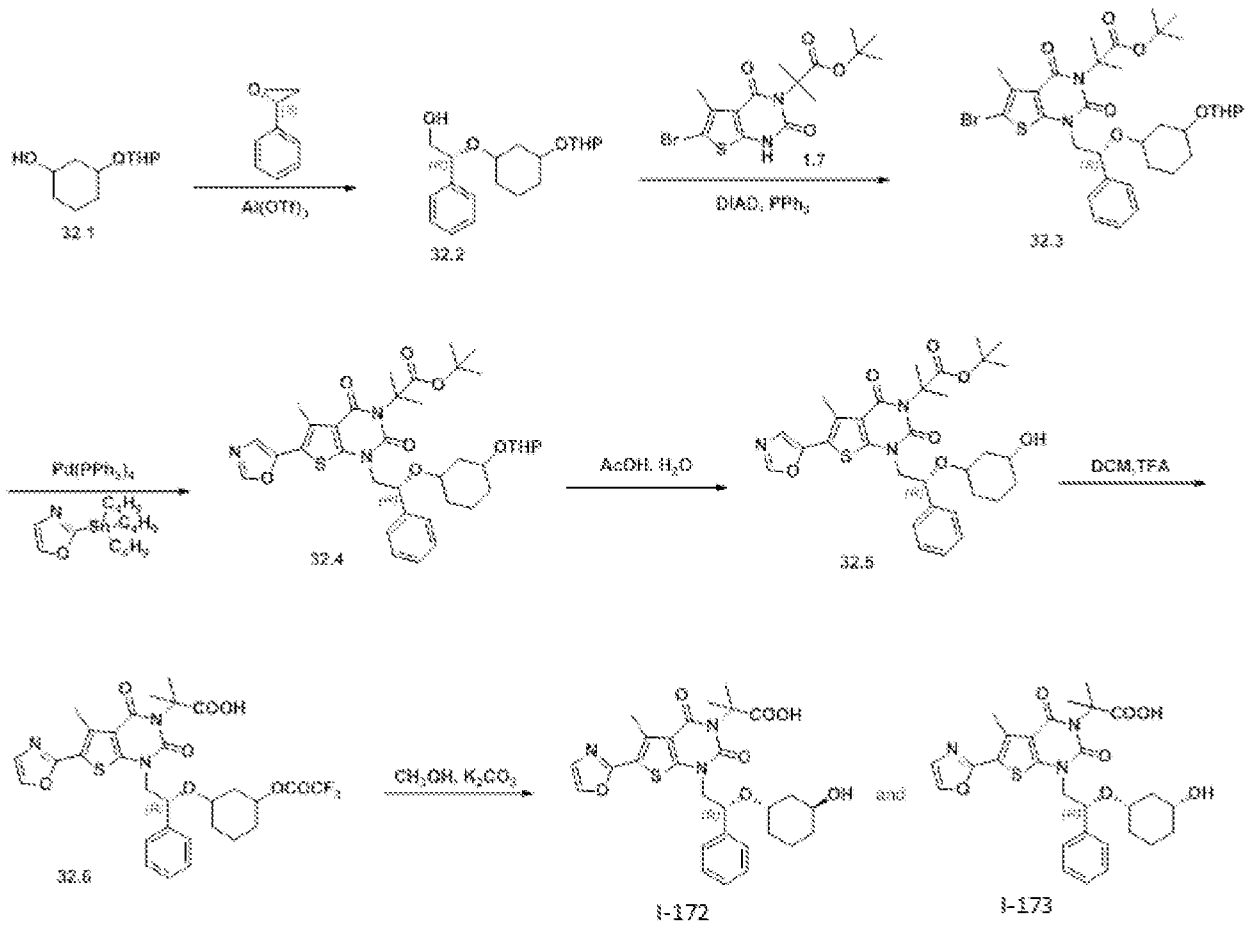
[0001] **Synthesis of Compounds I-170 and I-171.** Into a 50-mL round-bottom flask was placed methanol (5 mL), compound **31.7** (100 mg, 0.16 mmol, 1.00 equiv) and potassium methaneperoxoate potassium (50 mg, 0.36 mmol, 2.24 equiv). The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The crude

product (100 mg) was purified by preparative HPLC under the following conditions (Waters): Column: XBridge Prep C18 OBD column, 5 μm, 19*150 mm; mobile phase: water (50 mM NH_4HCO_3) and CH_3CN (10% CH_3CN up to 27% in 2 min, hold at 27% in 15 min, up to 95% in 2 min, down to 10% in 2 min); detector: UV 254/220 nm. Purification afforded 0.024 g (57%) of Compound **I-170** as a white solid (tR = 10.28 min) and 0.023 g (57%) of Compound **I-171**, also as a white solid (tR = 11.62 min).

Analytical data for Compound I-170: MS (ES): *m/z* 528 $(M+H)^+$. ^1H NMR (CD_3OD, 400 MHz): δ 0.74-0.81 (m, 3H), 1.81 (m, 7H), 2.83 (s, 3H), 3.24 (m, 4H), 3.88 (m, 1H), 4.20 (m, 1H), 7.28 (s, 1H), 7.35 (m, 1H), 7.44 (m, 4H), 7.98 (s, 1H).

Analytical data for Compound I-171: MS (ES): *m/z* 528 $(M+H)^+$. ^1H NMR (CD_3OD, 400 MHz): δ 0.74-0.81 (m, 3H), 1.81 (m, 7H), 2.83 (s, 3H), 3.24 (m, 4H), 3.88 (m, 1H), 4.20 (m, 1H), 7.28 (s, 1H), 7.35 (m, 1H), 7.44 (m, 4H), 7.98 (s, 1H).

[00382] Example 32: Synthesis of 2-(1-((R)-2-(((1S,3S)-3-hydroxycyclohexyl)oxy)-2-phenylethyl)-5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)-2-methylpropanoic acid (I-172) and Example 33: 2-(1-((R)-2-(((1S,3R)-3-hydroxycyclohexyl)oxy)-2-phenylethyl)-5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)-2-methylpropanoic acid (I-173).



[00383] **Synthesis of compound 32.6.** Compound **32.6** was prepared from **32.1** and **1.7** in a manner analogous to the synthesis of compound **30.6**. Isolated a colorless oil in 14% overall yield from **1.7** (1% from **32.1**).

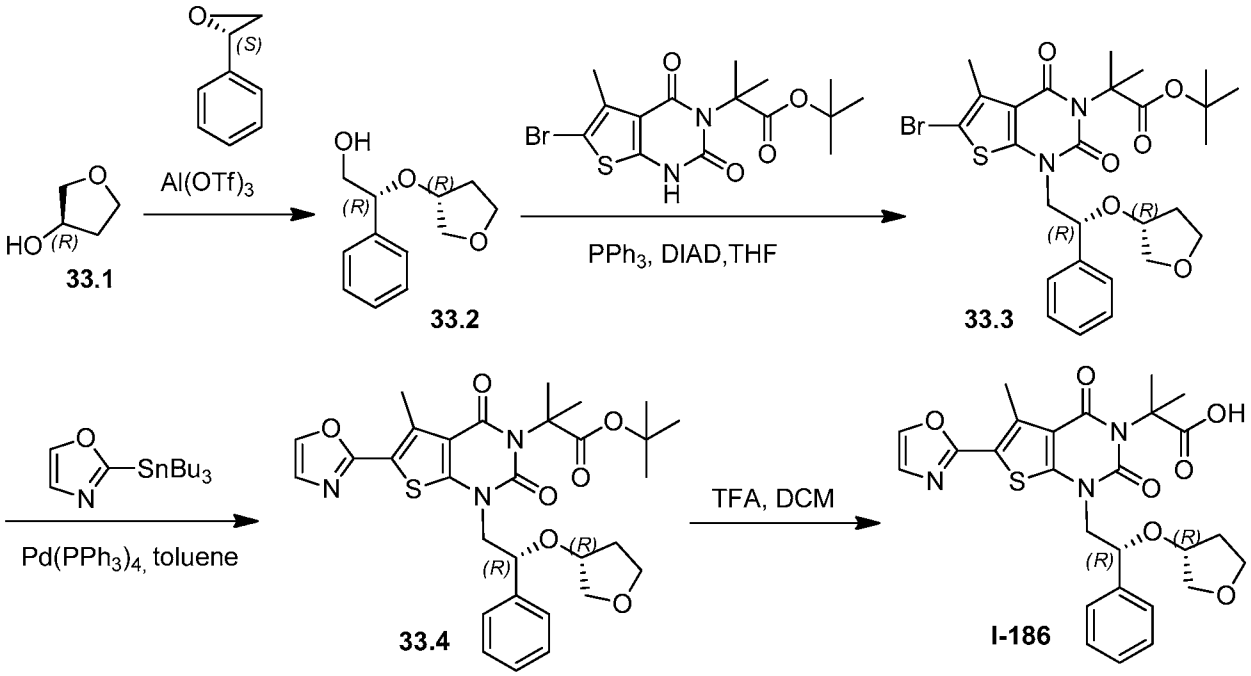
[00384] **Synthesis of Compounds I-172 and I-173.** Into a 50-mL round-bottom flask was placed methanol (5 mL), compound **32.6** (100 mg, 0.15 mmol, 1.00 equiv) and potassium carbonate (80 mg, 0.58 mmol, 3.76 equiv). The solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The crude product (100 mg) was purified by preparative HPLC under the following conditions (Waters): Column: XBridge Prep C18 OBD, 5 μm, 19*150 mm; mobile phase: water (50 mM NH_4HCO_3) and CH_3CN (17.0% CH_3CN up to 40.0% in 10 min, up to 95.0% in 2 min, down to 17.0% in 2 min); detector: UV 254, 220 nm. Purification afforded 17.2 mg (42%) of Compound **I-172** as a white solid and 16.1 mg (40%) of Compound **I-173**, also as a white solid.

Analytical data for Compound I-172: MS (ES): *m/z* 554 $(M+H)^+$. ^1H NMR (CD_3OD, 400 MHz): δ 0.88 (m, 1H), 1.20 (m, 3H), 1.35 (m, 1H), 1.60 (m, 2H), 1.80 (m, 6H), 2.10 (m,

1H), 2.83 (s, 3H), 3.20 (m, 1H), 3.60 (m, 1H), 3.80 (m, 1H), 4.20 (m, 1H), 5.00 (m, 1H), 7.29 (d, J = 2.4 Hz, 1H), 7.35 (dd, J = 6.8, 14.4 Hz, 1H), 7.43 (dd, J = 7.6, 15.2 Hz, 2H), 7.50 (t, J = 7.6 Hz, 2H), 7.99 (d, J = 2.0 Hz, 1H).

Analytical data for Compound I-173: MS (ES): *m/z* 554 $(M+H)^+$. ^1H NMR (CD_3OD, 400 MHz): δ 1.20 (m, 3H), 1.35 (m, 2H), 1.55 (m, 2H), 1.82 (m, 6H), 2.04 (m, 1H), 2.84 (s, 3H), 3.47 (d, J = 12.0 Hz, 1H), 3.61 (s, 1H), 3.70 (m, 1H), 4.33 (d, J = 12.8 Hz, 1H), 5.05 (m, 1H), 7.28 (s, 1H), 7.35 (t, J = 6.8 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.50 (d, J = 7.2 Hz, 2H), 7.99 (s, 1H).

[00385] Example 33: Synthesis of 2-methyl-2-[5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1-[(2R)-2-[(3R)-oxolan-3-yloxy]-2-phenylethyl]-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-186).

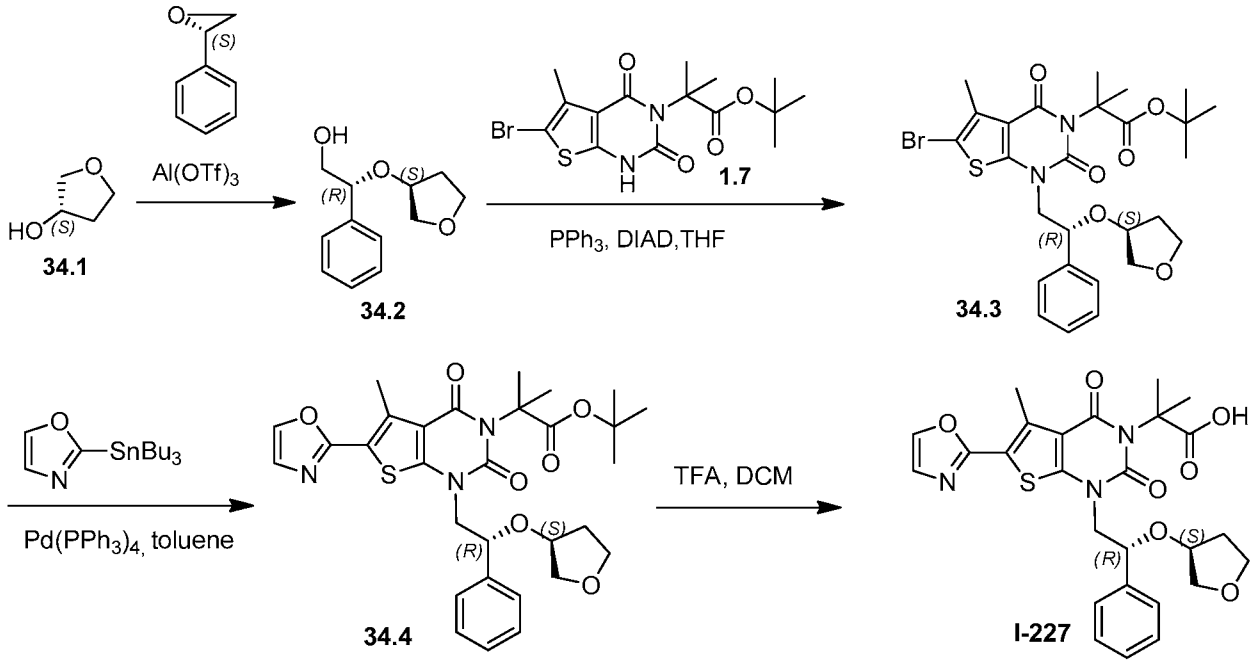


[00386] Synthesis of compound 33.4. Compound **33.4** was prepared from **33.1** in a manner analogous to the synthesis of compound **14.4**. Isolated a white solid in 6% overall yield from **33.1**.

[00387] Synthesis of Compound I-186. Into a 50-mL round-bottom flask was placed dichloromethane (5 mL), compound **33.4** (120 mg, 0.21 mmol, 1.00 equiv) and trifluoroacetic acid (1 mL). The solution was stirred for 2 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with

dichloromethane/methanol (100:1). The product (100 mg) thus obtained was repurified by flash preparative HPLC under the following conditions (IntelFlash-1): Column: C18 silica gel; mobile phase: acetonitrile:water = 0:100 increasing to acetonitrile:water = 100:0 within 25 min; detector: UV 254 nm. Purification afforded 72.7 mg (67%) of Compound **I-186** as a white solid. MS (ES): *m/z* 526 $(M+H)^+$, 548 $(M+Na)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 1.59-1.60 (m, 6H), δ 1.64-1.67 (m, 2H), 2.70 (s, 3H), 3.27-3.32 (m, 1H), 3.40-3.43 (m, 1H), 3.49-3.55 (m, 2H), 3.70-3.78 (m, 1H), 3.92 (s, 1H), 4.05-4.11 (m, 1H), 4.77-4.80 (m, 1H), 7.28-7.39 (m, 6H), 8.19 (s, 1H).

[00388] Example 34: Synthesis of 2-methyl-2-[5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1-[(2R)-2-[(3S)-oxolan-3-yloxy]-2-phenylethyl]-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-227).

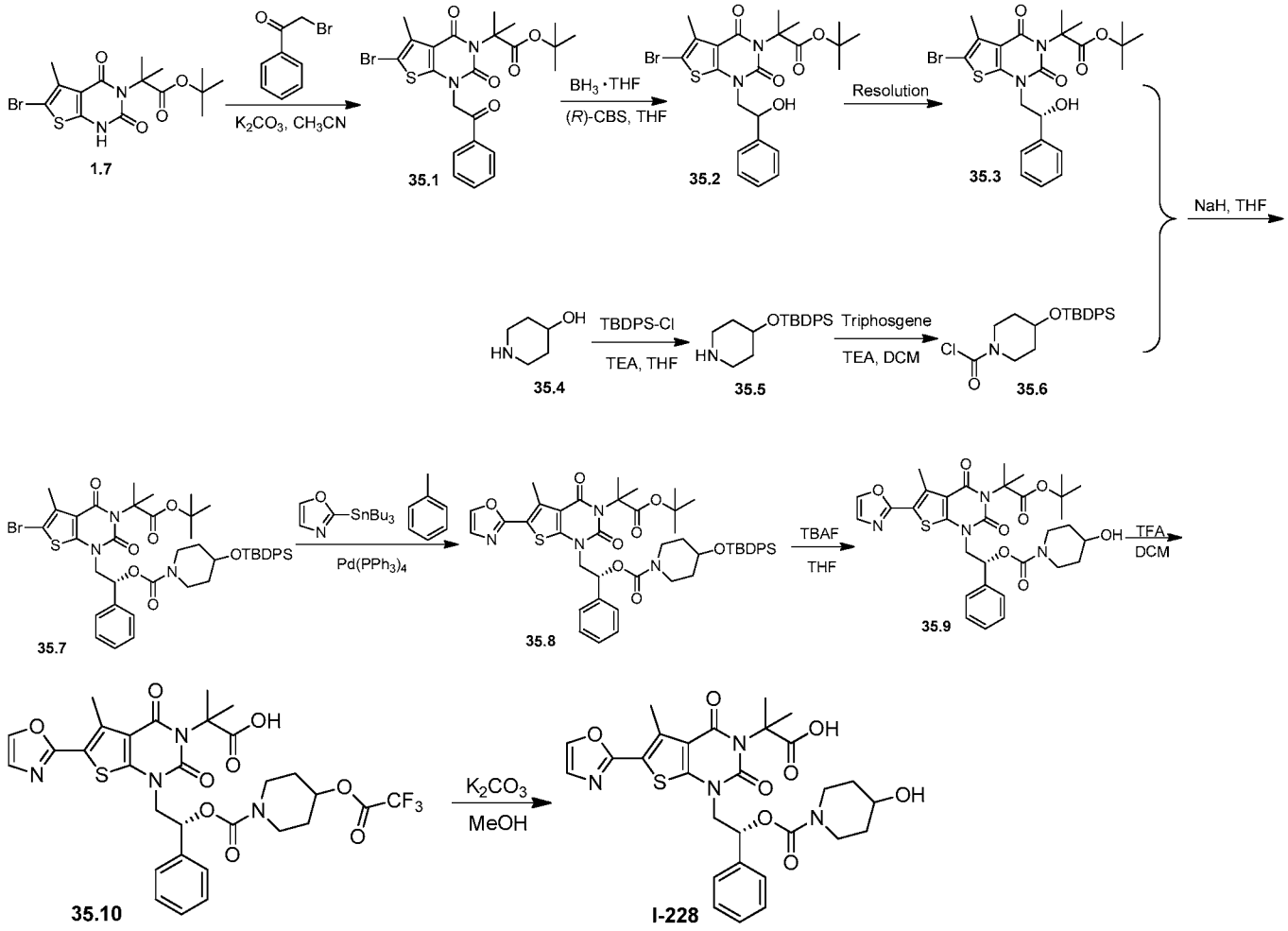


[00389] Synthesis of compound 34.4. Compound **34.4** was synthesized in a manner analogous to the synthesis of compound **33.4**. Isolated a white solid in 12% overall yield from **34.1**.

[00390] Synthesis of compound I-227. Into a 50-mL round-bottom flask was placed dichloromethane (5 mL), **34.4** (170 mg, 0.29 mmol, 1.00 equiv) and trifluoroacetic acid (1 mL). The solution was stirred for 2 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol

(100:1). The product (120 mg) thus obtained was repurified by flash preparative HPLC under the following conditions (IntelFlash-1): Column: C18 silica gel; mobile phase: acetonitrile:water = 0:100 increasing to acetonitrile:water = 100:0 within 29 min; Detector, UV 254 nm. Purification afforded 53.3 mg (35%) of Compound **I-227** as a white solid. MS (ES): *m/z* 526 $(M+H)^+$, 548 $(M+Na)^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.59-1.60 (m, 6H), 1.64-1.67 (m, 2H), 2.83 (s, 3H), 3.60-3.72 (m, 4H), 3.81-3.88 (m, 1H), 4.11-4.25 (m, 2H), 4.89-4.95 (m, 1H), 7.28 (s, 1H), 7.33-7.37 (m, 1H), 7.4 3 (t, *J* =7.6, 2H), 7.51 (d, *J* = 7.2, 2H), 7.98 (s, 1H).

[00391] Example 35: Synthesis of 2-[1-[(2R)-2-[(4-hydroxypiperidin-1-yl)carbonyloxy]-2-phenylethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-228).



[00392] Synthesis of compound 35.5. Into a 250-mL round-bottom flask was placed a solution of piperidin-4-ol (4 g, 39.55 mmol, 1.00 equiv) in tetrahydrofuran (100 mL), TEA (12 g,

118.59 mmol, 3.00 equiv) and tert-butyl(chloro)diphenylsilane (16 g, 58.21 mmol, 1.47 equiv). The resulting solution was stirred for 16 h at room temperature. The solids were filtered out. The filtrate was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:2). Purification afforded 1.1 g (8%) of 4-[(tert-butyldiphenylsilyl)oxy]piperidine as a colorless oil.

[00393] Synthesis of compound 35.6. Into a 50-mL round-bottom flask was placed a solution of 4-[(tert-butyldiphenylsilyl)oxy]piperidine (1.00 g, 2.95 mmol, 1.00 equiv) in dichloromethane (20 mL), triethylamine (780 mg, 7.71 mmol, 2.62 equiv), ditrichloromethyl carbonate (2.07 g, 6.98 mmol, 2.37 equiv). The resulting solution was stirred overnight at room temperature whereupon it was diluted with 40 mL of DCM and washed with 3x15 mL of water and 2x20 mL of sodium chloride (sat.). The combined organic solutions were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:4). Purification afforded 1.15 g (97%) of **35.6** as a light yellow oil.

[00394] Synthesis of compound 35.1. To a solution of intermediate **1.7** (1.5 g, 3.72 mmol, 1.00 equiv) in CH_3CN (20 mL) were added potassium carbonate (1.54 g, 11.14 mmol, 3.00 equiv) and 2-bromo-1-phenylethan-1-one (770 mg, 3.87 mmol, 1.05 equiv). The resulting solution was stirred for 3 h at room temperature. The reaction was then quenched by the addition of 20 mL of water. The resulting solution was extracted with 3x30 mL of ethyl acetate and the organic layers combined. The resulting mixture was washed with 2x40 mL of sodium chloride (sat.). The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). Purification afforded 1.8 g (93%) of **35.1** as a white solid.

[00395] Synthesis of compound 35.2. Into a 50-mL round-bottom flask was placed a solution of **35.1** (1.5 g, 2.88 mmol, 1.00 equiv) in tetrahydrofuran (15 mL) and (*R*)-CBS (239 mg, 0.86 mmol, 0.30 equiv). This was followed by the addition of a solution of BH_3-THF (4 mL, 1.50 equiv) in tetrahydrofuran (5 mL) dropwise with stirring over 8 hr. The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 15 mL of NH_4Cl (sat.). The resulting solution was extracted with 3x20 mL of ethyl acetate and the organic layers combined. The resulting mixture was washed with 2x30 mL of sodium chloride (sat.). The mixture was dried and concentrated. The residue was applied onto a silica gel column

with ethyl acetate/petroleum ether (1:15). Purification afforded 1.4 g (93%) of **35.2** as a white solid.

[00396] **Synthesis of compound 35.3.** The enantiomers of compound **35.2** (1.4 g, 2.67 mmol, 1.00 equiv) were separated by preparative SFC under the following conditions: Column: Phenomenex Lux 5u Cellulose-3, 5*25 cm,5 μm; mobile phase: CO_2 (80%), methanol (20%); detector: UV 254 nm. Purification afforded 0.98 g of **35.3** as a white solid.

[00397] **Synthesis of compound 35.7.** To a solution of **35.3** (300 mg, 0.57 mmol, 1.00 equiv) in tetrahydrofuran (10 mL) was added sodium hydride (69 mg, 1.73 mmol, 3.00 equiv, 60%) at 0 °C under N_2. The mixture was stirred for 30 min and then a solution of **35.6** (238 mg, 0.59 mmol, 1.50 equiv) in tetrahydrofuran (3 mL) was added. The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 10 mL of water. The resulting solution was extracted with 3x20 mL of ethyl acetate and the organic layers combined. The resulting mixture was washed with 2x20 mL of sodium chloride (sat.). The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:6). Purification afforded 360 mg (71%) of **35.7** as a white solid.

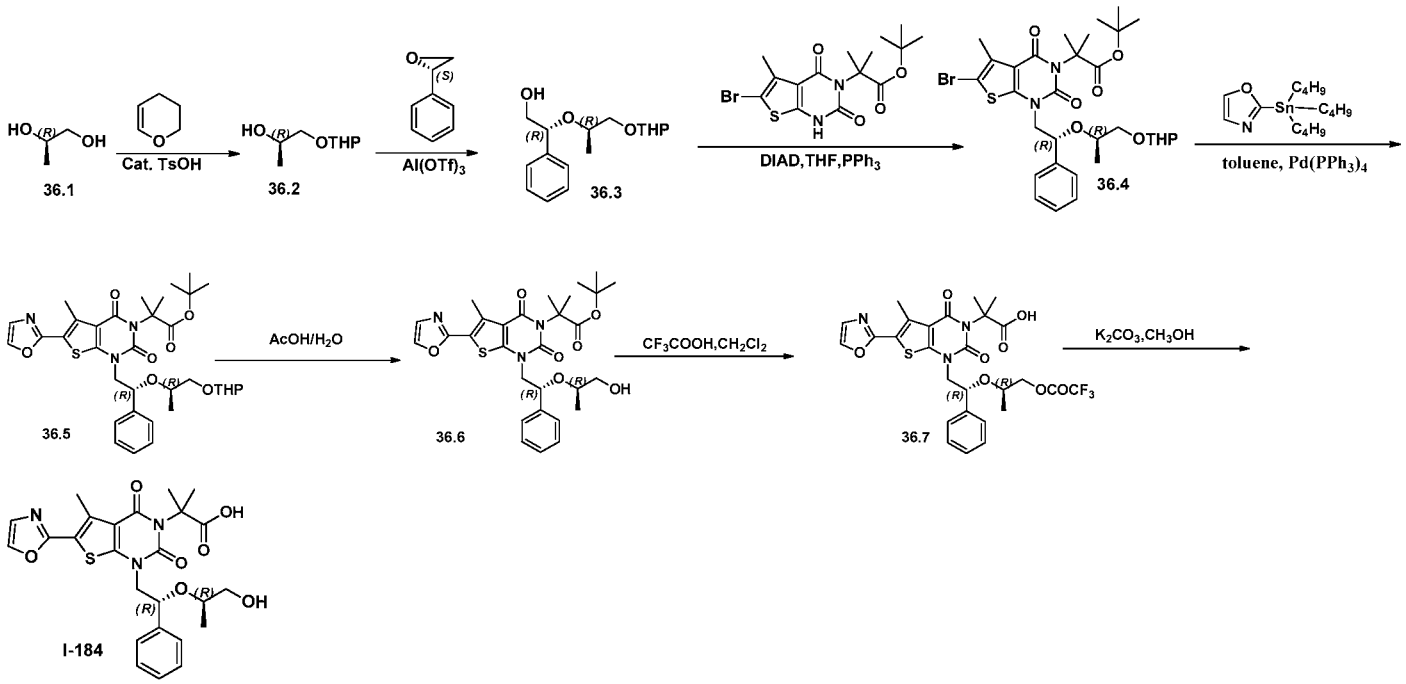
[00398] **Synthesis of compound 35.8.** Into a 25-mL round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed **35.7** (140 mg, 0.16 mmol, 1.00 equiv), $Pd(PPh_3)_4$ (28 mg, 0.02 mmol, 0.15 equiv), 2-(tributylstannyl)-1,3-oxazole (85 mg, 0.24 mmol, 1.51 equiv) and toluene (5 mL). The resulting solution was stirred overnight at 110 °C. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:40). Purification afforded 100 mg (72%) of **35.8** as a colorless oil.

[00399] **Synthesis of compound 35.9.** Into a 50-mL round-bottom flask was placed tetrahydrofuran (5 mL) and **35.8** (100 mg, 0.11 mmol, 1.00 equiv). This was followed by the addition of TBAF (33 mg, 0.13 mmol, 1.11 equiv) in portions. The resulting solution was stirred for 2 h at room temperature. The reaction was then quenched by the addition of 0.5 mL of water. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). Purification afforded 50 mg (69%) of **35.9** as a yellow oil.

[00400] **Synthesis of compound 35.10.** Into a 50-mL round-bottom flask was placed dichloromethane (5 mL), **35.9** (50 mg, 0.08 mmol, 1.00 equiv) and trifluoroacetic acid (1 mL). The resulting solution was stirred for 2 h at room temperature and then concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (100:1). Purification afforded 40 mg (crude) of **35.10** as a colorless oil.

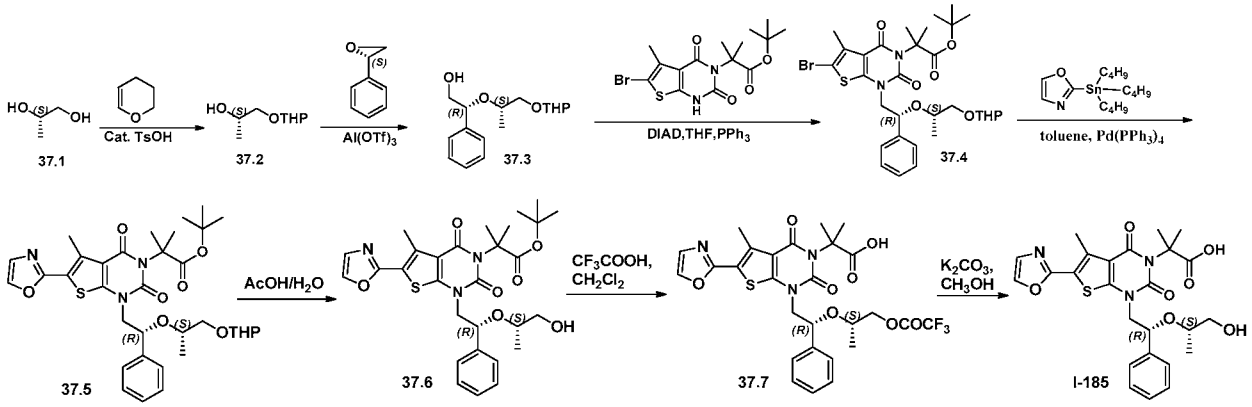
[00401] **Synthesis of Compound I-228.** Into a 50-mL round-bottom flask was placed **35.10** (40 mg, 0.06 mmol, 1.00 equiv), potassium carbonate (21 mg, 0.15 mmol, 2.58 equiv) and methanol (5 mL). The resulting solution was stirred for 2 h at room temperature. The solids were filtered out. The pH value of the filtrate was adjusted to 6 with TFA. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (100:1). Purification afforded 22.7 mg (66%) of Compound **I-228** as a white solid. MS (ES): *m/z* 583 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.05-1.40 (m, 2H), 1.67-1.74 (m, 2H), 1.80 (s, 6H), 2.84 (s, 3H), 3.03-3.23 (m, 2H), 3.50-4.16 (m, 4H), 4.33-4.43 (m, 1H), 6.19-6.22 (m, 1H), 7.29 (s, 1H), 7.36-7.51 (m, 5H), 7.99 (s, 1H).

[00402] **Example 36: Synthesis of 2-[1-[(2R)-2-[[(2R)-1-hydroxypropan-2-yl]oxy]-2-phenylethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-184).**



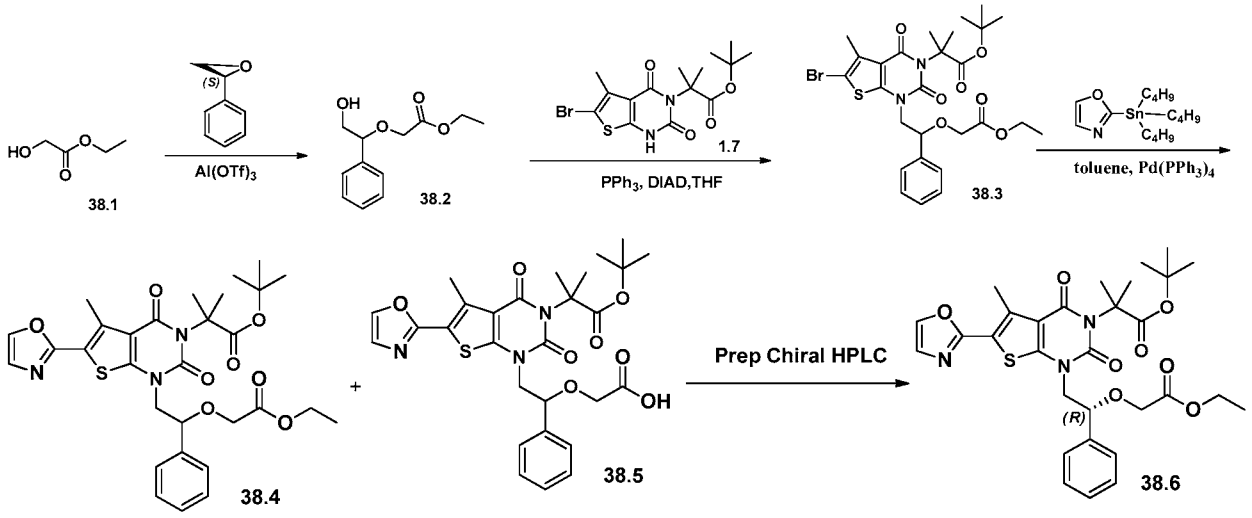
[00403] Compound **I-184** was prepared in a manner analogous to Example 31. Purification: Thin layer chromatography developed with dichloromethane/methanol (40:1). Isolated a white solid in 0.17% overall yield from **36.1**. MS (ES): *m/z* 514 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ 0.94 (s, 3H), 1.75-1.78 (d, 6H), 2.77 (s, 3H), 3.42-3.47 (m, 2H), 3.87-3.95 (m, 1H), 4.11-4.17 (m, 1H), 4.94-4.98 (m, 1H), 7.24-7.50 (m, 6H), 7.94 (s, 1H).

[00404] Example 37: Synthesis of 2-[1-[(2R)-2-[[(2S)-1-hydroxypropan-2-yl]oxy]-2-phenylethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-185).



[00405] Compound **I-185** was synthesized in a manner analogous to Example 31. Isolated a white solid in 0.061% overall yield from **37.1**. MS (ES): *m/z* 514 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ 0.94 (s, 3H), 1.76 (s, 6H), 2.76 (s, 3H), 3.42-3.48 (m, 2H), 3.89-3.97 (m, 1H), 4.08-4.14 (m, 1H), 5.03-5.08 (m, 1H), 7.24-7.45 (m, 6H), 7.94 (s, 1H).

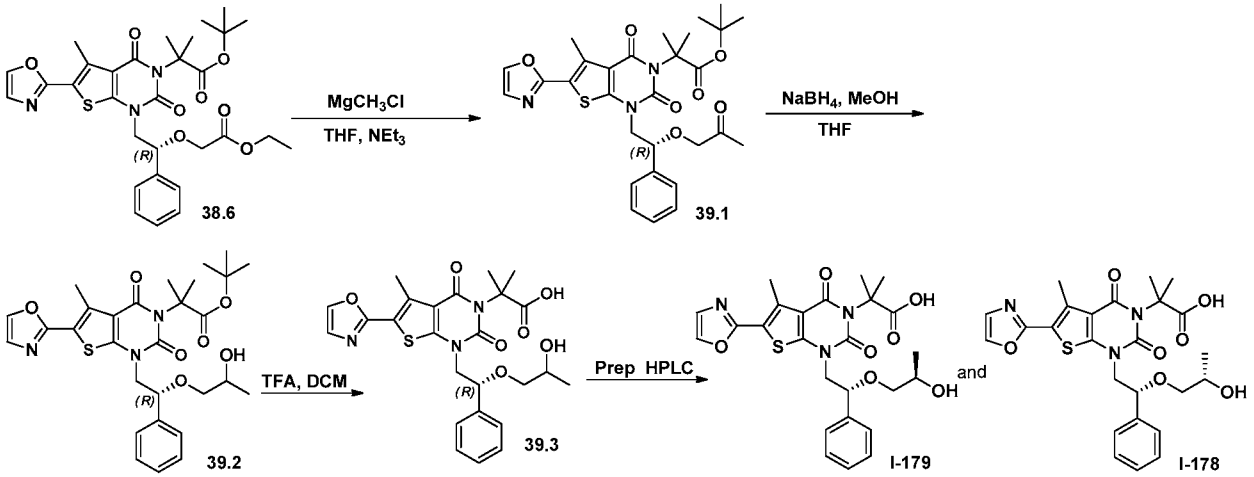
[00406] Example 38: Synthesis of Intermediate 38.6.



[00407] **Synthesis of compound 38.4.** Compound **38.4** was prepared from **38.1** in a manner analogous to the synthesis of compound **14.4**. Isolated a white solid in 16% overall yield from **1.7** (1.1% from **38.1**). The by-product **38.5** was also isolated.

[00408] **Synthesis of compound 38.6.** The enantiomers of **38.4** (240 mg) were separated by chiral preparative HPLC under the following conditions (Gilson Gx 281): Column: Chiralpak IC(SFC), 2*25 cm, 5 μm; mobile phase: hexanes and ethanol (hold at 25.0% ethanol for 25 min); detector: UV 220/254. 160 mg of a white solid product were obtained.

[00409] **Example 39: Synthesis of 2-[1-[(2R)-2-[(2R)-2-hydroxypropoxy]-2-phenylethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-179) and Example 40: 2-[1-[(2R)-2-[(2S)-2-hydroxypropoxy]-2-phenylethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-178).**



[00410] **Synthesis of compound 39.1.** Into a 100-mL 3-necked round-bottom flask was placed **38.6** (160 mg, 0.27 mmol, 1.00 equiv), tetrahydrofuran (20 mL) and Et_3N (54.1 mg, 0.54 mmol, 2.00 equiv). This was followed by the addition of chloro(methyl)magnesium (0.26 mL, 3M) in portions. The resulting solution was stirred for 3 h at -50 °C. The reaction was then quenched by the addition of 20 mL of NH_4Cl (sat., aq). The resulting solution was extracted with 2x30 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:15). Purification afforded 40 mg (26%) of **39.1** as a white solid.

[00411] **Synthesis of compound 39.2.** Into a 25-mL round-bottom flask was placed **39.1** (40 mg, 0.07 mmol, 1.00 equiv), methanol (10 mL) and $NaBH_4$ (2.6 mg, 0.07 mmol, 0.98 equiv).

The resulting solution was stirred for 3 h at room temperature. The reaction was then quenched by the addition of 10 mL of water. The resulting solution was extracted with 2x15 mL of ethyl acetate and the organic layers combined and dried in an oven under reduced pressure. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:2). Purification afforded 30 mg (75%) of **39.2** as a white solid.

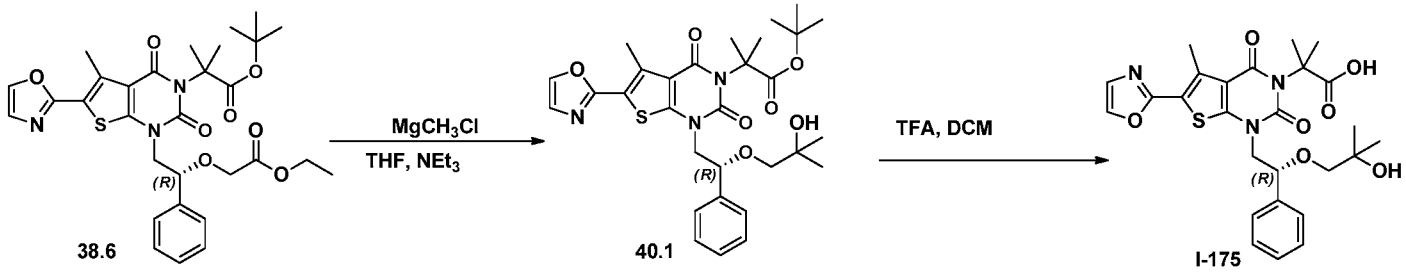
[00412] Synthesis of compound 39.3. Into a 25-mL round-bottom flask was placed **39.2** (30 mg, 0.05 mmol, 1.00 equiv), dichloromethane (5 mL) and trifluoroacetic acid (1 mL). The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by thin layer chromatography developed with dichloromethane/methanol (20:1) to afford 20 mg (74%) of **39.3** as a white solid.

[00413] Resolution of compounds I-179 and I-178. The enantiomers of **39.3** (20 mg) were purified by preparative HPLC under the following conditions (Waters): Column: XBridge Prep Phenyl OBD 5 μm, 19*150 mm; mobile phase: water (50 mM NH_4HCO_3) and CH_3CN (5.0% CH_3CN up to 95.0% in 10 min, hold at 95.0% in 2 min then down to 5.0% in 2 min); detector: UV 254/220 nm. Purification afforded 6.7 mg (34%; tR = 8.55 min) of Compound **I-179** as a white solid and 2.3 mg (12%, tR = 9.47 min) of Compound **I-178** as a white solid.

Analytical data for Compound I-179: MS (ES): *m/z* 514 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ 0.94 (d, *J* = 6.3Hz, 3H), 1.75 (s, 6H), 2.76 (s, 3H), 3.05 (m, 1H), 3.76 (m,1H), 3.92 (m, 1H), 4.16 (m, 1H), 7.22-7.46 (m, 6H), 7.92 (s, 1H).

Analytical data for Compound I-178: MS (ES): *m/z* 514 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ 0.94 (d, *J* = 6.3Hz, 3H), 1.75 (s, 6H), 2.76 (s, 3H), 3.05 (m, 1H), 3.76 (m,1H), 3.94 (m, 1H), 4.16 (m, 1H), 7.22-7.48 (m, 6H), 7.93 (s, 1H).

[00414] Example 40: Synthesis of 2-[1-[(2R)-2-(2-hydroxy-2-methylpropoxy)-2-phenylethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-175).

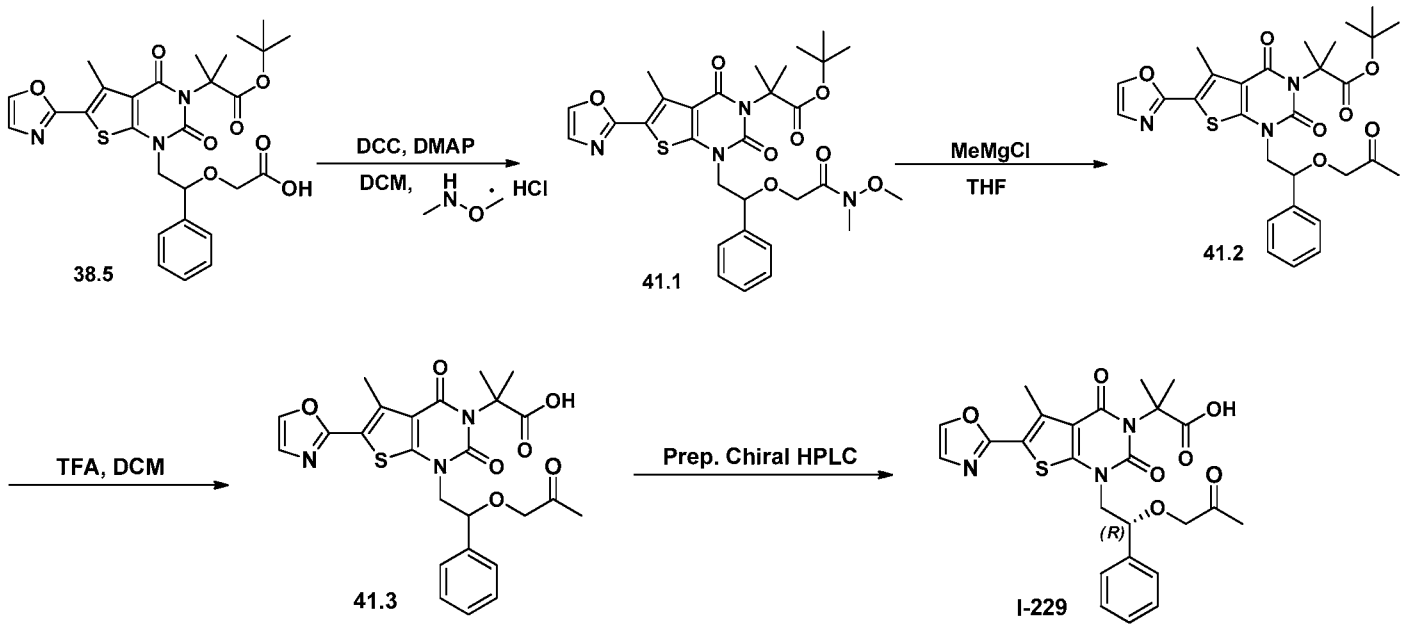


38.6 40.1 I-175

[00415] Synthesis of compound 40.1. Into a 25-mL round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed intermediate **38.6** (160 mg, 0.27 mmol, 1.00 equiv), tetrahydrofuran (10 mL), Et_3N (54.1 mg, 0.54 mmol, 2.00 equiv). This was followed by the addition of chloro(methyl)magnesium (0.26 mL, 3 M) dropwise with stirring at -78 °C. The resulting solution was stirred for 3 h at -50 °C. The reaction was then quenched by the addition of 10 mL of NH_4Cl (sat., aq.). The resulting solution was extracted with 3x15 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). Purification afforded 40 mg (26%) of **40.1** as a white solid.

[00416] Synthesis of Compound I-175. Into a 25-mL round-bottom flask was placed compound **40.1** (40 mg, 0.07 mmol, 1.00 equiv), dichloromethane (5 mL) and trifluoroacetic acid (1 mL). The resulting solution was stirred for 2 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (20:1). Purification afforded 23.4 mg (65%) of Compound **I-175** as a white solid. MS (ES): *m/z* 528 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ 0.97 (s, 3H), 1.03 (s, 3H), 1.77 (s, 6H), 2.76 (s, 6H), 3.00 (d, *J* = 9.0 Hz, 1H), 3.13 (d, *J* = 9.0Hz, 1H), 3.91 (dd, *J* = 14.4, 9.0 Hz, 1H), 4.19 (dd, *J* = 14.4, 3.9 Hz, 1H), 7.24-7.44 (m, 6H) , 7.92 (s, 1H).

[00417] Example 41: Synthesis of 2-methyl-2-[5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1-[(2R)-2-(2-oxopropoxy)-2-phenylethyl]-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-229).



[00418] **Synthesis of compound 41.1.** Compound **I-229** was prepared in a manner analogous to Compound **I-121** (Example 4). Isolated 100 mg (46%) of **41.1** as a white solid.

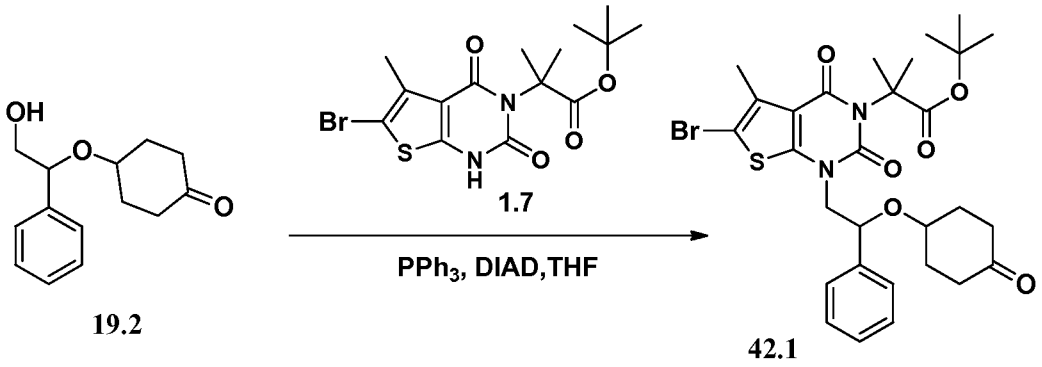
[00419] **Synthesis of compound 41.2.** Into a 50-mL 3-necked round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed **41.1** (100 mg, 0.16 mmol, 1.00 equiv) and tetrahydrofuran (10 mL). This was followed by the addition of chloro(methyl)magnesium (3 M) (0.05 mL, 2.00 equiv) dropwise with stirring at -50 °C. The resulting solution was stirred for 2 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:2). Purification afforded 55 mg (59%) of **41.2** as a white solid.

[00420] **Synthesis of compound 41.3.** Into a 10-mL round-bottom flask was placed trifluoroacetic acid (1 mL), **41.2** (55 mg, 0.10 mmol, 1.00 equiv) and dichloromethane (5 mL). The solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (40:1). Purification afforded 10 mg (20%) of **41.3** as a white solid.

[00421] **Synthesis of Compound I-229.** The crude product (1 g) was purified by chiral preparative HPLC under the following conditions (Gilson Gx 281): Column: Chiralpak IC, 2*25 cm, 5 μm; mobile phase: hexanes (0.1% TFA) and ethanol (0.1%TFA) (hold at 15% ethanol (0.1% TFA) in 30 min); detector: UV 220/254 nm. Purification afforded 3.0 mg (30%) of Compound **I-229** as a white solid. MS (ES): *m/z* 512 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ

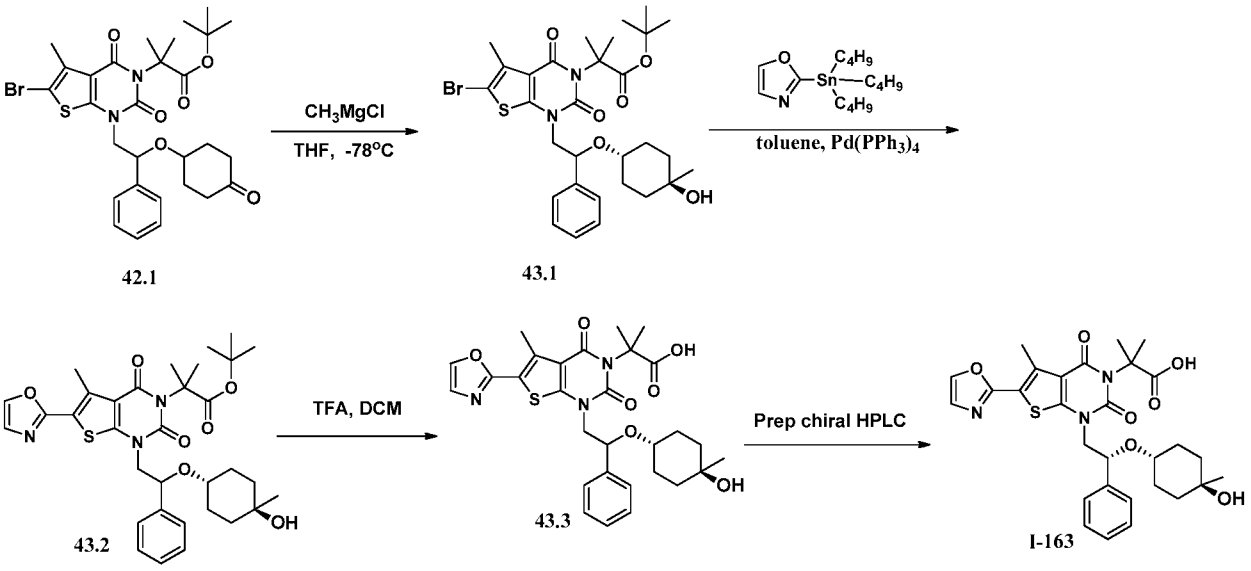
1.82 (s, 6H), 1.98 (s, 3H), 2.81 (s, 3H), 3.88-4.07 (m, 3H), 4.26 (d, 1H), 4.94 (m, 1H), 7.37 (s, 1H), 7.38-7.49 (m, 5H), 7.98 (s, 1H).

[00422] Example 42: Synthesis of intermediate 42.1.



[00423] Synthesis of intermediate 42.1. Into a 250-mL 3-necked round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed **19.2** (1.6 g, 6.83 mmol, 1.84 equiv), tetrahydrofuran (60 mL), DIAD (1.5 g, 7.42 mmol, 1.99 equiv), PPh_3 (1.9 g, 7.24 mmol, 1.95 equiv) and **1.7** (1.5 g, 3.72 mmol, 1.00 equiv). The resulting solution was stirred for 4 h at room temperature and then concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:50). Purification afforded 1 g (43%) of intermediate **42.1** as a white solid.

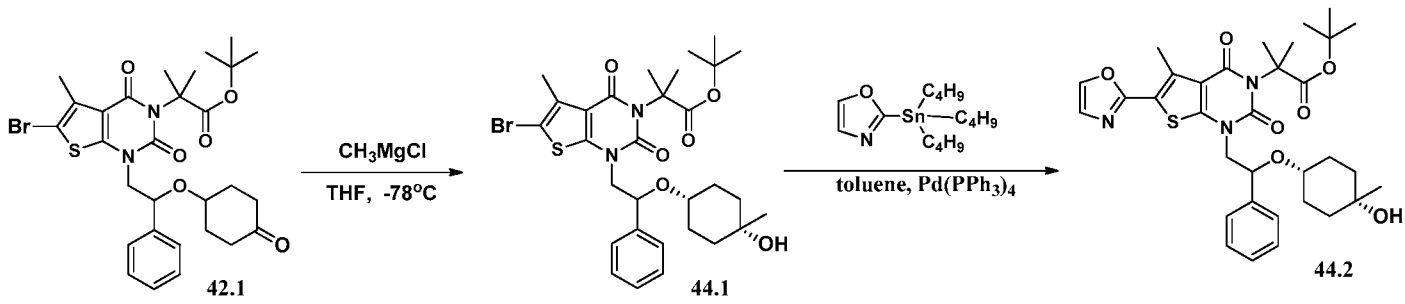
[00424] Example 43: Synthesis of 2-(1-((R)-2-(((1r,4R)-4-hydroxy-4-methylcyclohexyl)oxy)-2-phenylethyl)-5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)-2-methylpropanoic acid (I-163).

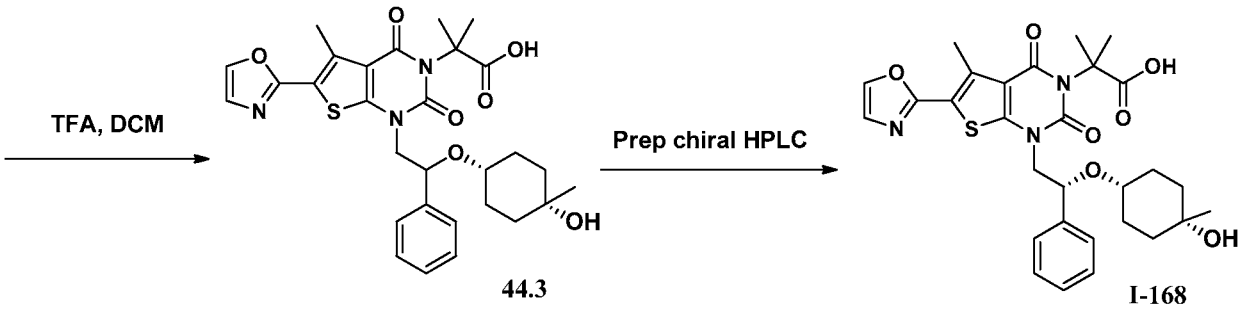


[00425] **Synthesis of compound 43.1.** Into a 50-mL 3-necked round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed intermediate **42.1** (500 mg, 0.81 mmol, 1.00 equiv) and tetrahydrofuran (25 mL). This was followed by the addition of chloro(methyl)magnesium (0.52 mL, 3 M) dropwise with stirring at -78 °C. The resulting solution was stirred for 4 h at -50 °C in a liquid nitrogen bath. The reaction was then quenched by the addition of 10 mL of NH_4Cl (sat., aq.). The resulting solution was extracted with 2x30 mL of ethyl acetate and the organic layers combined, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). Purification afforded 125 mg (24%) of **43.1** as a white solid.

[00426] **Synthesis of compound I-163.** Compound **I-163** was was prepared from **43.1** in a manner analogous to Example 14. Purification conditions: The enantiomers of **43.3** (40 mg) were purified by chiral preparative HPLC under the following conditions (Gilson Gx 281): Column: Chiralpak IC, 2*25 cm, 5 μm; mobile phase: hexanes and ethanol (hold at 20.0% ethanol for 12 min); detector: UV 220/254 nm. 6.8 mg (white solid) product was obtained in 0.13% overall yield from **42.1.**. MS (ES): *m/z* 568 $(M+H)^+$, 590 $(M+Na)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 0.91 (s, 3H), 1.03 (m, 2H), 1.21-1.42 (m, 6H), 1.61 (s, 6H), 2.69 (s, 3H), 3.03 (m, 1H), 3.61-4.07 (m, 3H), 4.82 (m, 1H), 7.28-7.37 (m, 6H) , 8.17 (s, 1H).

[00427] **Example 44: Synthesis of 2-(1-((R)-2-(((1s,4S)-4-hydroxy-4-methylcyclohexyl)oxy)-2-phenylethyl)-5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)-2-methylpropanoic acid (I-168).**

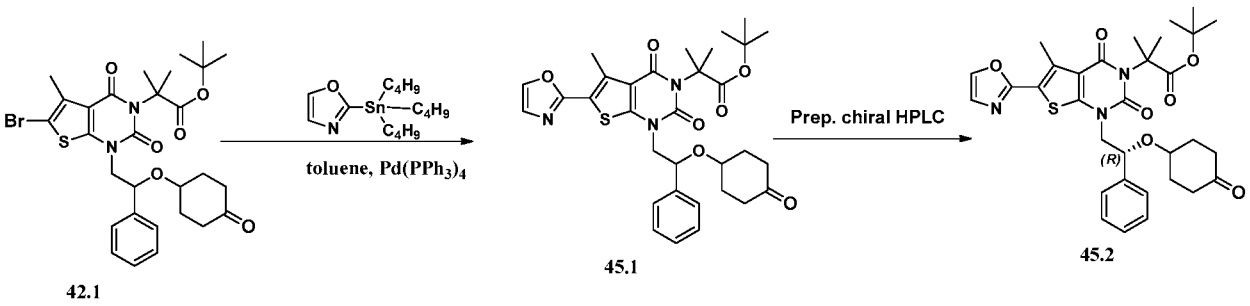




44.3 I-168

[00428] Compound **I-168** was prepared in a manner analogous to Example 43. Isolated a white solid in 5.1% overall yield from **42.1**. MS (ES): *m/z* 568 $(M+H)^+$, 590 $(M+Na)^+$. ^1H NMR (300 MHz, CD_3OD): δ 0.81 (s, 3H), 0.99 (m, 1H), 1.14 (m, 2H), 1.25-1.61 (m, 5H), 1.78 (m, 6H), 2.77 (s, 3H), 3.51 (m,1H), 3.71 (m, 1H), 4.33 (m, 1H), 4.92 (m, 1H), 7.25-7.47 (m, 6H) , 7.95(s, 1H).

[00429] Example 45: Synthesis of intermediate 45.2.

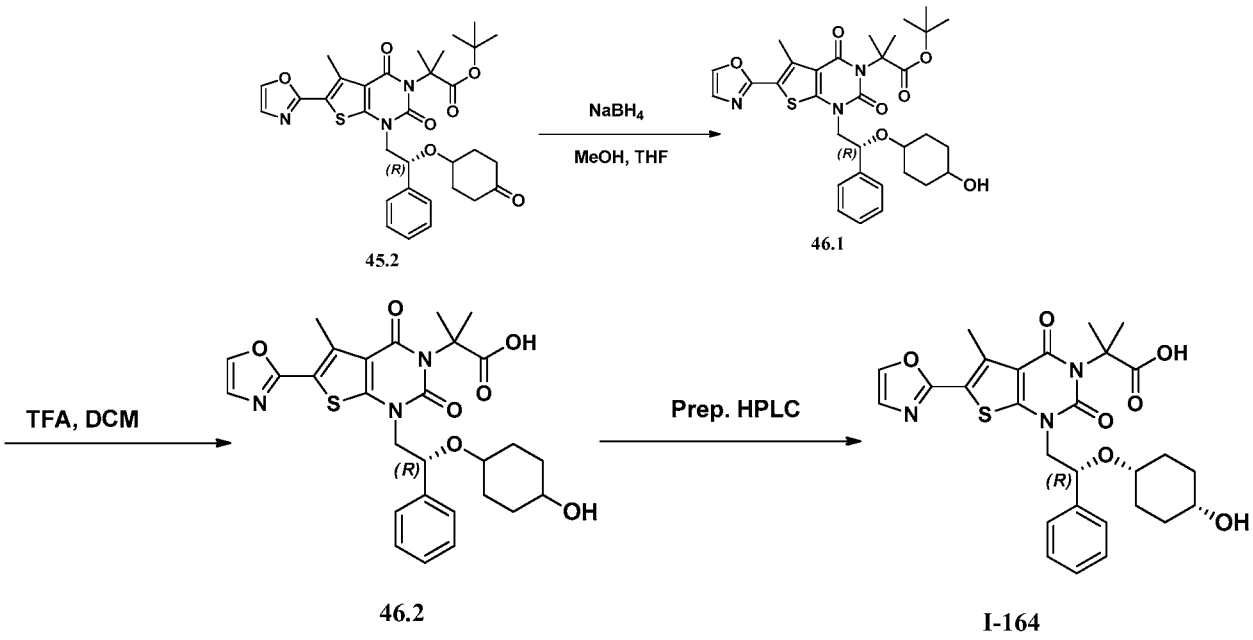


42.1 45.1 45.2

[00430] Synthesis of compound 45.1. Compound **45.1** was prepared from 2-(tributylstannyl)oxazole and **42.1** in a manner analogous to the synthesis of **I-120** (Example 2). Isolated a white solid in 45% yield.

[00431] Synthesis of intermediate 45.2. The enantiomers of racemic **45.1** (220 mg) were separated by chiral preparative HPLC under the following conditions (Gilson Gx 281): Column: Chiralpak IC, 2*25 cm, 5 μm; mobile phase: hexanes (0.1%TEA) and IPA (hold at 25.0% IPA for 40 min); detector: UV 220/254 nm. 80 mg (white solid) of the product were obtained.

[00432] Example 46: Synthesis of 2-[1-[(2R)-2-[(4-hydroxycyclohexyl)oxy]-2-phenylethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-164).

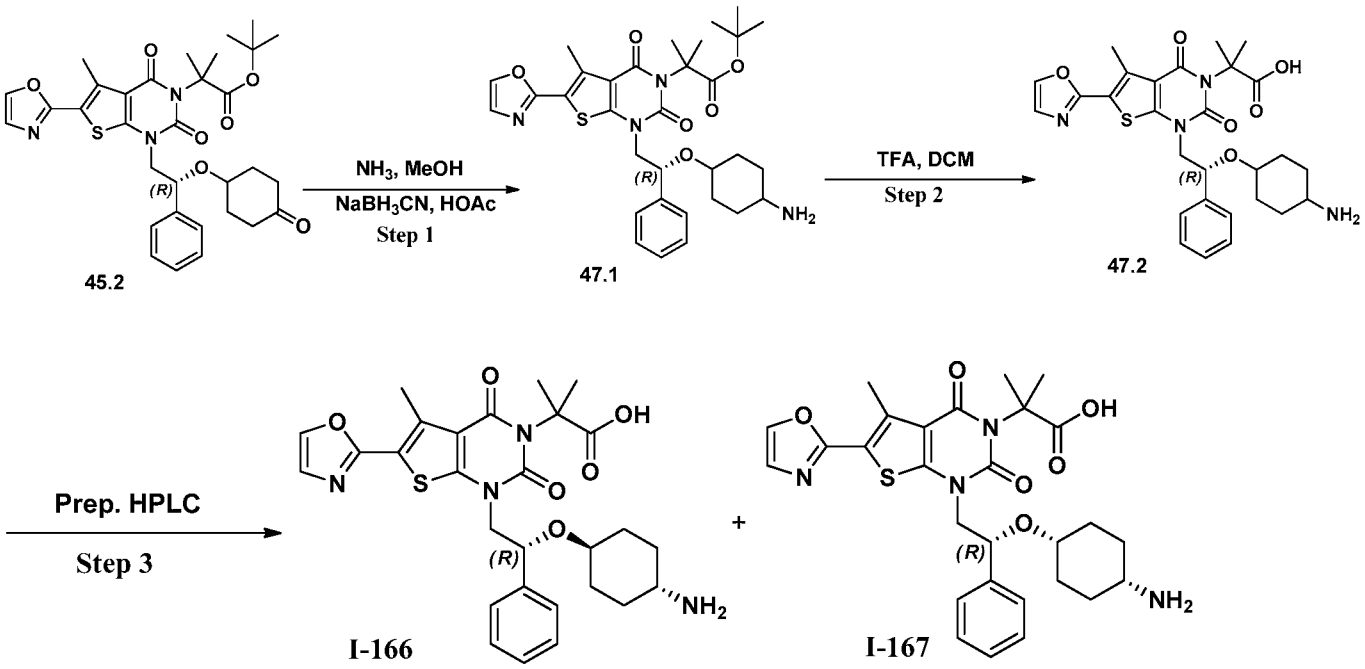


45.2 46.1 46.2 I-164

[00433] **Synthesis of 46.1**. Into a 50-mL round-bottom flask was placed intermediate **45.2** (40 mg, 0.07 mmol, 1.00 equiv), methanol (10 mL) and $NaBH_4$ (3.7 mg, 0.10 mmol, 1.53 equiv). The resulting solution was stirred for 3 h at room temperature whereupon it was concentrated under vacuum. The residue was purified by preparative TLC with ethyl acetate/petroleum ether (1:5) to afford 35 mg (87%) of **46.1** as a white solid.

[00434] **Synthesis of Compound I-164**. Compound **I-164** was prepared from **46.1** in a manner analogous to compound **2.5**. Isolated a white solid in 28% yield from **46.1**. Purification conditions: The crude product (30 mg) was purified by preparative HPLC under the following conditions (Waters): Column: XBridge Shield RP18 OBD column, 5 μm, 19*150 mm; mobile phase: water (50 mM NH_4HCO_3) and CH_3CN (6.0% CH_3CN up to 50.0% in 14 min); detector: UV 254/220 nm. Purification afforded 9 mg of Compound **I-164** (tR = 7.86 min) as a white solid. MS (ES): *m/z* 554 $(M+H)^+$, 576 $(M+Na)^+$, 617 $(M+Na+CH_3CN)^+$.

[00435] **Example 47: Synthesis of 2-(1-((R)-2-(((1r,4R)-4-aminocyclohexyl)oxy)-2-phenylethyl)-5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)-2-methylpropanoic acid (I-166) and Example 48: Synthesis of 2-(1-((R)-2-(((1s,4S)-4-aminocyclohexyl)oxy)-2-phenylethyl)-5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)-2-methylpropanoic acid (I-167).**



[00436] Synthesis of compound 47.1. Into a 50-mL round-bottom flask was placed intermediate **45.2** (40 mg, 0.07 mmol, 1.00 equiv), methanol/NH_3 (10 mL), acetic acid (4 mg, 0.07 mmol, 1.01 equiv) and $NaBH_3CN$ (8 mg, 0.13 mmol, 1.93 equiv). The resulting solution was stirred overnight at room temperature whereupon it was concentrated under vacuum. The residue was purified by preparative TLC with DCM/methanol (1:20) to afford 26 mg (65%) of **47.1** as a white solid.

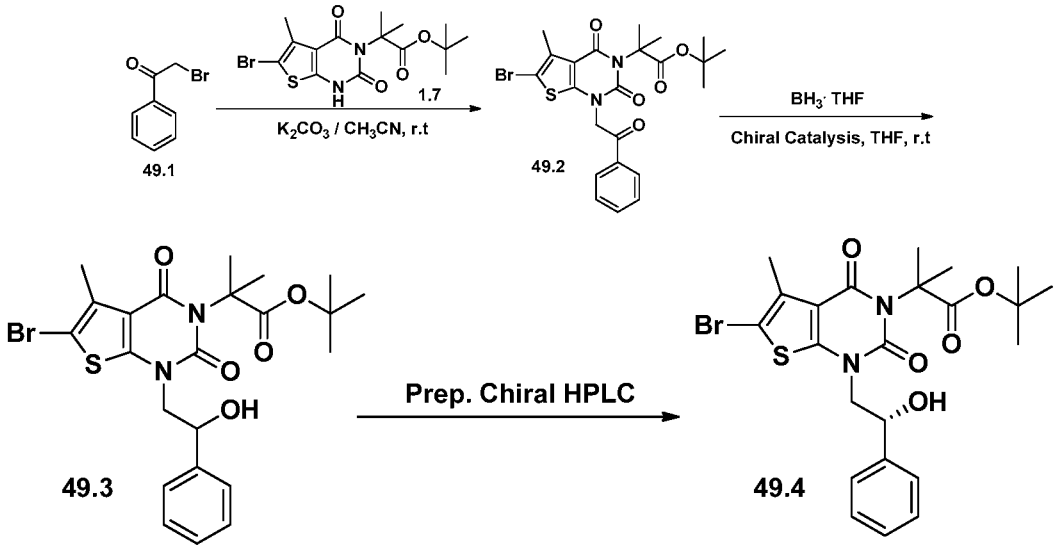
[00437] Synthesis of compound 47.2. Compound **47.2** was prepared from **47.1** in a manner analogous to compound **2.5**. Isolated a white solid in 64% yield.

[00438] Synthesis of Compounds I-166 and I-167. The enantiomers of **47.2** (15 mg) were separated by preparative HPLC under the following conditions (Waters): Column: XBridge Shield RP18 OBD Column, 5 μm, 19*150 mm; mobile phase: water (with 50 mM NH_4HCO_3) and CH_3CN (20.0% CH_3CN up to 80.0% in 25 min); detector: UV 254/220 nm. 0.6 mg of Compound **I-166** (tR = 18.73 min; white solid, 5.1% yield from **47.2**) and 0.5 mg of Compound **I-167** (tR = 22.06 min; white solid, 1.9% yield from **47.2**) were obtained.

Analytical data for Compound I-166: MS (ES): *m/z* 553 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ 0.82-0.86 (m, 2H), 1.09-1.26 (m, 12H), 1.76-1.95 (m, 10H), 2.77 (s, 3H), 3.41-3.70 (m, 2H), 4.96-5.01 (m, 2H), 7.23-7.47 (m, 6H), 7.93 (s, 1H).

Analytical data for Compound I-167: MS (ES): *m/z* 553 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.18 -1.78 (m, 14H), 1.90-1.95 (m, 1H), 2.79 (s, 3H), 2.86-2.91 (m, 1H), 3.45-3.51 (m, 1H), 3.92-3.96 (m, 1H), 4.23 (m, 1H), 4.85-5.04 (m, 1H), 7.25-7.57 (m, 6H), 7.95 (s, 1H).

[00439] Example 49: Synthesis of Intermediate 49.4.

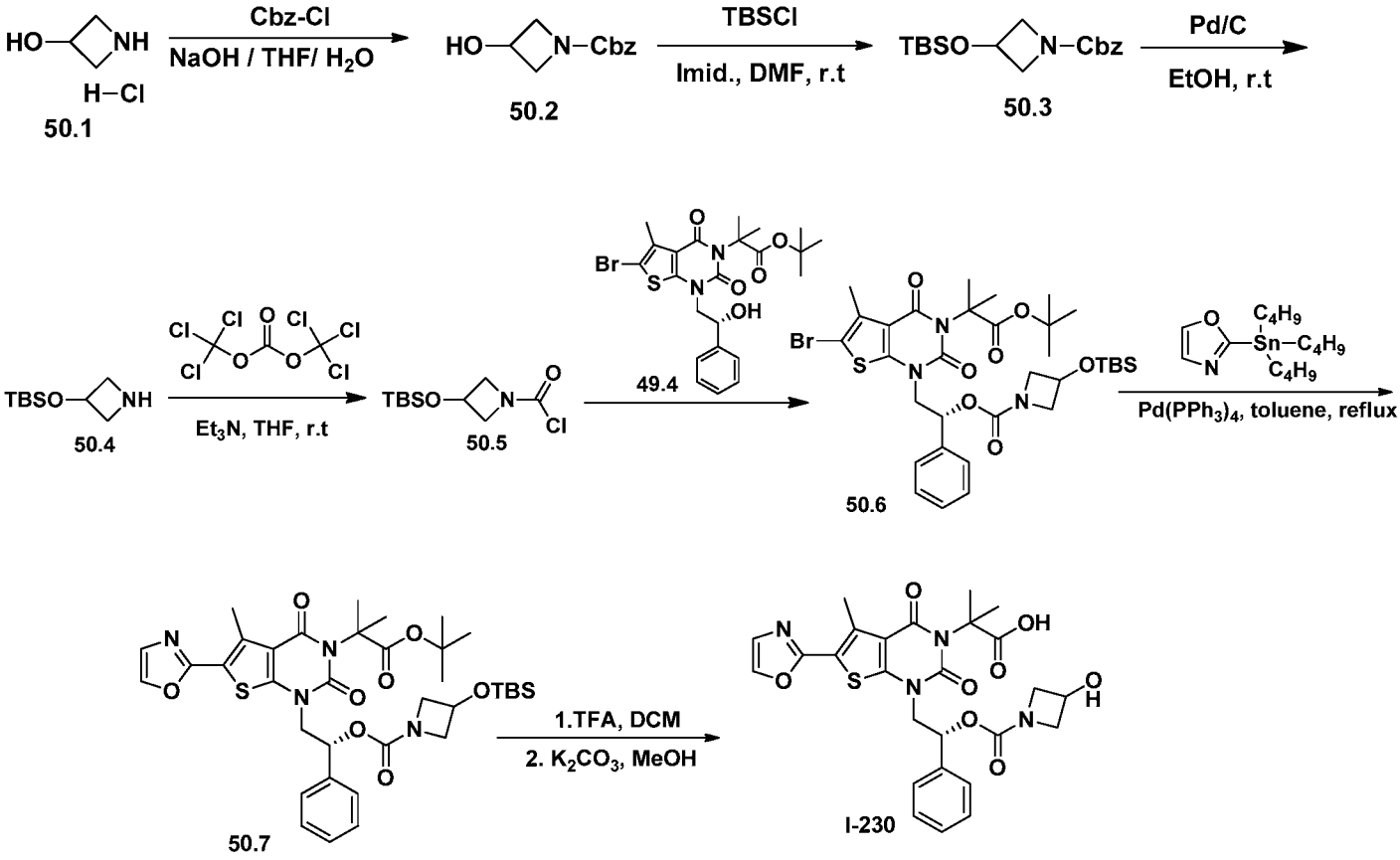


[00440] Synthesis of compound 49.2. To a solution of **1.7** (1.5 g, 3.72 mmol, 1.00 equiv) in CH_3CN (20 mL) were added potassium carbonate (1.54 g, 11.14 mmol, 3.00 equiv) and 2-bromo-1-phenylethan-1-one (770 mg, 3.87 mmol, 1.05 equiv). The resulting solution was stirred for 3 h at room temperature. The reaction was then quenched by the addition of 20 mL of water. The mixture was extracted with 3x30 mL of ethyl acetate and the organic layers combined, washed with 2x40 mL of sodium chloride (sat.), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). Purification afforded 1.8 g (93%) of **49.2** as a white solid.

[00441] Synthesis of compound 49.3. Into a 50-mL round-bottom flask was placed a solution of **49.2** (1.5 g, 2.88 mmol, 1.00 equiv) and (*R*)-CBS (239 mg, 0.86 mmol, 0.30 equiv) in tetrahydrofuran (15 mL). This was followed by the addition of a solution of BH_3-THF (4 mL, 1.50 equiv) in tetrahydrofuran (5 mL) dropwise with stirring in 8 hr. The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 15 mL of NH_4Cl (sat., aq.). The mixture was extracted with 3x20 mL of ethyl acetate and the organic layers combined and washed with 2x30 mL of sodium chloride (sat.). The solid was dried in an oven under reduced pressure. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:15). Purification afforded 1.4 g (93%) of **49.3** as a white solid.

[00442] **Synthesis of compound 49.4.** The enantiomers of **49.3** (1.4 g, 2.67 mmol, 1.00 equiv) were separated by preparative SFC under the following conditions: Column: Phenomenex Lux 5u Cellulose-3, 5*25 cm, 5 μm; mobile phase: CO_2 (80%), methanol (20%); detector: UV 254 nm. Purification afforded 0.98 g of **49.4** as a white solid as well as 0.3 g of tert-butyl 2-[6-bromo-1-[(2S)-2-hydroxy-2-phenylethyl]-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoate, also as a white solid.

[00443] **Example 50: Synthesis of 2-[1-[(2R)-2-[(3-hydroxyazetidin-1-yl)carbonyloxy]-2-phenylethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-230).**



[00444] **Synthesis of compound 50.2.** To a solution of azetidin-3-ol hydrochloride (2 g, 18.26 mmol, 1.00 equiv) and sodium hydroxide (1.53 g, 38.25 mmol, 2.10 equiv) in water (10 mL) and tetrahydrofuran (25 mL) was added Cbz-Cl (3.27 g, 19.17 mmol, 1.05 equiv) dropwise with stirring at 0 °C over 30 min. The resulting solution was stirred for 3 h at room temperature. The reaction was then quenched by the addition of 20 mL of water. The mixture was extracted with 3x30 mL of ethyl acetate and the organic layers combined. The resulting mixture was washed

with 2x40 mL of sodium chloride (sat.). The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:1). Purification afforded 2.0 g (53%) of benzyl 3-hydroxyazetidine-1-carboxylate (**50.2**) as a light yellow liquid.

[00445] Synthesis of compound 50.3. Into a 50-mL round-bottom flask was placed benzyl 3-hydroxyazetidine-1-carboxylate (2.15 g, 10.38 mmol, 1.00 equiv), TBSCl (2.34 g, 15.60 mmol, 1.50 equiv), imidazole (1.27 g, 18.68 mmol, 1.80 equiv) and N,N-dimethylformamide (15 mL). The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 30 mL of water. The mixture was extracted with 3x40 mL of ethyl acetate and the organic layers combined. The resulting mixture was washed with 2x50 mL of sodium chloride (sat.). The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). Purification afforded 3.0 g (90%) of benzyl 3-[(tert-butyldimethylsilyl)oxy]azetidine-1-carboxylate (**50.3**) as a light yellow liquid.

[00446] Synthesis of compound 50.4. Into a solution of benzyl 3-[(tert-butyldimethylsilyl)oxy]azetidine-1-carboxylate (4.2 g, 13.06 mmol, 1.00 equiv) in ethanol (15 mL) was added palladium carbon (1.3 g, 0.30 equiv) at 0 °C in water/ice bath. The resulting solution was stirred overnight at room temperature. The solids were filtered off. The resulting mixture was concentrated under vacuum to afford 2.2 g (90%) of 3-[(tert-butyldimethylsilyl)oxy]azetidine (**50.4**) as a light yellow liquid.

[00447] Synthesis of compound 50.5. To a solution of ditrichloromethyl carbonate (2.38 g, 8.02 mmol, 1.50 equiv) in dichloromethane (20 mL) was added a solution of 3-[(tert-butyldimethylsilyl)oxy]azetidine (1 g, 5.34 mmol, 1.00 equiv) in dichloromethane (5 mL) dropwise with stirring at 0 °C over 30 min. Stirring was continued for 30 min whereupon a solution of triethylamine (810 mg, 8.00 mmol, 1.50 equiv) in dichloromethane (5 mL) was added dropwise with stirring at 0 °C in 30 min. The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 20 mL of sodium bicarbonate (sat.). The resulting solution was extracted with 3x20 mL of ethyl acetate and the organic layers combined, washed with 2x40 mL of sodium chloride (sat.), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl

acetate/petroleum ether (1:15). Purification afforded 1.3 g (97%) of 3-[(tert-butyldimethylsilyl)oxy]azetidine-1-carbonyl chloride as a light yellow liquid.

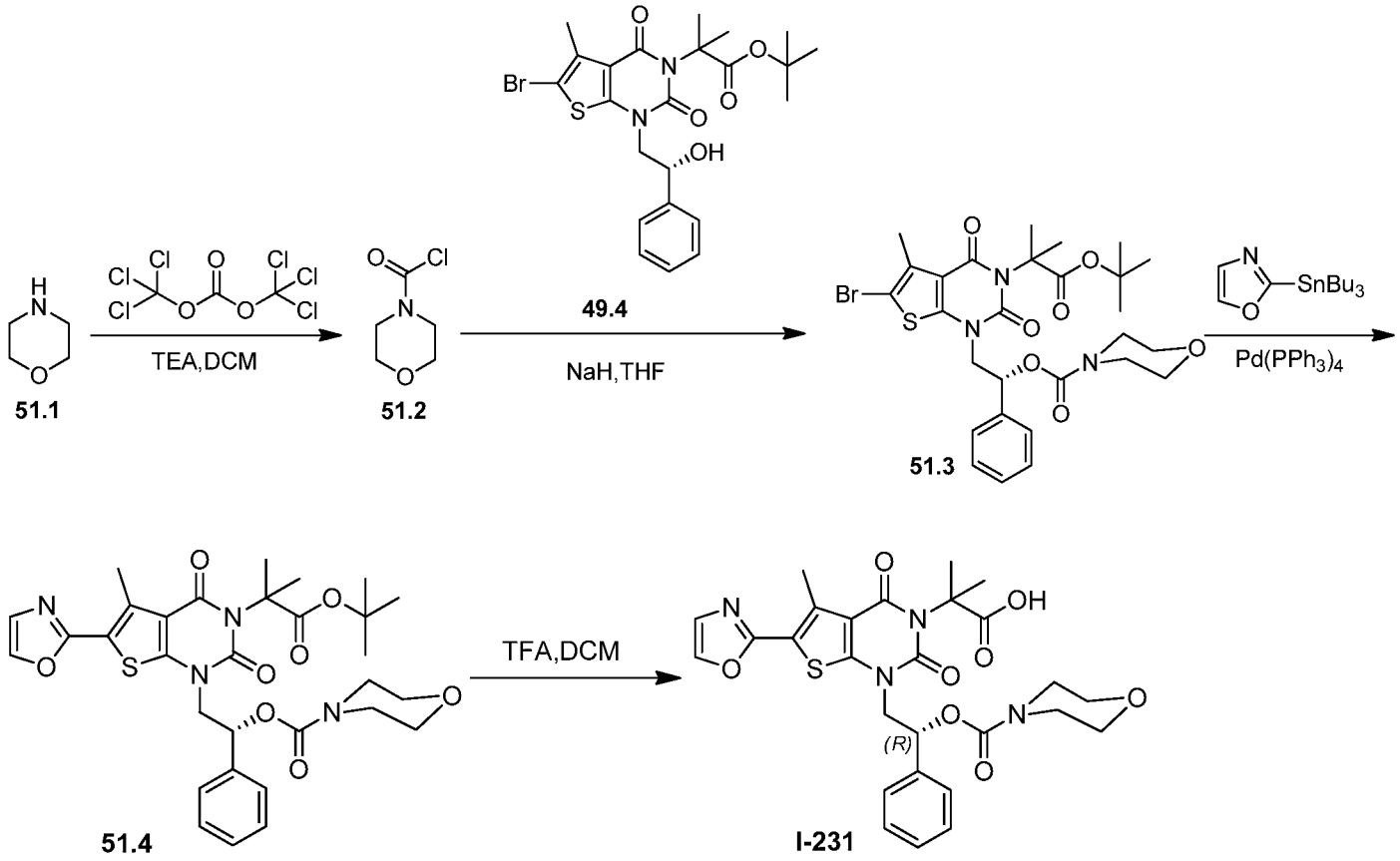
[00448] **Synthesis of compound 50.6.** Into a 50-mL 3-necked round-bottom flask was placed a solution of **49.4** (200 mg, 0.38 mmol, 1.00 equiv) in tetrahydrofuran (10 mL). This was followed by the addition of sodium hydride (46 mg, 1.15 mmol, 3.00 equiv, 60%) at 0 °C. The resulting solution was stirred for 0.5 h at 0 °C. To this was added a solution of 3-[(tert-butyldimethylsilyl)oxy]azetidine-1-carbonyl chloride (142 mg, 0.57 mmol, 1.50 equiv) in tetrahydrofuran (3 mL) dropwise with stirring at 0 °C. The resulting solution was allowed to react, with stirring, overnight at room temperature. The reaction was then quenched by the addition of 10 mL of water. The resulting solution was extracted with 3x20 mL of ethyl acetate and the organic layers combined. The resulting mixture was washed with 2x20 mL of brine. The mixture was dried over sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with PE/EA (6/1). Purification afforded 220 mg (78%) of **50.6** as a white solid.

[00449] **Synthesis of compound 50.7.** Into a 50-mL round-bottom flask flushed with nitrogen was placed toluene (10 mL), **50.6** (310 mg, 0.42 mmol, 1.00 equiv), $Pd(PPh_3)_4$ (97 mg, 0.08 mmol, 0.20 equiv) and 2-(tributylstannyl)-1,3-oxazole (181 mg, 0.51 mmol, 1.20 equiv). The resulting solution was heated to reflux overnight in an oil bath. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). Purification afforded 0.190 g (62%) of **50.7** as a white solid.

[00450] **Synthesis of Compound I-230.** Into a 50-mL round-bottom flask was placed dichloromethane (20 mL), **50.7** (190 mg, 0.26 mmol, 1.00 equiv) and trifluoroacetic acid (4 mL). The resulting solution was stirred for 4 h at room temperature whereupon it was concentrated under vacuum. The residue was dissolved in 5 mL of methanol. The pH value of the solution was adjusted to 10 with potassium carbonate. The resulting mixture was concentrated under vacuum. The crude product (150 mg) was purified by preparative HPLC under the following conditions (Waters): Column: XBridge Prep C18 OBD, 5 μm, 19*150 mm; mobile phase: water (50 mM NH_4HCO_3) and CH_3CN (5% CH_3CN up to 23% in 3 min, hold at 23% for 11.5 min, then up to 95% in 2 min, then down to 5% in 2 min); detector: UV 254/220 nm. 56.5 mg (39.5%) of **I-230** were obtained as a white solid. MS (ES): *m/z* 555 $(M+H)^+$. ^1H NMR (300MHz, CD_3OD): δ 1.72-

1.75 (d, 6H), 2.79 (s, 3H), 3.37-3.80 (m, 2H), 3.97-4.41 (m, 4H), 6.05-6.09 (m, 1H), 7.24 (s, 1H), 7.29-7.46 (m, 5H), 7.95 (s, 1H).

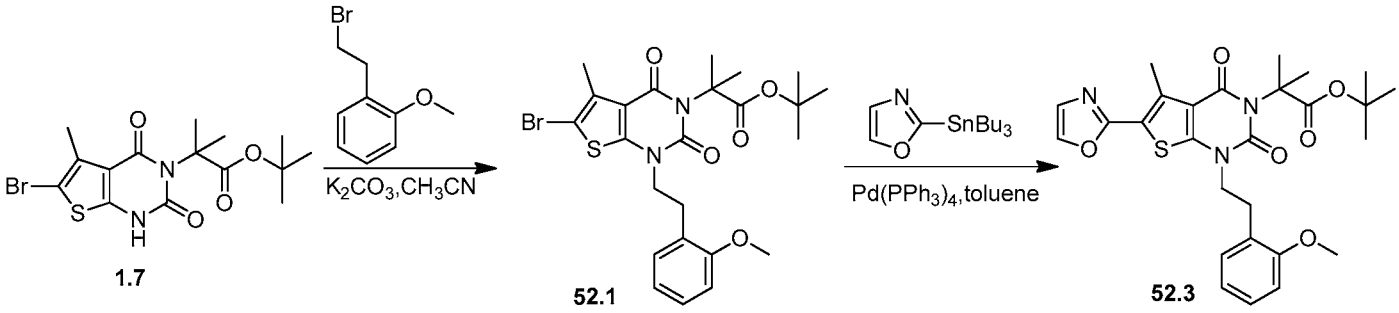
[00451] Example 51: Synthesis of 2-methyl-2-[5-methyl-1-[(2R)-2-[(morpholin-4-yl)carbonyloxy]-2-phenylethyl]-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-231).

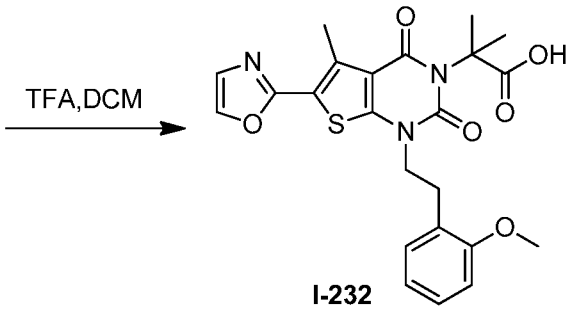


[00452] Synthesis of compound 51.2. Into a 500-mL round-bottom flask was placed ditrichloromethyl carbonate (10.2 g, 34.37 mmol, 1.50 equiv) and dichloromethane (100 mL). This was followed by the addition of morpholine (2 g, 22.96 mmol, 1.00 equiv) dropwise with stirring at 0 °C in 2 min. To this was added TEA (4.2 g, 41.51 mmol, 1.81 equiv) dropwise with stirring at 0°C in 3 min. The resulting solution was stirred for 3 h at room temperature. The reaction was then washed by the addition of 100 mL of water. The mixture was dried over anhydrous sodium sulfate. The solids were filtered out. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). Purification afforded 2.238 g (65%) of morpholine-4-carbonyl chloride as a light yellow oil.

[00453] Synthesis of Compound I-231. Compound **I-231** was prepared from **51.3** and 2-(tributylstannyl)-1,3-oxazole in a manner analogous to **I-133** (Example 9). Isolated a white solid in 9% overall yield. MS (ES): *m/z* 569 $(M+H)^+$. ^1H NMR (400 MHz , CD_3OD): δ 1.84 (d, *J* = 6 Hz), 2.87 (s, 3H), 3.15-3.64 (m, 8H), 4.11-4.17 (m, 1H), 4.41-4.45 (m, 1H), 6.27-6.30 (m, 1H), 7.32 (s, 1H), 7.38-7.52 (m, 5H), 8.03 (s, 1H).

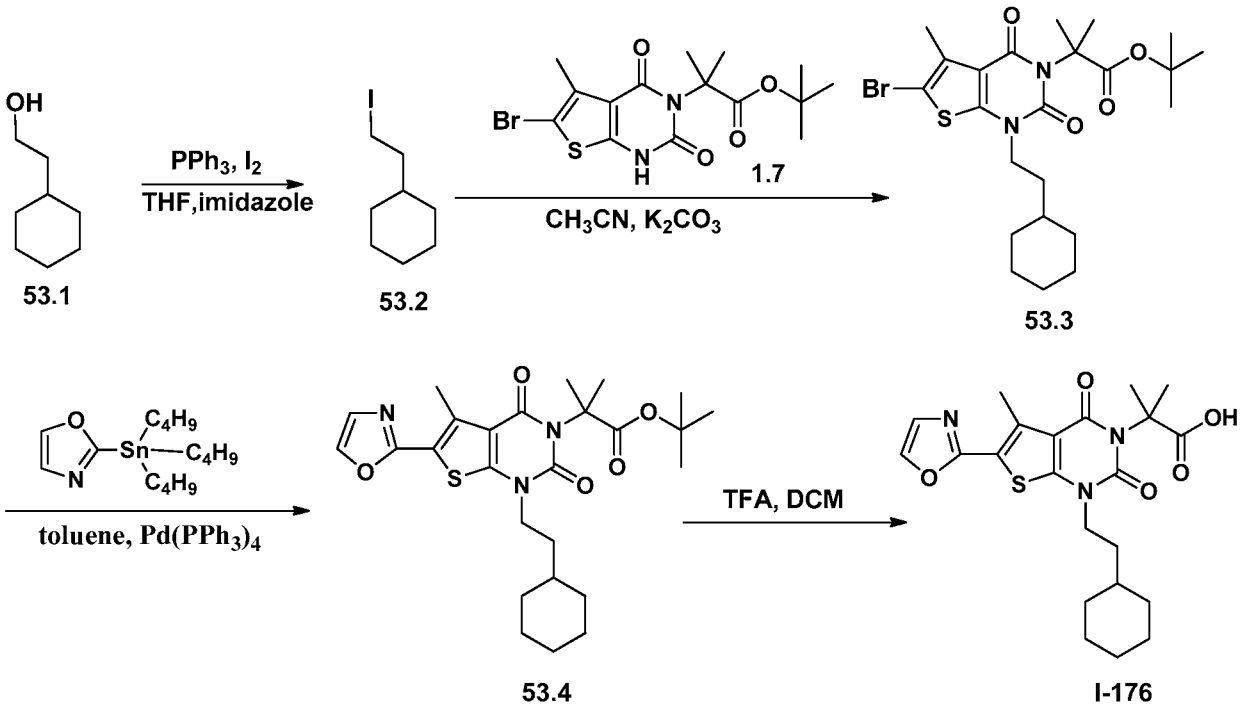
[00454] Example 52: Synthesis of 2-[1-[2-(2-methoxyphenyl)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-232).





[00455] Compound **I-232** was prepared in a manner analogous to **I-133** (Example 9). Isolated a white solid in 33% overall yield from **1.7**. MS (ES): *m/z* 470 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.79 (s, 6H), 2.78(s, 3H), 3.11-3.16 (t, 2H), 3.84 (s, 1H), 4.16-4.19 (t, *J* = 6.8 Hz, 2H), 6.83-6.89 (m, 2H) , 6.71-6.27 (m, 2H), 7.27 (s, 1H), 7.97 (s, 1H).

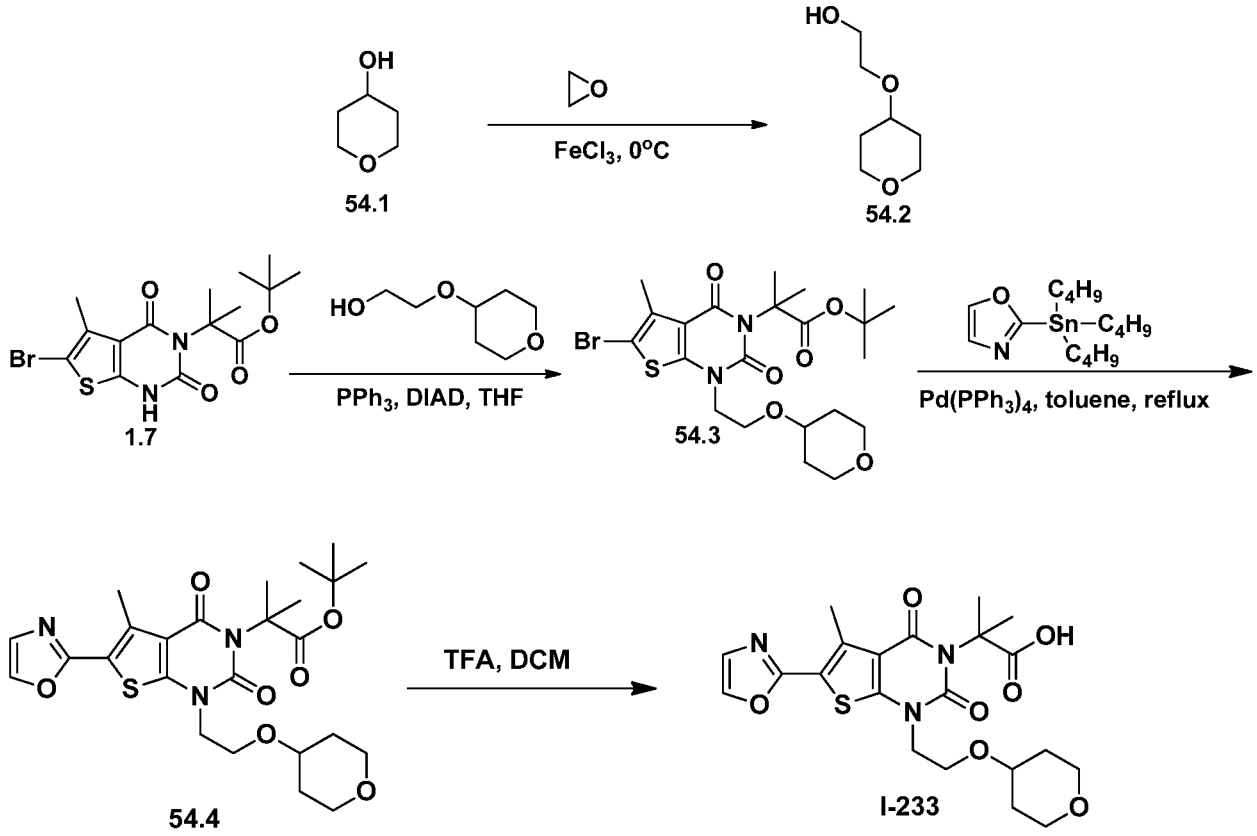
[00456] Example 53: Synthesis of 2-[1-(2-cyclohexylethyl)-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-176).



[00457] **Synthesis of compound 53.2.** Into a 250-mL 3-necked round-bottom flask was placed 2-cyclohexylethan-1-ol (3 g, 23.40 mmol, 1.00 equiv), imidazole (2 g, 29.41 mmol, 1.26 equiv), PPh_3 (8 g, 30.50 mmol, 1.30 equiv), tetrahydrofuran (60 mL) and I_2 (7.7 g, 30.31 mmol, 1.30 equiv). The resulting solution was stirred for 4 h at room temperature. The reaction was then quenched by the addition of 100 mL of sodium bicarbonate (sat.). The resulting solution was extracted with 2x100 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with petroleum ether. Purification afforded 4.4 g (79%) of (2-iodoethyl)cyclohexane as a colorless oil.

[00458] **Synthesis of Compound I-176.** Compound **I-176** was synthesized in a manner analogous to **I-133** Example 9. Isolated a white solid in 34% overall yield from **1.7**. MS (ES): *m/z* 446 $(M+H)^+$. ^1H NMR (DMSO-d_6, 300 MHz): δ 0.94 (m,2H), 1.27 (m, 5H), 1.63 (m, 12H), 2.73 (s, 3H), 3.85 (t, 2H), 7.36 (s, 1H), 8.19 (s, 1H), 12.34 (brs, 1H).

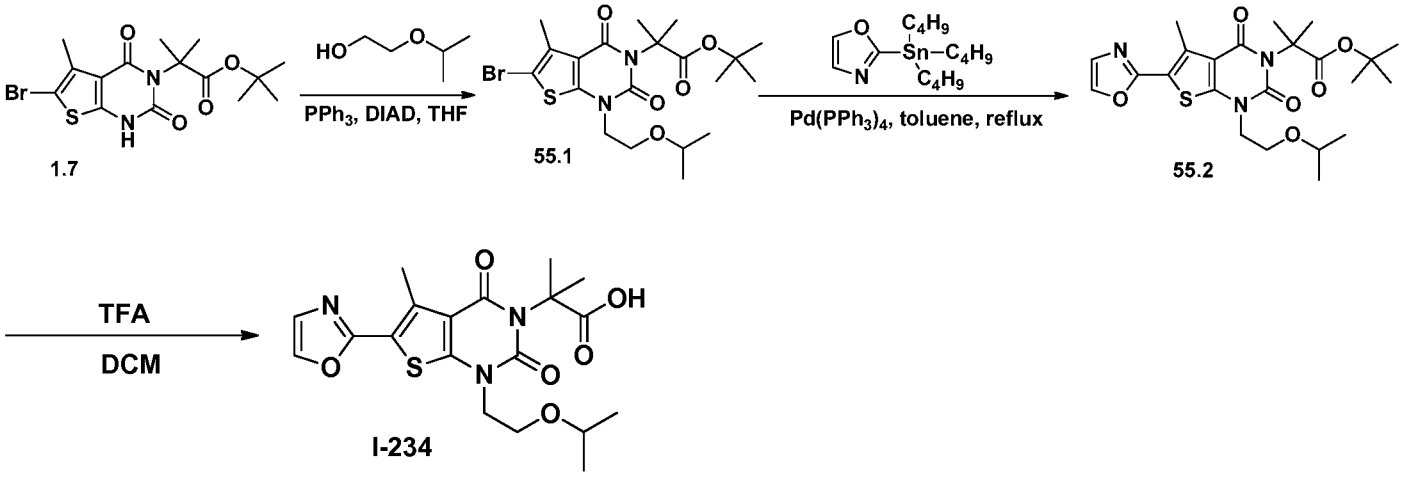
[00459] **Example 54: Synthesis of 2-methyl-2-[5-methyl-1-[2-(oxan-4-yloxy)ethyl]-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-233).**



[00460] **Synthesis of compound 54.2.** Into a 50-mL 3-necked round-bottom flask, was placed $FeCl_3$ (800 mg, 4.94 mmol, 0.10 equiv). This was followed by the addition of oxan-4-ol (5 g, 48.96 mmol, 1.00 equiv) at 0 °C. To this was added oxirane (20 mL) dropwise with stirring at 0 °C. The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 10 mL of water. The resulting solution was extracted with 2x50 mL of ethyl acetate and the organic layers combined. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:30-1:1). Purification afforded 2.25 g (crude) of 2-(oxan-4-yloxy)ethan-1-ol (**54.2**) as a colorless oil.

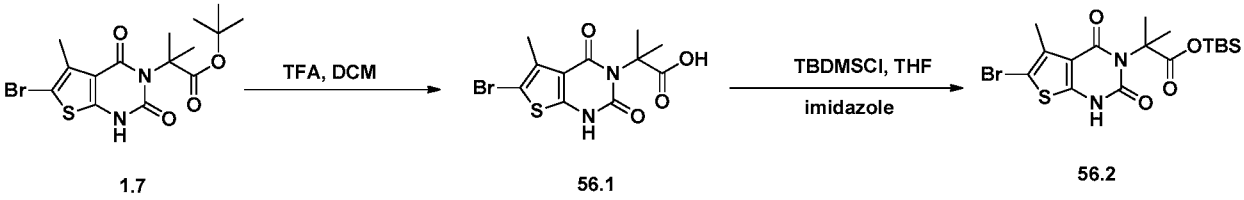
[00461] **Synthesis of Compound I-233.** Compound **I-233** was prepared in a manner analogous to compound **14.5**. Isolated a white solid in 11% overall yield from **1.7.** Purification: thin layer chromatography developed with dichloromethane/methanol (30:1:0.15). MS (ES): *m/z* 464 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD): δ 7.99 (1H, s), 7.29 (1H, s), 4.17-4.15 (2H, t, J = 4.4 Hz), 3.87-3.85 (2H, t, J = 4.4 Hz), 3.79-3.75 (2H, m), 3.61-3.58 (1H, m), 3.50-3.33 (2H, m), 2.82 (3H, s), 1.81 (8H, s), 1.53-1.31 (2H, m).

[00462] Example 55: Synthesis of 2-methyl-2-[5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1-[2-(propan-2-yloxy)ethyl]-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-234).



[00463] Compound **I-234** was prepared from **1.7** and 2-(propan-2-yloxy)ethan-1-ol in a manner analogous to compound **14.5**. Isolated a white solid in 12% overall yield from **1.7**. Purification: preparative TLC with dichloromethane/methanol (40:1). MS (ES): *m/z* 423 $(M+H)^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 1.09-1.11 (d, 6H), 1.87 (s, 6H), 2.84 (s, 3H), 3.57-3.63 (m, 1H), 3.72-3.76 (t, 2H), 4.03-4.10 (t, 2H), 7.26(s, 1H), 7.68 (s, 1H).

[00464] Example 56: Synthesis of Intermediate 56.2.

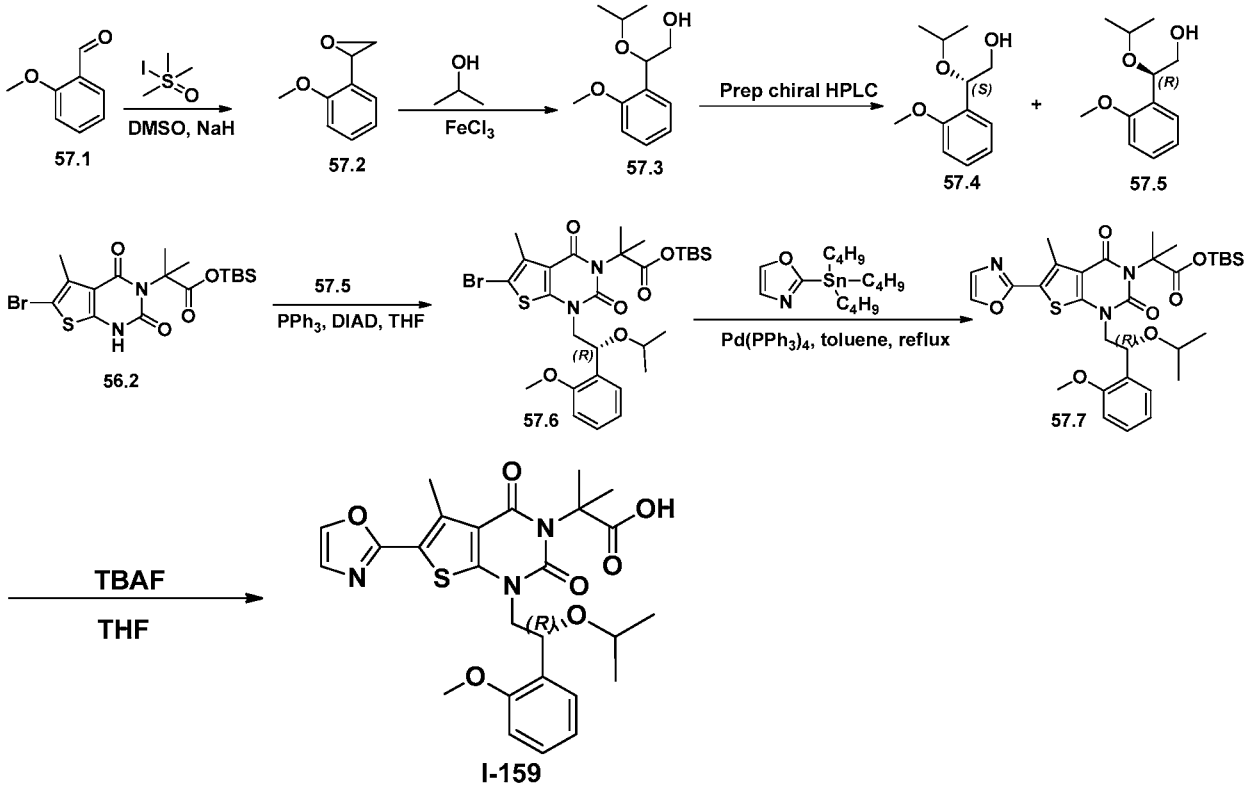


[00465] Synthesis of compound 56.1. Into a 250-mL round-bottom flask, was placed **1.7** (4 g, 9.92 mmol, 1.00 equiv), dichloromethane (100 mL) and trifluoroacetic acid (20 mL). The resulting solution was stirred overnight at room temperature. The mixture was concentrated under vacuum. Purification afforded 3.3 g (crude) of **56.1** as a white solid.

[00466] Synthesis of intermediate 56.2. Into a 250-mL round-bottom flask was placed **56.1** (3.3 g, 9.51 mmol, 1.00 equiv), tetrahydrofuran (60 mL), imidazole (775 mg, 10.37 mmol, 1.2 equiv) and TBDMSCl (1.7 g, 11.26 mmol, 1.18 equiv). The resulting solution was stirred for 3 h at room temperature. The solids were filtered off. The filtrate was concentrated under vacuum.

The residue was applied onto a silica gel column and eluted with PE/EA (10/1) to afford 3.9 g (89%) of **56.2** as a white solid.

[00467] Example 57: Synthesis of 2-[1-[(2R)-2-(2-methoxyphenyl)-2-(propan-2-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-159).



[00468] Synthesis of compound 57.2. Into a 1000-mL 3-necked round-bottom flask was placed DMSO (400 mL) and sodium hydride (7 g, 175.00 mmol, 1.19 equiv, 60%). This was followed by the addition of S,S-dimethylmethanesulfinyl iodide (38 g, 172.67 mmol, 1.18 equiv). The mixture was stirred for 1 h at 40 °C. To this was added a solution of 2-methoxybenzaldehyde (20 g, 146.90 mmol, 1.00 equiv) in DMSO (100 mL) dropwise with stirring at 15 °C. The resulting solution was stirred for 1 h at room temperature. The reaction was then quenched by the addition of 400 mL of NH_4Cl (aq.). The resulting solution was extracted with 1000 mL of ethyl acetate and the organic layers combined. The resulting mixture was washed with 1000 mL of H_2O. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. Purification afforded 14 g (63%) of 2-(2-methoxyphenyl)oxirane as a yellow oil.

[00469] **Synthesis of compound 57.3. 57.3** was prepared using the same method as for the preparation of **54.2**. Isolated a white solid in 33% yield.

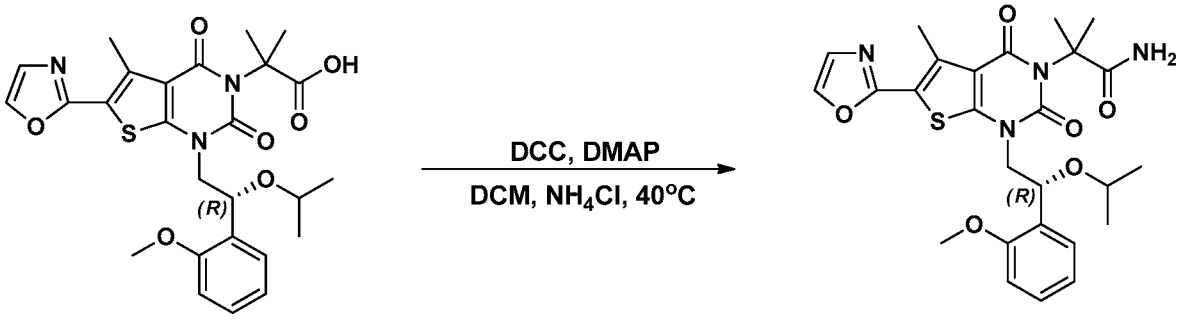
[00470] **Synthesis of compound 57.5.** The enantiomers of **57.3** (8.5 g) were separated by chiral preparative HPLC under the following conditions (Gilson Gx 281): Column: Venusil Chiral OD-H, 21.1*25 cm, 5 μm; mobile phase: hexanes and HPLC-grade ethanol (hold at 5% ethanol for 12 min); detector: UV 220/254 nm. 3.3 g of **57.5** (tR = 8 min) were obtained.

[00471] **Synthesis of compound 57.6.** Into a 500-mL 3-necked round-bottom flask was placed **56.2** (3 g, 6.50 mmol, 1.00 equiv), **57.5** (2.73 g, 12.98 mmol, 2.00 equiv), tetrahydrofuran (150 mL) and DIAD (1.97 g, 9.74 mmol, 1.50 equiv). This was followed by the addition of a solution of PPh_3 (2.55 g, 9.72 mmol, 1.50 equiv) in tetrahydrofuran (50 mL) dropwise with stirring at 0 °C. The resulting solution was stirred overnight at room temperature and then concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:50). Purification afforded 4.2 g (crude) of **57.6** as a yellow solid.

[00472] **Synthesis of compound 57.7.** Into a 500-mL 3-necked round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed **57.6** (4.2 g, 6.42 mmol, 1.00 equiv), toluene (100 mL), 2-(tributylstannyl)-1,3-oxazole (3.44 g, 9.61 mmol, 1.50 equiv) and $Pd(PPh_3)_4$ (740 mg, 0.64 mmol, 0.10 equiv). The resulting solution was stirred overnight at 110 °C in an oil bath. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:25). Purification afforded 1.15 g (impure) of **57.7** as a yellow solid.

[00473] **Synthesis of Compound I-159.** Into a 100-mL round-bottom flask was placed **57.7** (1.15 g, 1.79 mmol, 1.00 equiv), tetrahydrofuran (20 mL) and $TBAF{\cdot}3H_2O$ (306 mg, 0.97 mmol, 0.54 equiv). The resulting solution was stirred for 15 min at room temperature and then concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:2). Purification afforded 583 mg (62%) of Compound **I-159** as a white solid. MS (ES): *m/z* 528 $(M+H)^+$, 550 $(M+Na)^+$, 591 $(M+Na+CH_3CN)^+$. ^1H NMR (300 MHz, CD_3OD): δ 0.98 (d, 3H), 1.01 (d, 3H), 1.72 (s, 3H), 1.76 (s, 3H), 1.77 (s, 3H), 3.47 (m, 1H), 3.78 (s, 3H), 4.04 (m, 2H) , 4.84 (m, 1H), 6.95-7.93 (m, 6H).

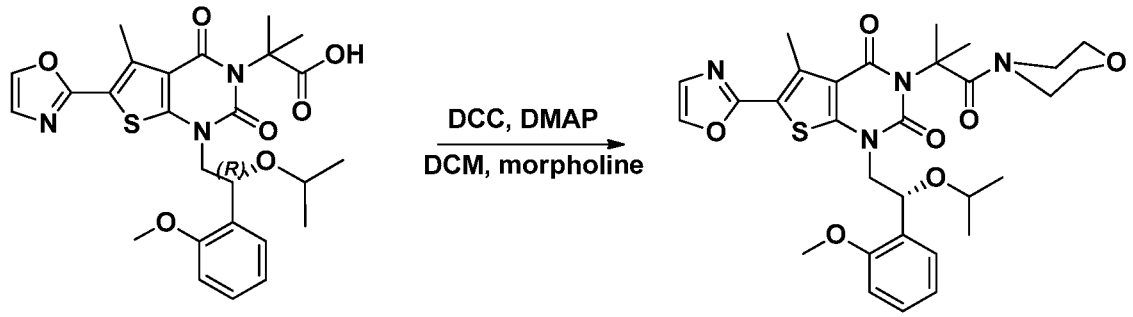
[00474] **Example 58: Synthesis of 2-[1-[(2R)-2-(2-methoxyphenyl)-2-(propan-2-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanamide (I-174).**



I-158 I-174

[00475] Compound **I-174** was prepared from Compound **I-158** using the method of Example 4. Purification: thin layer chromatography developed with dichloromethane/methanol (20:1). Isolated a white solid in 52% yield. MS (ES): *m/z* 527 $(M+H)^+$, 549 $(M+Na)^+$. ^1H NMR (300 MH_Z, CD_3OD): δ 1.07 (m, 6H), 1.76-1.77 (d, 6H), 2.75 (s, 3H), 3.41-3.51 (m, 1H), 3.77 (s, 3H), 3.97-4.12 (m, 2H), 5.28-5.33 (m, 1H) , 6.85-6.88 (d, 1H), 6.94-6.99 (t, 1H), 7.19-7.24 (m, 2H), 7.47-7.50 (d, 1H), 7.93 (s, 1H).

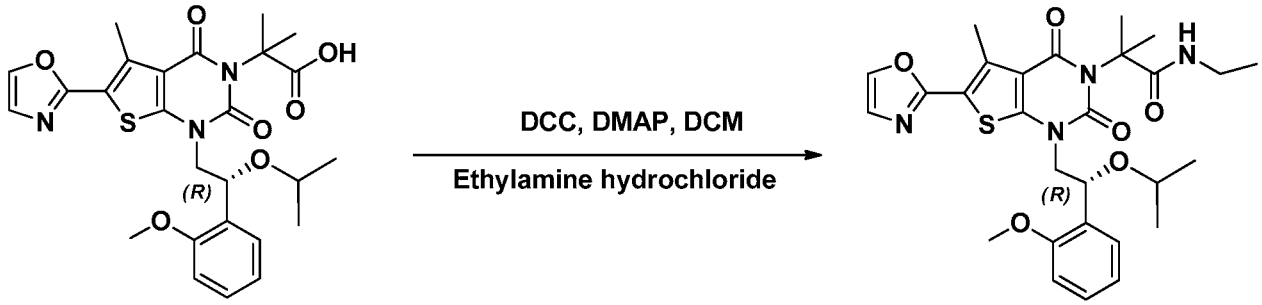
[00476] Example 59: Synthesis of 1-[(2R)-2-(2-methoxyphenyl)-2-(propan-2-yloxy)ethyl]-5-methyl-3-[2-methyl-1-(morpholin-4-yl)-1-oxopropan-2-yl]-6-(1,3-oxazol-2-yl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-2,4-dione (I-235).



I-158 I-235

[00477] Compound **I-235** was prepared from Compound **I-158** and morpholine using the method of Example 4. Purification: Preparative HPLC (Waters) under the following conditions: Column: XBridge Prep Phenyl OBD, 5 μm, 19*150 mm; mobile phase, water (50 mM NH_4HCO_3) and CH_3CN (5.0% CH_3CN up to 95.0% in 10 min, hold at 95.0% in 2 min, down to 5.0% in 2 min); detector: UV 254, 220 nm. 34.2 mg (60%) of Compound **I-235** were obtained. ^1H NMR (400 MHz, CD_3OD): δ 1.03-1.08 (m, 6H), 1.77 (s, 6H), 2.82 (s, 3H), 3.44-3.66 (m, 9H), 3.85 (s, 3H), 4.08-4.24 (m, 2H), 5.38 (m, 1H), 6.89-7.03 (m, 2H) , 7.29 (m, 2H), 7.51 (m,1H), 7.99 (s, 1H). MS (ES): *m/z* 619 $(M+Na)^+$.

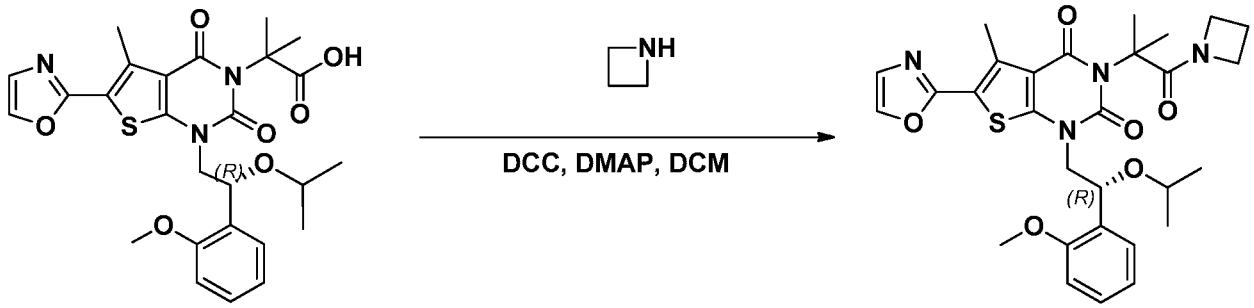
[00478] Example 60: Synthesis of N-ethyl-2-[1-[(2R)-2-(2-methoxyphenyl)-2-(propan-2-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanamide (I-236).



I-158 I-236

[00479] Compound **I-236** was prepared from Compound **I-158** and ethylamine hydrochloride using the method of Example 4. Purification: Preparative HPLC (Waters) under the following conditions: Column: XBridge Prep Phenyl OBD, 5 μm, 19*150 mm; mobile phase, water (50 mM NH_4HCO_3) and CH_3CN (5.0% CH_3CN up to 95.0% in 10 min, hold at 95.0% in 2 min, down to 5.0% in 2 min); detector: UV 254, 220 nm. MS (ES): *m/z* 577 $(M+Na)^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.13-1.15 (m, 9H), 1.77 (d, 6H), 2.79 (s, 3H), 3.26 (m, 2H), 3.52 (m, 1H), 3.81 (s, 3H), 4.10 (m, 2H), 5.34 (m, 1H), 6.89-7.01 (m, 2H), 7.29 (m, 2H), 7.51 (m, 1H), 7.97 (s, 1H).

[00480] Example 61: Synthesis of 3-[1-(azetidin-1-yl)-2-methyl-1-oxopropan-2-yl]-1-[(2R)-2-(2-methoxyphenyl)-2-(propan-2-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-2,4-dione (I-237).

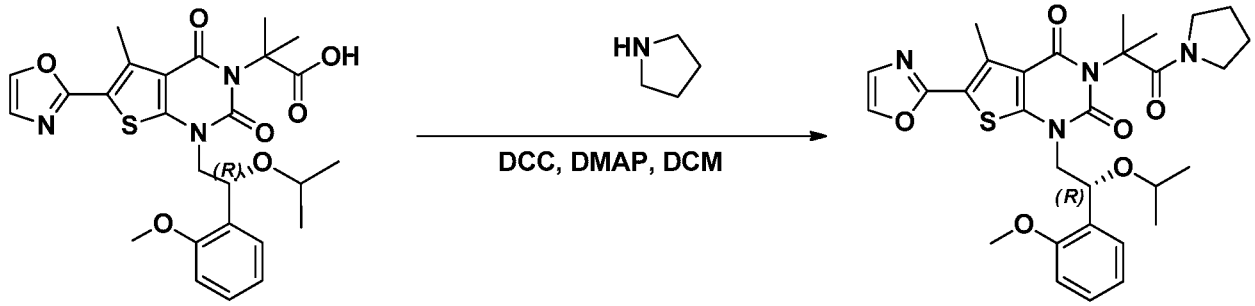


I-158 I-237

[00481] Compound **I-237** was prepared from Compound **I-158** and azetidine using the method of Example 4. Purification: The reaction mixture was concentrated under vacuum. The

residue was applied onto a silica gel column with dichloromethane/methanol (40:1). Purification afforded 38.3 mg (48%) of Compound **I-237** as a white solid. MS (ES): *m/z* 568 $(M+H)^+$, 589 $(M+Na)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.05 (t, 6H), 1.76 (s, 6H), 2.19-2.27 (m, 2H), 2.83 (s, 3H), 3.41-3.55 (m, 1H), 3.85 (s, 3H), 4.06-4.17 (m, 6H), 5.35-5.39 (t, 1H), 6.94-7.04 (m, 2H), 7.26-7.32 (m, 2H), 7.50-7.51 (d, 1H), 7.99 (s, 1H).

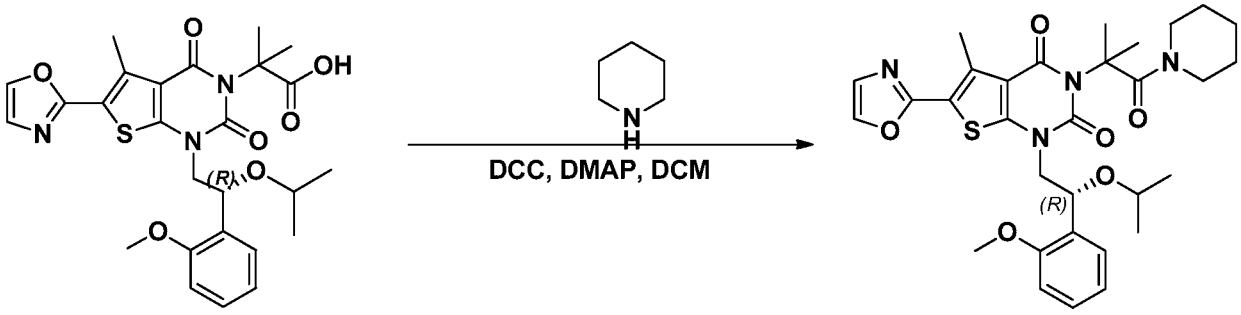
[00482] Example 62: Synthesis of 1-[(2R)-2-(2-methoxyphenyl)-2-(propan-2-yloxy)ethyl]-5-methyl-3-[2-methyl-1-oxo-1-(pyrrolidin-1-yl)propan-2-yl]-6-(1,3-oxazol-2-yl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-2,4-dione (I-238).



I-158 I-238

[00483] Compound **I-238** was prepared from Compound **I-158** and pyrrolidine using the method of Example 4. Purification: The reaction mixture was concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (40:1). Purification afforded 41.6 mg (50%) of Compound **I-238** as a white solid. MS (ES): *m/z* 603 $(M+Na)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.03-1.07 (m, 6H), 1.77-1.82 (m, 10H), 2.80 (s, 3H), 3.09-3.15 (m, 2H), 3.46-3.56 (m, 3H), 3.86 (s, 3H), 4.15 (br s, 2H), 5.35-5.39 (t, 1H), 6.95-7.04 (m, 2H), 7.26-7.32 (m, 2H), 7.50-7.52 (d, 1H), 7.99 (s, 1H).

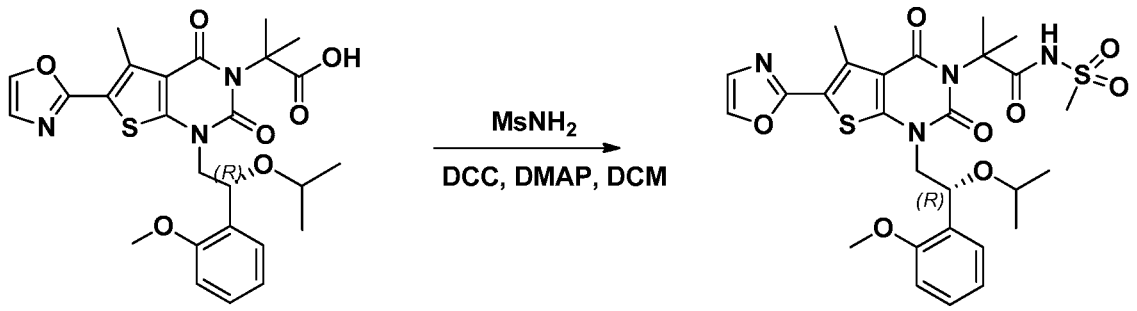
[00484] Example 63: Synthesis of 1-[(2R)-2-(2-methoxyphenyl)-2-(propan-2-yloxy)ethyl]-5-methyl-3-[2-methyl-1-oxo-1-(piperidin-1-yl)propan-2-yl]-6-(1,3-oxazol-2-yl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-2,4-dione (I-239).



I-158 I-239

[00485] Compound **I-239** was prepared from Compound **I-158** and piperidine using the method of Example 4. Purification: The reaction mixture was concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (40:1). Purification afforded 41.6 mg (49%) of Compound **I-239** as a white solid. MS (ES): *m/z* 617 $(M+Na)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.02 (m, 6H), 1.29-1.41 (m, 2H), 1.41-1.95 (m, 10H), 2.81 (s, 3H), 3.45-3.61 (m, 3H), 3.87 (s, 3H), 4.10-4.24 (m, 1H), 5.38-5.39 (m, 1H) , 6.95-7.04 (m, 2H), 7.27-7.32 (m, 2H), 7.43-7.65 (m, 1H), 8.03 (s, 1H).

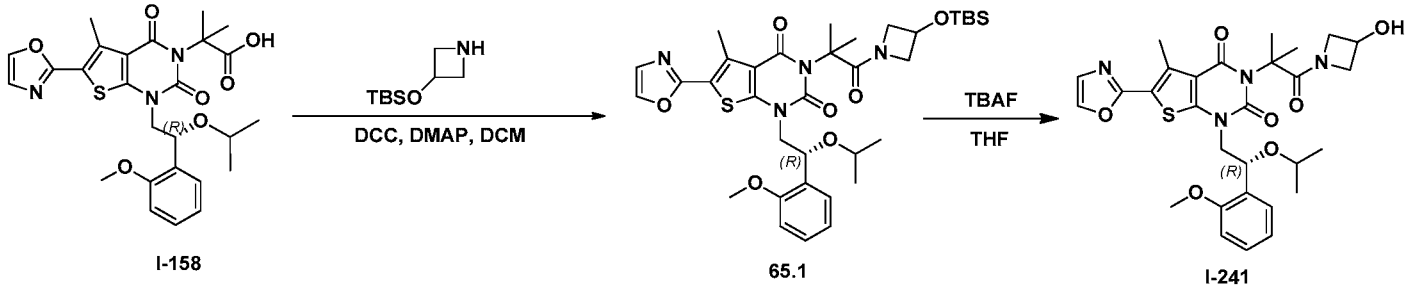
[00486] Example 64: Synthesis of N-methanesulfonyl-2-[1-[(2R)-2-(2-methoxyphenyl)-2-(propan-2-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanamide (I-240).



I-158 I-240

[00487] Compound **I-240** was prepared from Compound **I-158** and methanesulfonamide using the method of Example 4. Purification: The reaction mixture was concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (40:1). Purification afforded 13.6 mg (16%) of Compound **I-240** as a white solid. MS (ES): *m/z* 605 $(M+H)^+$, 627 $(M+Na)^+$. ^1H NMR (300 MHz, CD_3OD): δ 0.80-0.94 (m, 6H), 1.67-1.68 (d, 6H), 2.75 (s, 3H), 3.15 (s, 3H), 3.35-3.43 (m, 1H), 3.70 (s, 3H), 3.97-3.99 (m, 1H), 5.20-5.26 (m, 1H), 6.79-6.82 (d, 1H), 6.88-6.93 (t, 1H), 7.13-7.17 (m, 2H), 7.41-7.43 (d, 2H), 7.87(s, 1H).

[00488] Example 65: 3-[1-(3-hydroxyazetidin-1-yl)-2-methyl-1-oxopropan-2-yl]-1-[(2R)-2-(2-methoxyphenyl)-2-(propan-2-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-2,4-dione (I-241).

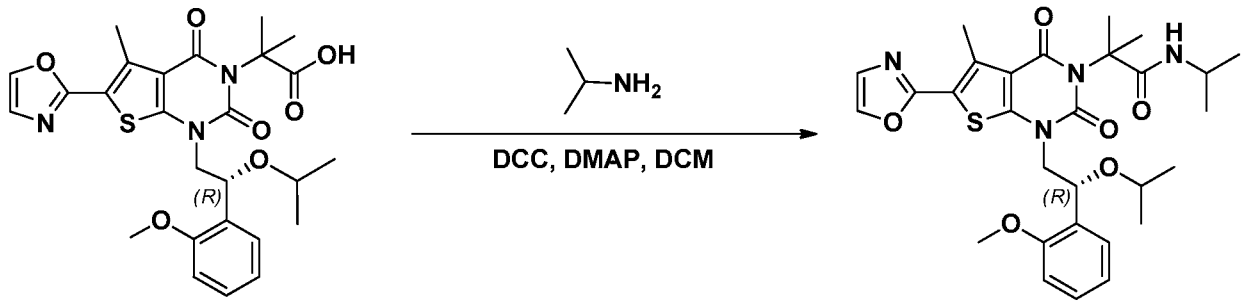


I-158 65.1 I-241

[00489] Synthesis of compound 65.1. Compound **65.1** was prepared from Compound **I-158** and 3-[(tert-butyldimethylsilyl)oxy]azetidine using the method of Example 4, except that microwave irradiation at 50 °C was the heat source. Purification: The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:2). Purification afforded 100 mg (50%) of Compound **65.1** as a white solid.

[00490] Synthesis of compound I-241. Into a 50-mL round-bottom flask was **65.1** (100 mg, 0.14 mmol, 1.00 equiv), oxolane (10 mL) and TBAF (37.4 mg, 0.14 mmol, 1.00 equiv). The resulting solution was stirred for 2 h at room temperature and then concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (30:1). Purification afforded 53.6 mg (64%) of Compound **I-241** as a white solid. MS (ES): *m/z* 605 $(M+Na)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.03-1.07 (m, 6H), 1.74-1.75 (d, 6H), 2.83 (s, 3H), 3.47-3.55 (m, 1H), 3.76-3.80 (m, 2H), 3.85 (s, 3H), 4.16-4.24 (m, 4H), 4.47-4.55 (m, 1H), 5.35-5.39 (t, 1H), 6.94-7.04 (m, 2H), 7.26-7.32 (m, 2H), 7.50-7.53 (d, 1H), 7.99 (s, 1H).

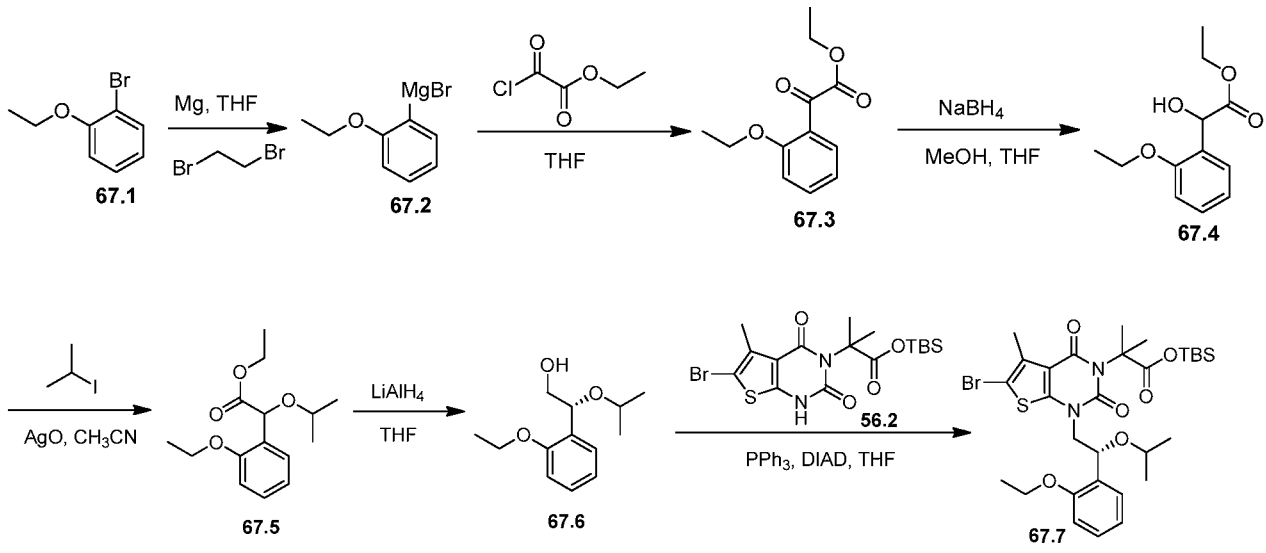
[00491] Example 66: Synthesis of 2-[1-[(2R)-2-(2-methoxyphenyl)-2-(propan-2-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methyl-N-(propan-2-yl)propanamide (I-242).



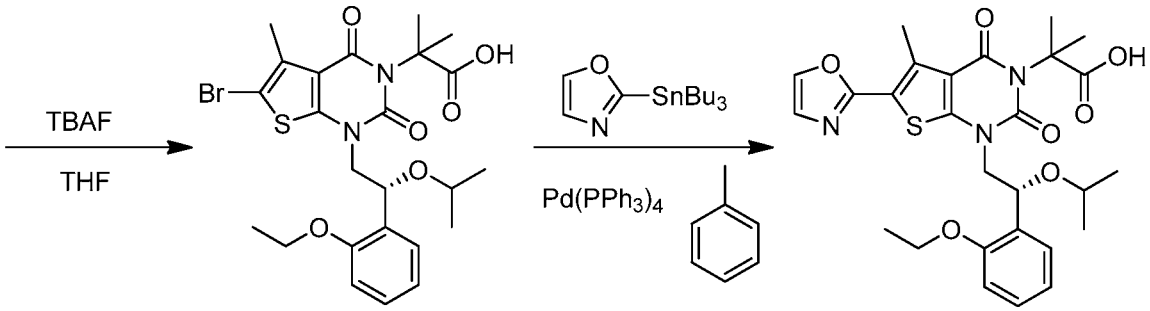
I-158 I-242

[00492] Compound **I-242** was prepared from Compound **I-158** and propan-2-amine using the method of Example 4. Purification: The reaction mixture was concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (40:1). Purification afforded 31.5 mg (39%) of Compound **I-242** as a white solid. MS (ES): *m/z* 591 $(M+Na)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.03-1.07 (m, 6H), 1.10-1.20 (m, 6H), 1.77-1.83 (d, 6H), 2.85 (s, 3H), 3.46-3.56 (m, 1H), 3.81 (s, 3H), 3.97-4.10 (m, 3H), 5.33-5.38 (t, 1H), 6.89-6.92 (d, 1H), 6.99-7.04 (t, 1H), 7.23-7.32 (m, 2H), 7.52-7.55 (m, 1H), 7.98 (s, 1H).

[00493] Example 67: Synthesis of 2-[1-[(2R)-2-(2-ethoxyphenyl)-2-(propan-2-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-177).



67.1 67.2 67.3 67.4 67.5 67.6 67.7



67.8 I-177

[00494] **Synthesis of compound 67.2.** Into a 100-mL 3-necked round-bottom flask was placed Mg (1.55 g) and 10 mL of tetrahydrofuran. Then 1-bromo-2-ethoxybenzene (1 g) and 1,2-dibromoethane (100 mg, 0.53 mmol, 0.01 equiv) were added to initiate the reaction. Then a second batch of 1-bromo-2-ethoxybenzene (9 g) were dissolved in 40 mL THF was added dropwise. The resulting solution was stirred for 2 h at room temperature. The mixture was directly used in the next step.

[00495] **Synthesis of compound 67.3.** Into a 100-mL 3-necked round-bottom flask was placed tetrahydrofuran (20 mL) and ethyl 2-chloro-2-oxoacetate (17 g, 124.51 mmol, 2.51 equiv). This was followed by the addition of bromo(2-ethoxyphenyl)magnesium (20 mL, 1.00 equiv) dropwise with stirring at -80 °C. The resulting solution was stirred for 30 min at -80 °C. The reaction was then quenched by the addition of 50 mL of water. The resulting solution was extracted with 3x100 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:20). Purification afforded 8.5 g (77%) of **67.3** as a colorless oil.

[00496] **Synthesis of compound 67.4.** Into a 100-mL 3-necked round-bottom flask was placed methanol (10 mL), ethyl 2-(2-ethoxyphenyl)-2-oxoacetate (8.5 g, 38.25 mmol, 1.00 equiv) and tetrahydrofuran (50 mL). This was followed by the addition of $NaBH_4$ (730 mg, 19.30 mmol, 0.50 equiv), in portions at 0 °C. The resulting solution was stirred for 30 min at room temperature. The reaction was then quenched by the addition of 50 mL of water. The resulting solution was extracted with 3x100 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:20). Purification afforded 7.1 g (83%) of **67.4** as a colorless oil.

[00497] **Synthesis of compound 67.5.** Into a 250-mL round-bottom flask was placed ethyl 2-(2-ethoxyphenyl)-2-hydroxyacetate (7.1 g, 31.66 mmol, 1.00 equiv), CH_3CN (50 mL), Ag_2O

(22.1 g) and 2-iodopropane (27 g, 158.83 mmol, 5.02 equiv). The resulting solution was stirred overnight at 40 °C. The solids were filtered out. The filtrate was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:100). Purification afforded 1.3 g (15%) of **67.5** as a colorless oil.

[00498] **Synthesis of compound 67.6.** Into a 50-mL 3-necked round-bottom flask was placed tetrahydrofuran (20 mL) and **67.5** (1.3 g, 4.88 mmol, 1.00 equiv). Then $LiAlH_4$ (186 mg, 4.90 mmol, 1.00 equiv) was added at 0 °C. The resulting solution was stirred for 30 min at 0 °C. The reaction was then quenched by the addition of 20 mL of NH_4Cl (aq.). The resulting solution was extracted with 3x100 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:20). The crude product was purified by chiral preparative HPLC under the following conditions (Gilson Gx 281): Column: Venusil Chiral OD-H, 21.1*25 cm, 5 μm; mobile phase: hexanes and ethanol (hold at 2.0% ethanol for 11 min); detector: UV 220/254nm. Purification afforded 0.35 g (32%) of **67.6** as a yellow solid.

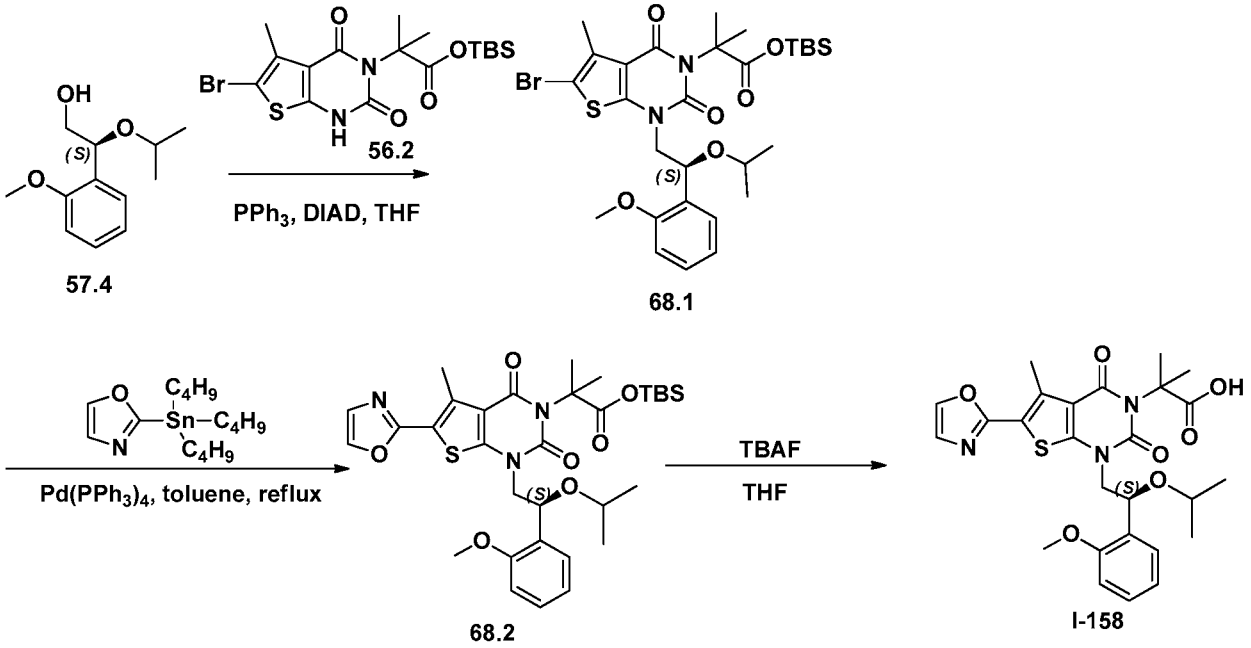
[00499] **Synthesis of compound 67.7.** Into a 50-mL round-bottom flask was placed Ph_3P (545 mg, 2.08 mmol, 2.00 equiv), **67.6** (350 mg, 1.56 mmol, 1.50 equiv), tetrahydrofuran (10 mL), **56.2** (480 mg, 1.04 mmol, 1.00 equiv) and DIAD (420 mg, 2.08 mmol, 2.00 equiv). The resulting solution was stirred overnight at room temperature and then concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:50). Purification afforded 400 mg (crude) of **67.7** as a yellow oil.

[00500] **Synthesis of compound 67.8.** Into a 50-mL round-bottom flask was placed tetrahydrofuran (5 mL), **67.7** (400 mg, 0.60 mmol, 1.00 equiv) and TBAF (172 mg, 0.66 mmol, 1.10 equiv). The resulting solution was stirred for 2 h at room temperature. The reaction was then quenched by the addition of 0.5 mL of water. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). Purification afforded 350 mg (crude) of **67.8** as a yellow oil.

[00501] **Synthesis of Compound I-177.** Compound **I-177** was prepared from **67.8** and 2-(tributylstannyl)-1,3-oxazole according to the method of Example 2. Purification: The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). Purification afforded 106.1 mg (31%) of Compound **I-177** as a white solid. MS (ES): *m/z* 542 $(M+H)^+$, 564 $(M+Na)^+$. ^1H NMR (400 MHz, CD_3OD): δ 0.99-1.04 (m, 6H), 1.44 (t, *J* = 7.2, 3H), 1.75-1.76

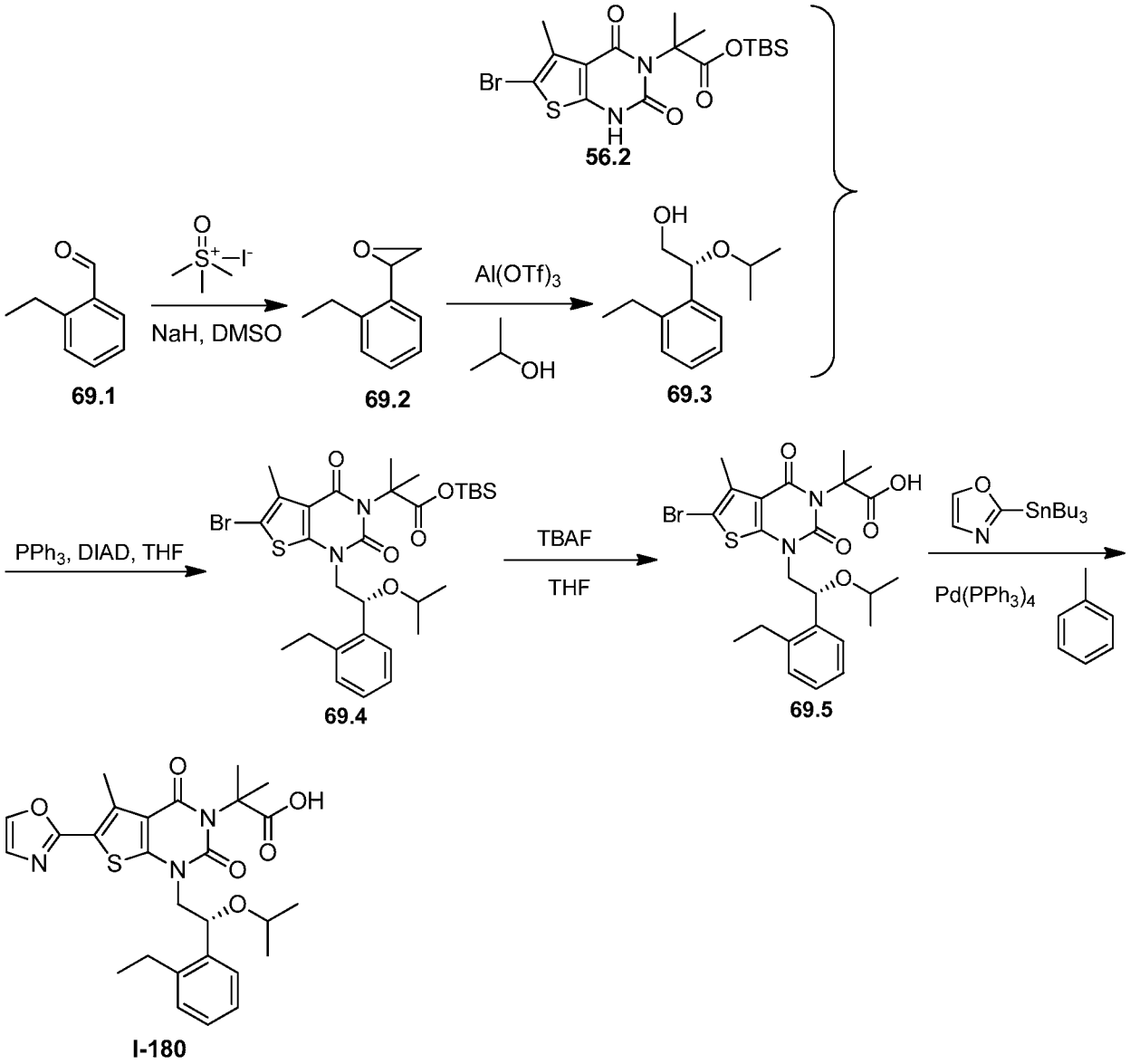
(m, 6H), 2.83 (s, 3H), 3.43-3.51 (m, 1H), 4.05-4.13 (m, 4H), 5.37-5.41 (m, 1H), 6.93 (d, J = 8.4, 1H), 7.00 (t, J = 7.2, 1H), 7.23-7.28 (m, 2H), 7.53 (d, J = 7.6, 1H), 7.97 (s, 1H).

[00502] Example 68: Synthesis of 2-[1-[(2S)-2-(2-methoxyphenyl)-2-(propan-2-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-158).



[00503] Compound **I-158** was prepared from **57.4** and intermediate **56.2** using the same procedure as for Example 57. Purification: silica gel column with ethyl acetate/petroleum ether (1:5). Isolated 541 mg (20%) of Compound **I-158** as a white solid. MS (ES): *m/z* 528 $(M+H)^+$, 550 $(M+Na)^+$, 591 $(M+Na+CH_3CN)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.02 (d, 3H), 1.05 (d, 3H), 1.76 (s, 3H), 1.81 (s, 3H), 2.80 (s, 3H), 3.46 (m, 1H), 3.83 (s, 3H), 4.09 (m, 2H) , 5.32 (m, 1H), 6.91-7.04 (m, 2H), 7.25 (m, 2H), 7.53 (d, 1H), 7.97 (s, 1H).

[00504] Example 69: Synthesis of 2-[1-[(2R)-2-(2-ethylphenyl)-2-(propan-2-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-180).



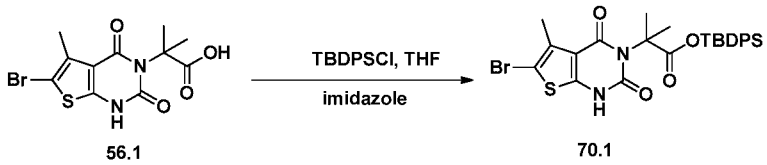
[00505] **Synthesis of compound 69.2.** Compound **69.2** was prepared from **69.1** using the same method as for the synthesis of **57.2**. Isolated a colorless oil in quantitative yield.

[00506] **Synthesis of compound 69.3.** Into a 50-mL round-bottom flask was placed $Al(OTf)_3$ (641 mg, 1.35 mmol, 0.05 equiv), propan-2-ol (20 mL) and **69.2** (4 g, 26.99 mmol, 1.00 equiv). The resulting solution was stirred for 1 h at room temperature. The reaction was then quenched by the addition of 1 mL of water. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:100). From the purified racemate the desired enantiomer was isolated by chiral preparative HPLC under the following conditions (Gilson GX 281): Column: Venusil Chiral OD-H, 21.1*25 cm, 5 μm ;

mobile phase: hexanes (0.2% TEA) and IPA (hold at 2.0% IPA in 11 min); detector: UV 220/254 nm. The second peak to elute was collected. Concentration afforded 1.2 g (21%) of **69.3** as a yellow oil.

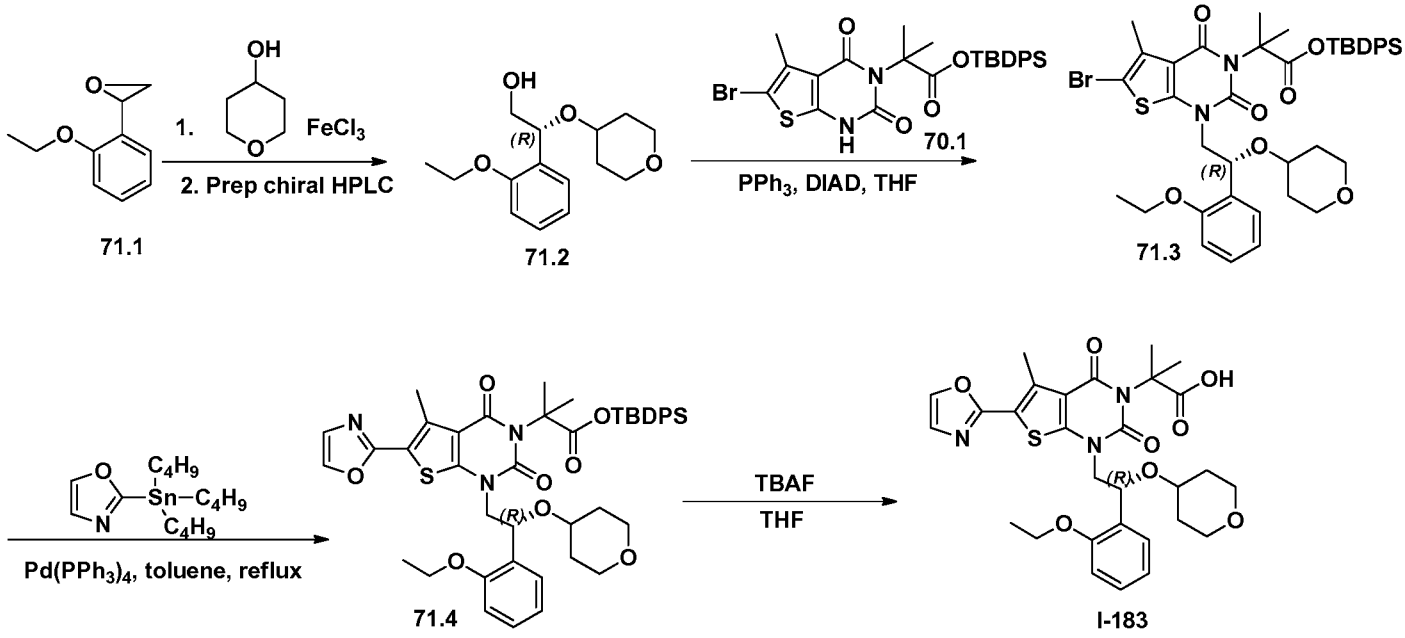
[00507] **Synthesis of Compound I-180.** Compound **I-180** was prepared in a manner analogous with Example 67. Purification: silica gel column with ethyl acetate/petroleum ether (1:10). 47.8 mg (11% overall yield from **56.2**) of Compound **I-180** were isolated as a white solid. MS (ES): *m/z* 526 $(M+Na)^+$, 589 $(M+H+CH_3CN)^+$. ^1H NMR (300 MHz, CD_3OD): δ 0.95 (t, *J* = 6.3 Hz, 6H), 1.25 (t, *J* = 7.5Hz, 3H), 1.78-1.80 (m, 6H), 2.68-2.75 (m, 1H), 2.79 (s, 3H), 2.89-2.94 (m, 1H), 3.37-3.45 (m, 1H), 3.65-3.70 (m, 1H), 4.18-4.24 (m, 1H), 5.14-5.18 (m, 1H), 7.19-7.27 (m, 4H), 7.57-7.60 (m, 1H), 7.95 (s, 1H).

[00508] **Example 70: Synthesis of Intermediate 70.1.**



[00509] Intermediate **70.1** was prepared in a manner analogous to intermediate **56.2.** Isolated a white solid in 84%.

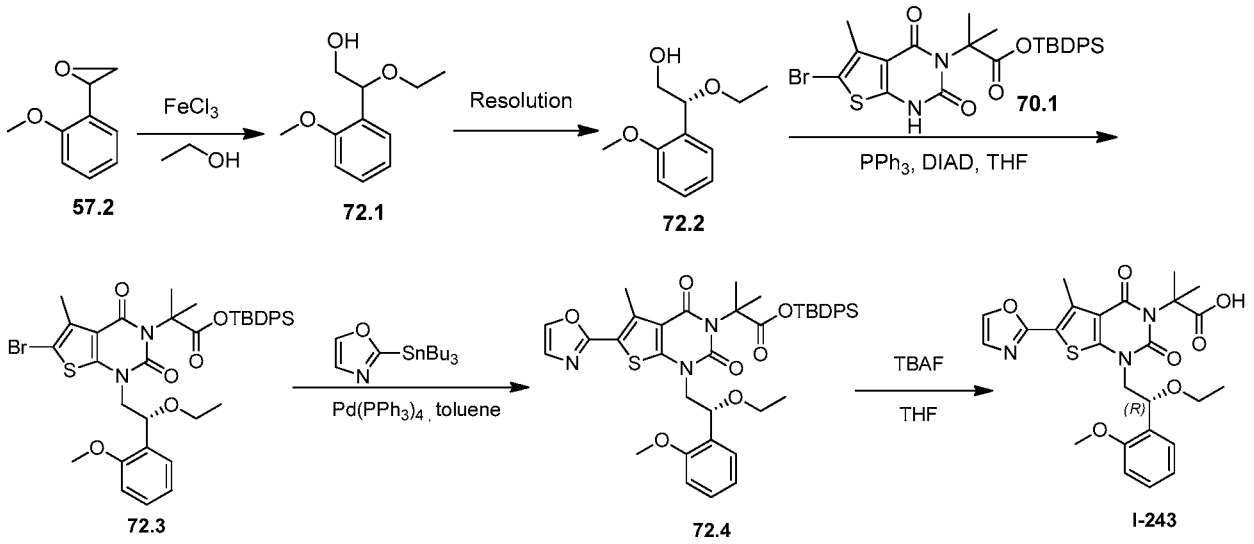
[00510] **Example 71: Synthesis of 2-[1-[(2R)-2-(2-ethoxyphenyl)-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-183).**



[00511] **Synthesis of compound 71.2.** Compound **71.2** was synthesized using the method for the synthesis of **20.1**. Purification: The residue obtained after work-up was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10) to obtain a pure racemic product. The enantiomers were then separated by chiral preparative HPLC under the following conditions (Gilson Gx 281): Column: Lichrom OD-H 2*25 cm, 5 μm; mobile phase: hexanes and IPA (hold at 5% IPA for 15 min); detector: UV 220/254 nm. 0.870 g (8%) of **71.2** were obtained as a colorless oil.

[00512] **Synthesis of Compound I-183.** Compound **I-183** was prepared following the same procedure as for Example 57. Purification: The crude material was applied onto a silica gel column with ethyl acetate/petroleum ether (1:2, 0.5%, AcOH). The product (100 mg) thus obtained was further purified by preparative HPLC under the following conditions ((Waters): Column: XBridge Prep C18 OBD column, 5 μm, 19*150 mm; mobile phase: water (with 50 mM NH_4HCO_3) and CH_3CN (20.0% CH_3CN up to 50.0% in 10 min, up to 95.0% in 2 min, down to 20.0% in 2 min); detector: UV 254, 220 nm. Purification afforded 0.046 g (12% from **70.1**) of Compound **I-183** as a white solid. MS (ES): *m/z* 606 $(M+Na)^+$ 606. ^1H NMR (CD_3OD, 300 MHz): δ 1.41 (m, 5H), 1.73 (m, 8H), 2.77 (s, 3H), 3.34 (m, 2H), 3.41 (m, 1H), 3.50-3.70 (m, 2H), 3.90 (m, 1H), 4.02 (m, 2H), 4.20 (m, 1H), 5.40 (dd, J = 4.2 Hz, 9.0 Hz, 1H), 6.95 (m, 2H), 7.23 (m, 2H), 7.49 (dd, J = 1.5 Hz, 7.5 Hz, 1H), 7.93 (s, 1H).

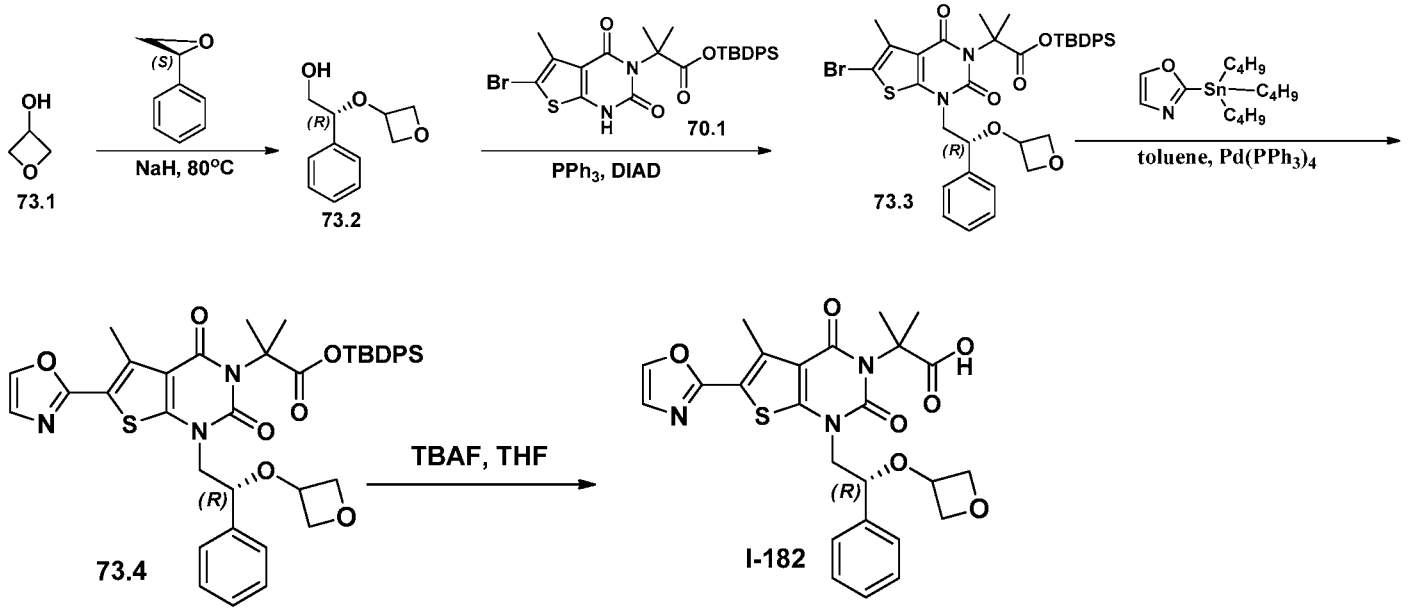
[00513] **Example 72: Synthesis of 2-[1-[(2R)-2-ethoxy-2-(2-methoxyphenyl)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-243).**



[00514] **Synthesis of compound 72.2.** Compound **72.2** was prepared in a manner analogous to compound **57.5**, substituting ethanol for isopropanol in the epoxide-opening step. Purification: The crude product (1.5 g) was purified by chiral preparative HPLC under the following conditions (Gilson Gx 281): Column: Venusil Chiral OD-H, 21.1*25 cm, 5 μm; mobile phase: hexanes and ethanol (hold at 5.0% ethanol for 12 min); detector: UV 220/254 nm. The second peak was collected. 0.59 g (36% from **57.2**) of **72.2** were obtained as a white solid.

[00515] **Synthesis of Compound I-243.** Compound **I-243** was prepared in a manner analogous to the synthesis of compound **I-158** (Example 57). Purification: silica gel column with dichloromethane/methanol (100:1). Isolated a white solid in 37% overall yield from **70.1**. MS (ES): *m/z* 514 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.13 (t, *J* = 6.9 Hz, 3H), 1.75 (s, 3H), 1.79 (s, 3H), 2.79 (s, 3H), 3.32-3.53 (m, 2H), 3.80 (s, 3H), 4.06-4.10 (m, 1H), 4.21-4.28 (m, 1H), 5.21-5.26 (m, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 7.02 (t, *J* = 7.8, 1H), 7.24-7.29 (m, 2H), 7.46-7.49 (m, 1H), 7.97 (s, 1H).

[00516] **Example 73: Synthesis of 2-methyl-2-[5-methyl-6-(1,3-oxazol-2-yl)-1-[(2R)-2-(oxetan-3-yloxy)-2-phenylethyl]-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-182).**

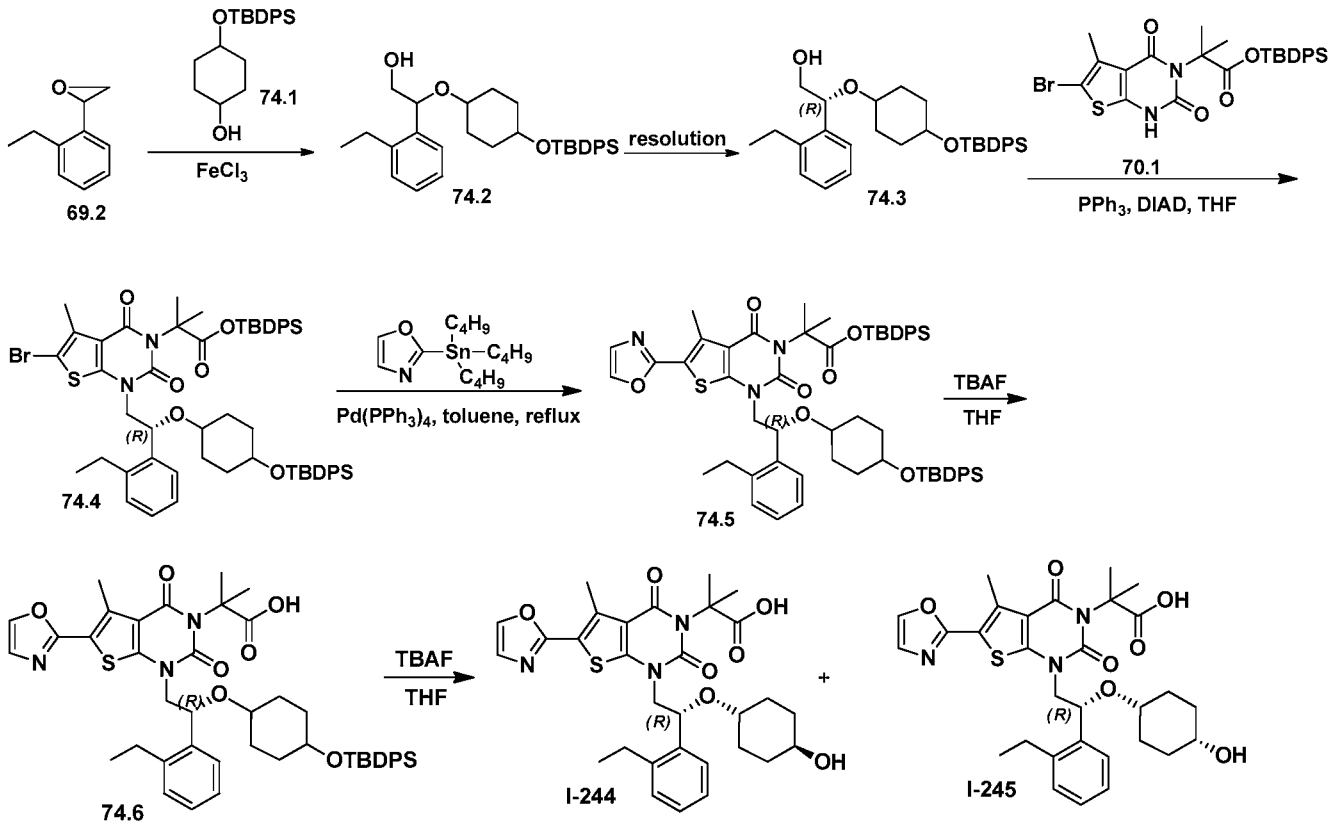


[00517] **Synthesis of compound 73.2.** Into a 50-mL round-bottom flask was placed (2S)-2-phenyloxirane (4 g, 33.29 mmol, 1.00 equiv) and oxetan-3-ol (16 mL). This was followed by the addition of sodium hydride (1.3 g, 32.50 mmol, 1.00 equiv, 60%) in several batches. The resulting solution was stirred for 1 h at 80 °C in an oil bath. The reaction was then quenched by

the addition of 50 mL of NH_4Cl (sat., aq.). The resulting solution was extracted with 2x50 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with PE/EA (8:1). Purification afforded 1.6 g (25%) of (2R)-2-(oxetan-3-yloxy)-2-phenylethan-1-ol (**73.2**) as a yellow oil.

[00518] Synthesis of Compound I-182. Compound **I-182** was prepared in a manner analogous to Example 57. Purification: The crude product was applied onto a silica gel column with dichloromethane/methanol (20:1). 23.6 mg (27%) of Compound **I-182** were obtained as a white solid. MS (ES): *m/z* 512 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.83 (s, 6H), 2.85 (s, 3H), 3.41-3.45 (t, 1H), 3.47-3.56 (t, 1H), 3.89-3.99 (m, 2H), 4.07-4.23 (m, 3H), 4.57-4.61 (m, 1H), 7.27-7.38 (m, 6H) ,7.99 (s, 1H).

[00519] Example 74: Synthesis of 2-(1-((R)-2-(2-ethylphenyl)-2-(((1r,4R)-4-hydroxycyclohexyl)oxy)ethyl)-5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)-2-methylpropanoic acid (I-244) and Example 75: Synthesis of 2-(1-((R)-2-(2-ethylphenyl)-2-(((1s,4S)-4-hydroxycyclohexyl)oxy)ethyl)-5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)-2-methylpropanoic acid (I-245).



[00520] **Synthesis of compound 74.1.** Into a 1000-mL 3-necked round-bottom flask was placed cyclohexane-1,4-diol (20 g, 172.18 mmol, 1.00 equiv), 1,4-dioxane (500 mL) and 1H-imidazole (17.58 g, 258.24 mmol, 1.50 equiv). This was followed by the addition of a solution of tert-butyl(chloro)diphenylsilane (49.69 g, 180.78 mmol, 1.05 equiv) in dioxane (100 mL) dropwise with stirring at 15 °C. The resulting solution was stirred for 15 h at 15-20 °C. The solids were filtered out. The filtrate was diluted with 200 mL of water. The resulting solution was extracted with 3x200 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (0:1-1:60-1:50-1:30-1:20). Purification afforded 32.98 g (54%) of 4-[(tert-butyldiphenylsilyl)oxy]cyclohexan-1-ol (**74.1**) as a white semi-solid.

[00521] **Synthesis of compound 74.2**. Compound **74.2** was prepared in a manner analogous to compounds **57.4** and **57.5**, substituting **74.1** for isopropanol in the epoxide-opening step. Purification: The crude product was applied onto a silica gel column with ethyl acetate/petroleum ether (1/10). The material thus obtained (1.8 g) was repurified by flash preparative HPLC under the following conditions (IntelFlash-1): Column: C18 silica gel; mobile phase: acetonitrile/water = 3/1 increasing to acetonitrile/water = 19/1 within 30 min; detector: UV 220 nm. 1.64 g of **74.2** were obtained as a colorless oil.

[00522] **Resolution of compound 74.3.** The enantiomers of **74.2** (2.09 g) were separated by chiral preparative HPLC under the following conditions (Gilson Gx 281): Column: Venusil Chiral OD-H, 21.1*25 cm, 5 μm; mobile phase: hexanes and IPA.

[00523] **Synthesis of compound 74.4.** Compound **74.4** was prepared in a manner analogous to compound **57.7**. Isolated a light yellow oil in 54% yield from **70.1**.

[00524] **Synthesis of compound 74.6.** Into a 100-mL round-bottom flask was placed **74.5** (486 mg, 0.46 mmol, 1.00 equiv), tetrahydrofuran (10 mL) and TBAF (120 mg, 0.46 mmol, 1.00 equiv). The resulting solution was stirred overnight at room temperature and then concentrated under vacuum. The residue was purified by thin layer chromatography developed with DCM/MeOH/HOAc (30/1/0.15). 78 mg (21%) of **74.7** were obtained as a white solid.

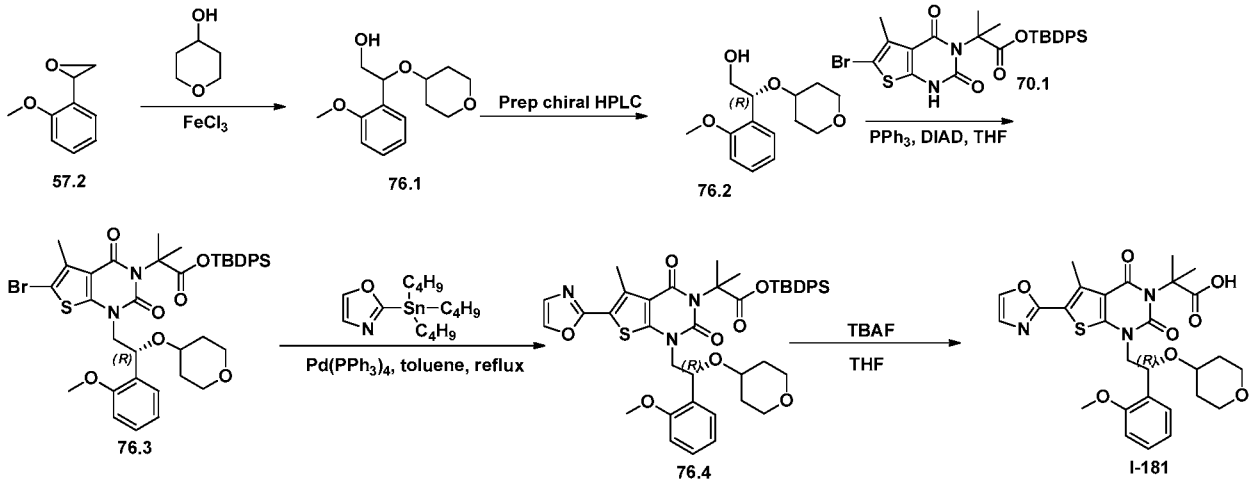
[00525] **Synthesis of Compounds I-244 and I-245**. Into a 25-mL round-bottom flask was placed compound **74.7** (78 mg, 0.10 mmol, 1.00 equiv), tetrahydrofuran (2 mL) and TBAF (100 mg, 0.38 mmol, 4.02 equiv). The resulting solution was stirred for 4 days at room temperature and then concentrated under vacuum. The residue was applied onto a silica gel column with

DCM/MeOH/HOAc (1:16:0.1). The product (70 mg) thus obtained was further purified by preparative HPLC under the following conditions (Waters): Column: SunFire Prep C18, 19*150 mm 5 μm; mobile phase: water (with 50 mM NH_4CO_3) and CH_3CN (5.0% CH_3CN up to 42.0% in 10 min, up to 95.0% in 2 min, down to 5.0% in 2 min); detector: UV 254/220 nm. 10.5 mg (38%) of Compound **I-244** and 4.6 mg (16%) of Compound **I-245** were obtained, both as white solids. MS (ES): *m/z* 582 $(M+H)^+$.

Analytical data for Compound **I-244**: ^1H NMR (CD_3OD, 300 MHz): δ 7.99 (1H, s), 7.63-7.60 (1H, m), 7.23-7.22 (4H, m), 5.26-5.22 (1H, dd, J_1 = 9.0 Hz, J_2 = 3.0 Hz), 4.30-4.25 (1H, d, J = 12.0 Hz), 3.70-3.62 (1H, t, J = 12.0 Hz), 3.50-3.47 (1H, m), 3.20-3.19 (1H, m), 3.08-2.90 (1H, m), 2.82 (3H, s), 2.80-2.69 (1H, m), 1.83 (3H, s), 1.81 (3H, s), 1.73-1.62 (4H, m), 1.36-1.31 (4H, m), 1.25-1.10 (3H, m).

Analytical data for Compound **I-245**: MS (ES): *m/z* 582 $(M+H)^+$; 604 $(M+Na)^+$. ^1H NMR (CD_3OD, 300 MHz): δ 7.97 (1H, s), 7.65-7.62 (1H, m), 7.32-7.25 (4H, m), 5.29-5.26 (1H, m), 4.30-4.26 (1H, m), 3.70-3.63 (1H, m), 3.54-3.45 (1H, m), 3.19-2.96 (1H, m), 2.82 (3H, s), 2.76-2.63 (1H, m), 1.94 (3H, s), 1.91 (3H, s), 1.81-1.67 (2H, m), 1.53-1.38 (9H, m).

[00526] Example 76: Synthesis of 2-[1-[2-(2-methoxyphenyl)-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-181).



[00527] Synthesis of compound 76.1. Into a 250-mL 3-necked round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed oxan-4-ol (86 g, 842.05 mmol, 2.01 equiv) and $FeCl_3$ (10 g). This was followed by the addition of **57.2** (63 g, 419.51 mmol, 1.00 equiv) dropwise with stirring at 0 °C. The resulting solution was stirred for 3 h at room

temperature. The resulting solution was diluted with 500 mL of H_2O. The resulting solution was extracted with 3x1000 mL of ethyl acetate and the organic layers combined. The resulting solution was extracted with 3x300 mL of sodium chloride (sat.) and the organic layers combined and dried over anhydrous sodium sulfate. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). This resulted in 22 g (21%) of **76.1** as a white solid.

[00528] **Synthesis of compound 76.2.** The enantiomers of **76.1** (22g) were resolved by chiral preparative HPLC under the following conditions (Gilson Gx 281): Column: Venusil Chiral OD-H, 21.1*25 cm, 5 μm; mobile phase: hexanes (0.2% TEA) and ethanol (0.2% TEA) (hold at 10% ethanol (0.2%TEA) for 13 min); detector: UV 220/254 nm. 11.4 g (52%) of **76.2** were obtained as a white solid.

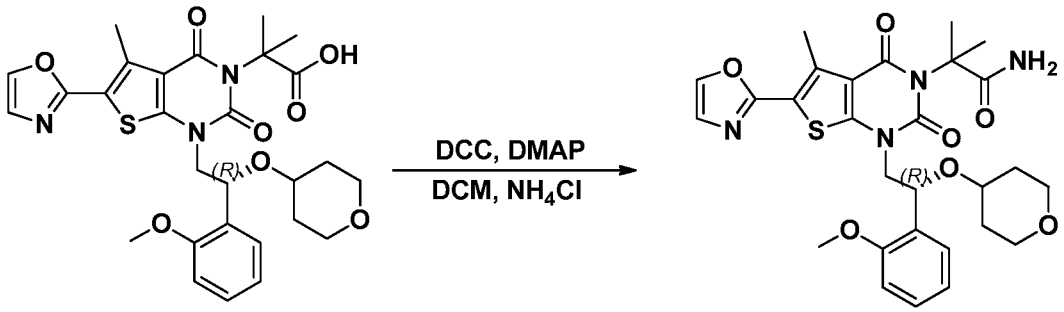
[00529] **Synthesis of compound 76.3.** Into a 500-mL 3-necked round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed **70.1** (12 g, 20.49 mmol, 1.00 equiv), tetrahydrofuran (200 mL), **76.2** (6.2 g, 24.57 mmol, 1.20 equiv) and DIAD (6.5 g, 32.18 mmol, 1.57 equiv). This was followed by the addition of a solution of triphenylphosphane (8.4 g, 32.03 mmol, 1.56 equiv) in tetrahydrofuran (100 mL) dropwise with stirring at 0 °C in 60 min. The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). This resulted in 17 g (crude) of **76.3** as a white solid.

[00530] **Synthesis of compound 76.4.** Into a 500-mL 3-necked round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed **76.3** (17 g, crude), toluene (300 mL), $Pd(PPh_3)_4$ (1.7 g, 1.47 mmol, 0.07 equiv) and 2-(tributylstannyl)-1,3-oxazole (8.6 g, 24.02 mmol, 1.16 equiv). The resulting solution was stirred overnight at 110 °C. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). Purification afforded 6 g of **76.4** as a white solid.

[00531] **Synthesis of compound I-181.** Into a 250-mL 3-necked round-bottom flask, was placed **76.4** (6 g, 7.43 mmol, 1.00 equiv), tetrahydrofuran (100 mL), TBAF (2.3 g, 8.80 mmol, 1.18 equiv). The resulting solution was stirred for 1 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (50:1). This resulted in 3.4 g (80%) of Compound **I-181** as a white solid.

[00532] Purification: MS (ES): *m/z* 570 $(M+H)^+$, 592 $(M+Na)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 1.22-1.36 (m, 2H), 1.62 (m, 8H), 2.75 (s, 3H), 3.20-3.39 (m, 3H), 3.48-3.58 (m, 2H), 3.80 (s, 3H), 3.85-4.20 (m, 2H), 5.30 (m, 1H), 7.03 (m, 2H), 7.33-7.50 (m, 3H), 8.2 (s, 1H).

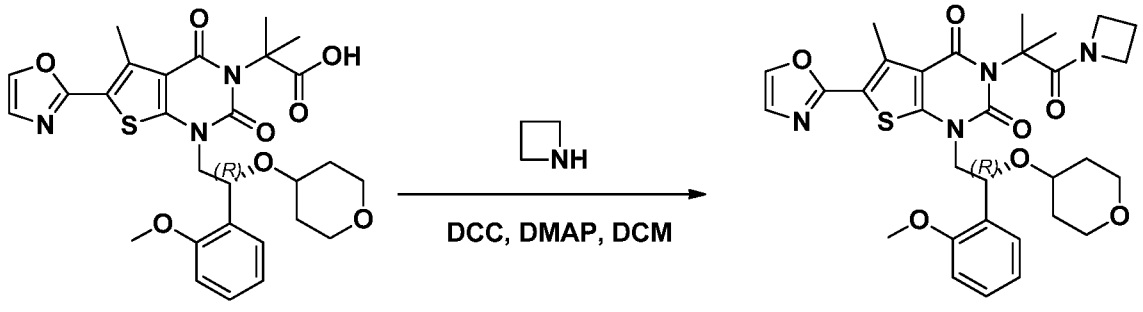
[00533] Example 77: Synthesis of 2-[1-[(2R)-2-(2-methoxyphenyl)-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanamide (I-246).



I-181 I-246

[00534] Compound **I-246** was prepared from Compound **I-181** according to the method of Example 4. Purification: silica gel column with dichloromethane/methanol (40:1). Isolated a white solid in 37% yield. MS (ES): *m/z* 591 $(M+Na)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.29-1.36 (m, 2H), 1.65-1.67 (m, 8H), 2.75 (s, 3H), 3.20-3.26 (m, 2H), 3.50-3.59 (m, 2H), 3.79 (s, 3H), 3.95-4.09 (m, 2H), 5.26-5.31 (t, 1H), 6.78 (brs, 1H), 6.97-7.10 (m, 3H), 7.27-7.33 (m, 1H), 7.39 (s, 1H),7.47-7.49 (m, 1H), 8.22 (s, 1H).

[00535] Example 78: Synthesis of 3-[1-(azetidin-1-yl)-2-methyl-1-oxopropan-2-yl]-1-[(2R)-2-(2-methoxyphenyl)-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-2,4-dione (I-247).

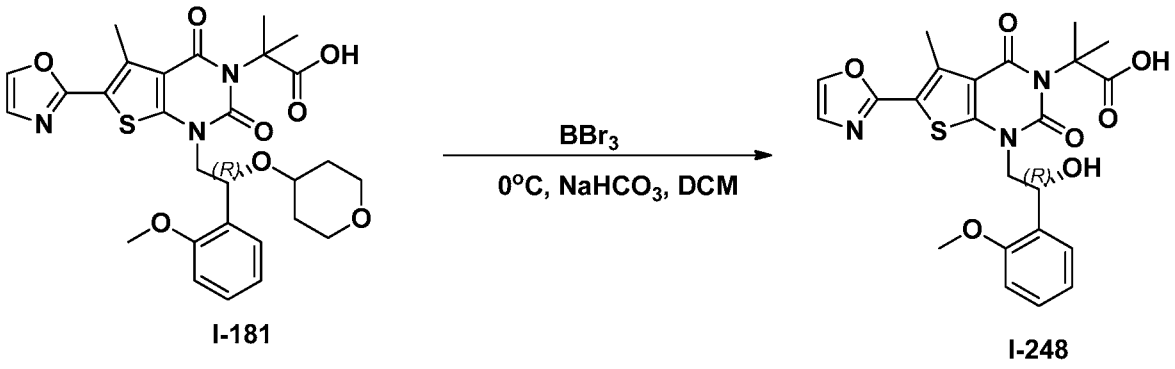


I-181 I-247

[00536] Compound **I-247** was prepared from Compound **I-181** and azetidine according to the method of Example 4. Purification: MS (ES): *m/z* 609 $(M+H)^+$. ^1H NMR (DMSO-d_6, 300 MHz):

δ 8.24 (1H, s), 7.48-7.46 (1H, d), 7.40 (1H, s), 7.31-7.29 (1H, t), 7.06-7.00 (2H, m), 5.31-5.29 (1H, m), 3.91-3.89 (2H, m), 3.86-3.81 (4H, m), 3.81 (3H, s), 3.70-3.58 (2H, m), 3.38-3.24 (1H, m), 3.23-3.21 (2H, m), 2.78 (3H, s), 2.14-2.09 (2H, t), 1.64-1.63 (8H, m), 1.40-1.15 (2H, m).

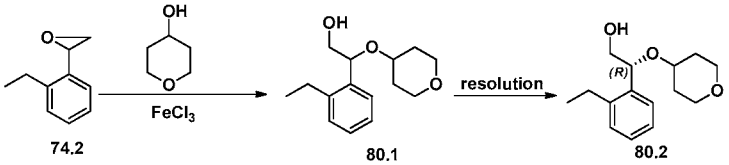
[00537] Example 79: Synthesis of 2-[1-[(2R)-2-hydroxy-2-(2-methoxyphenyl)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-248).



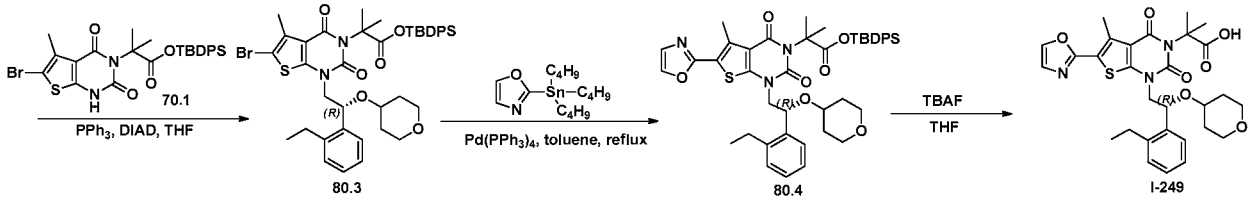
I-181 I-248

[00538] Into a 50-mL round-bottom flask was placed **I-181** (100 mg, 0.18 mmol, 1.00 equiv), sodium bicarbonate (798 mg, 9.50 mmol, 50.11 equiv) and dichloromethane (10 mL). This was followed by the addition of BBr_3 (476 mg, 10.03 equiv) dropwise with stirring at 0 °C. The resulting solution was stirred for 0.5 h at room temperature and then concentrated under vacuum. The residue was purified by thin layer chromatography developed with methanol/DCM (1:20). 9.6 mg (11%) of Compound **I-248** were obtained as a white solid. MS (ES): *m/z* 586 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.79-1.82 (d, 6H), 2.78 (s, 3H), 3.33 (s, 3H), 4.00-4.05 (m, 1H), 4.25-4.31 (m, 1H), 5.14-5.17 (t, 1H), 6.71-6.73 (d, 1H), 6.87-6.90 (t, 1H), 7.07-7.11 (t, 1H), 7.25 (s, 1H), 7.35-7.36 (d, 1H), 7.96 (s, 1H).

[00539] Example 80: Synthesis of 2-[1-[(2R)-2-(2-ethylphenyl)-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-249).



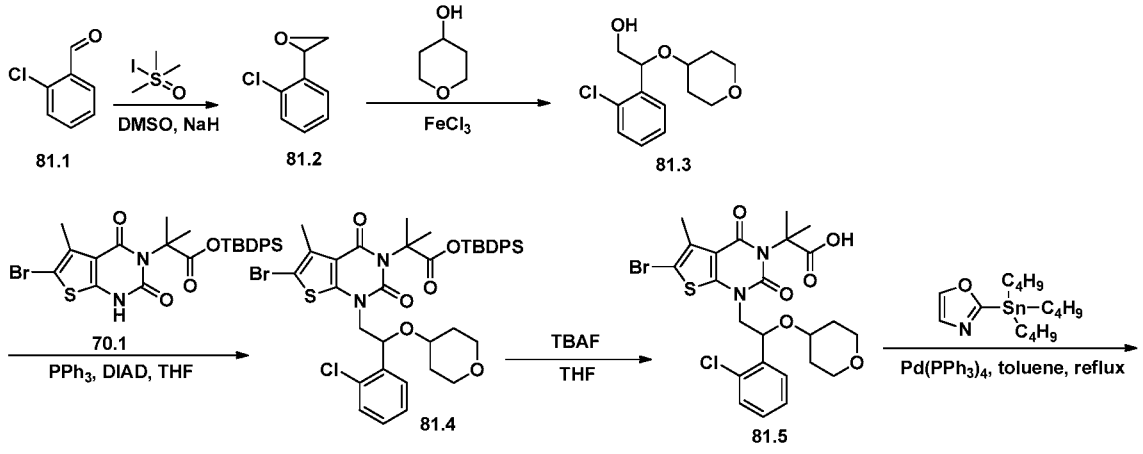
74.2 80.1 80.2

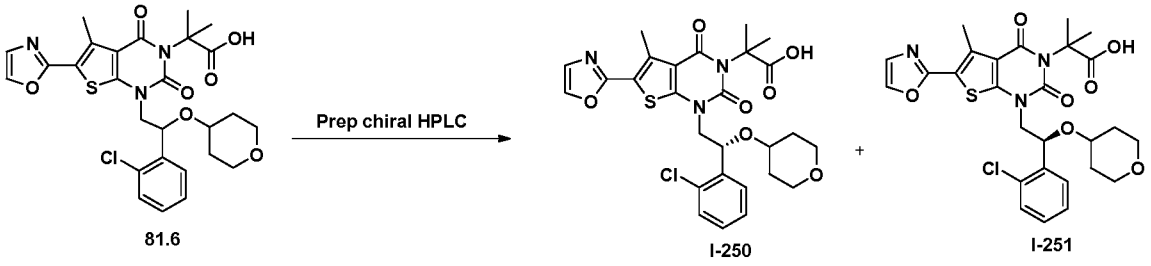


[00540] **Synthesis of compound 80.2.** Compound **80.2** was prepared according to the method for the preparation of compound **57.5**. Purification: The enantiomers of the racemic product (550 mg) were separated by chiral preparative HPLC under the following conditions (Gilson Gx 281): column: Venusil Chiral OD-H, 21.1*25 cm, 5 μm; mobile phase: hexanes and ethanol (hold at 5% ethanol for 7 min); detector: UV 220/254 nm. 300 mg product were obtained (0.05% yield from **74.2**).

[00541] **Synthesis of Compound I-249.** Compound **I-249** was prepared according to the method of Example 57. Purification: silica gel column with dichloromethane/methanol (40:1). 56.6 mg (80%) of Compound **I-249** were obtained as a white solid. MS (ES): *m/z* 568 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.23-1.28 (t, 3H), 1.40-1.42 (m, 2H), 1.64-1.68 (m, 2H), 1.77-1.81 (d, 6H), 2.72-2.76 (m, 1H), 2.80 (s, 3H), 2.89-2.94 (m, 1H), 3.32-3.62 (m, 6H), 4.26-4.27 (d, 1H), 5.22-5.26 (d, 1H), 7.22-7.27 (m, 4H), 7.59-7.62 (m, 1H), 7.96(s, 1H).

[00542] **Example 81: Synthesis of 2-[1-[(2R)-2-(2-chlorophenyl)-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-250) and Example 82: Synthesis of 2-[1-[(2S)-2-(2-chlorophenyl)-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-251).**





[00543] **Synthesis of compound 81.3.** Compound **81.3** was prepared according to the method used for the preparation of **57.3**, substituting 4-hydroxypyran for isopropanol in the epoxide-opening step. Isolated a light yellow liquid in 5% overall yield.

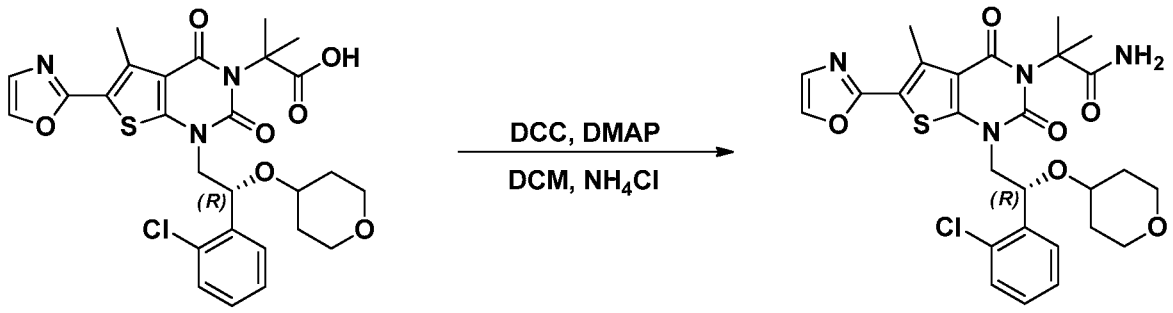
[00544] **Synthesis of compound 81.6.** Compound **81.6** was prepared from **81.3** and **70.1** following the procedure for Example 67. Purification: The residue obtained after work-up was applied onto a silica gel column and eluted with DCM/MeOH = 100:1. The product thus obtained was repurified by flash preparative HPLC under the following conditions (IntelFlash-1): Column: C18 silica gel; mobile phase: acetonitrile : water = 0 : 100 increasing to acetonitrile : water = 100 : 0 within 16 min; detector: UV 220 nm. 40 mg (23%) of **81.6** were obtained as a colorless oil.

[00545] **Synthesis of Compounds I-250 and I-251.** The enantiomers of **81.6** were separated by chiral preparative HPLC under the following conditions (Gilson Gx 281): Column: Chiralpak IA, 2*25 cm, 5 μm; mobile phase: hexanes and IPA (hold at 20% IPA for 22 min); detector: UV 220/254 nm. 2.8 mg (7%) of Compound **I-250** and 3.5 mg (9%) of **I-251** were obtained as white solids.

Analytical data for Compound **I-250**: MS (ES): *m/z* 574 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ 8.00 (s, 1H), 7.75 (d, 1H, *J* = 6.0 Hz), 7.45 (m, 2H), 7.35 (d, 1H, *J* = 5.1 Hz), 7.29 (s, 1H), 5.49 (q, 1H, *J* = 5.1 Hz), 4.32 (m, 1 H), 3.99 (m, 1H), 3.70 (m, 2 H), 3.50 (m, 1H), 3.40 (m, 2H), 2.83 (s, 3H), 1.82 (s, 3H), 1.80 (s, 3H), 1.75 (m, 2H), 1.52 (m, 2H).

Analytical data for Compound **I-251**: MS (ES): *m/z* 574 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ 7.99 (s, 1 H), 7.75 (d, 1 H, *J* = 6.0 Hz), 7.45 (m, 3 H), 7.29 (s, 1 H), 5.49 (q, 1 H, *J* = 3.3 Hz), 4.32 (m, 1 H), 3.99 (m, 1 H), 3.71-3.49 (m, 3 H), 3.38 (m, 2H), 2.83 (s, 3 H), 1.82(s, 3 H), 1.80 (s, 3 H), 1.74 (m, 2H), 1.50 (m, 2H).

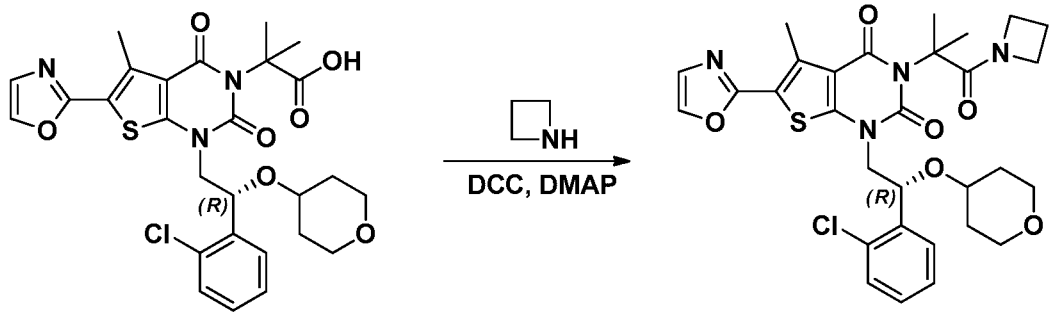
[00546] **Example 83: Synthesis of 2-[1-[(2R)-2-(2-chlorophenyl)-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanamide (I-252).**



I-250 I-252

[00547] Compound **I-252** was prepared from Compound **I-250** (Example 81) and ammonium chloride according to the method of Example 4. Isolated a white solid in 60% yield. MS (ES): *m/z* 595 $(M+Na)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 8.22 (1H, s), 7.70-7.67 (1H, d), 7.49-7.37 (4H, m), 7.30-6.70 (2H, m), 5.35-5.30 (1H, m), 4.30-4.15 (1H, m), 3.90-3.80 (1H, m), 3.54-3.52 (2H, m), 3.40-3.36 (1H, m), 3.32-3.21 (2H, m), 2.75 (3H, s), 1.66-1.60 (8H, m), 1.32-1.24 (2H, m).

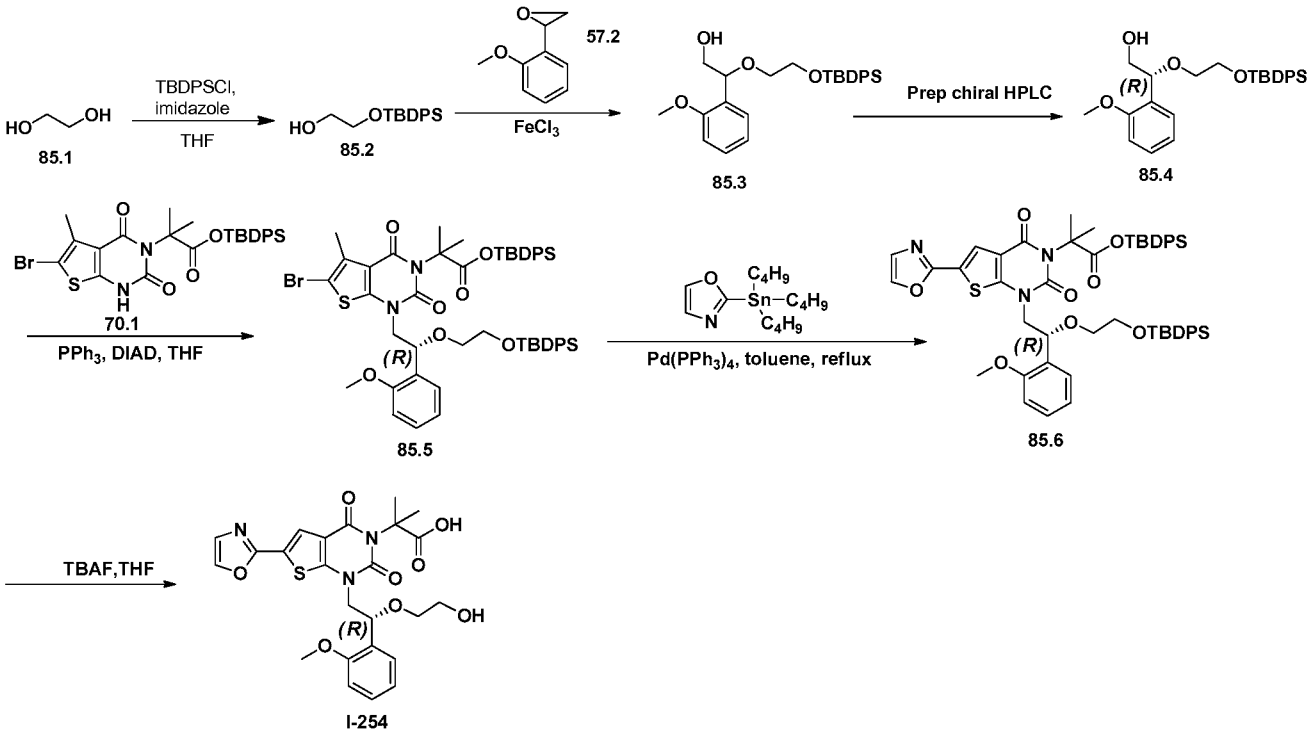
[00548] Example 84: Synthesis of 3-[1-(azetidin-1-yl)-2-methyl-1-oxopropan-2-yl]-1-[(2R)-2-(2-chlorophenyl)-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-2,4-dione (I-253).



I-250 I-253

[00549] Compound **I-253** was prepared from Compound **I-250** (Example 81) and azetidine according to the method of Example 4. Isolated a white solid in 49% yield. MS (ES): *m/z* 613 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 8.24 (1H, s), 7.69-7.66 (1H, d), 7.48-7.38 (4H, m), 5.35-5.30 (1H, m), 4.30-4.21 (1H, m), 3.90-3.88 (4H, m), 3.57-3.48 (2H, m), 3.33-3.30 (1H, m), 3.27-3.24 (3H, m), 2.77 (3H, s), 2.12 (2H, m), 1.70-1.61 (8H, m), 1.38-1.25 (2H, m).

[00550] Example 85: Synthesis of 2-[1-[(2R)-2-(2-hydroxyethoxy)-2-(2-methoxyphenyl)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-254).



[00551] **Synthesis of compound 85.2.** Into a 2-L 3-necked round-bottom flask was placed tetrahydrofuran (800 mL), ethane-1,2-diol (40 g, 644.46 mmol, 1.00 equiv) and imidazole (61.4 g, 901.92 mmol, 1.40 equiv). This was followed by the addition of TBDPSCl (186.3 g) dropwise with stirring at 0 °C in 30 min. The resulting solution was stirred overnight at room temperature. The solids were filtered out, and the filtrate cake was washed with 200 mL of EA. The resulting mixture was washed with 200 mL of brine and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:25). Purification afforded 83 g (43%) of 2-[(tert-butyldiphenylsilyl)oxy]ethan-1-ol (**85.2**) as a colorless oil.

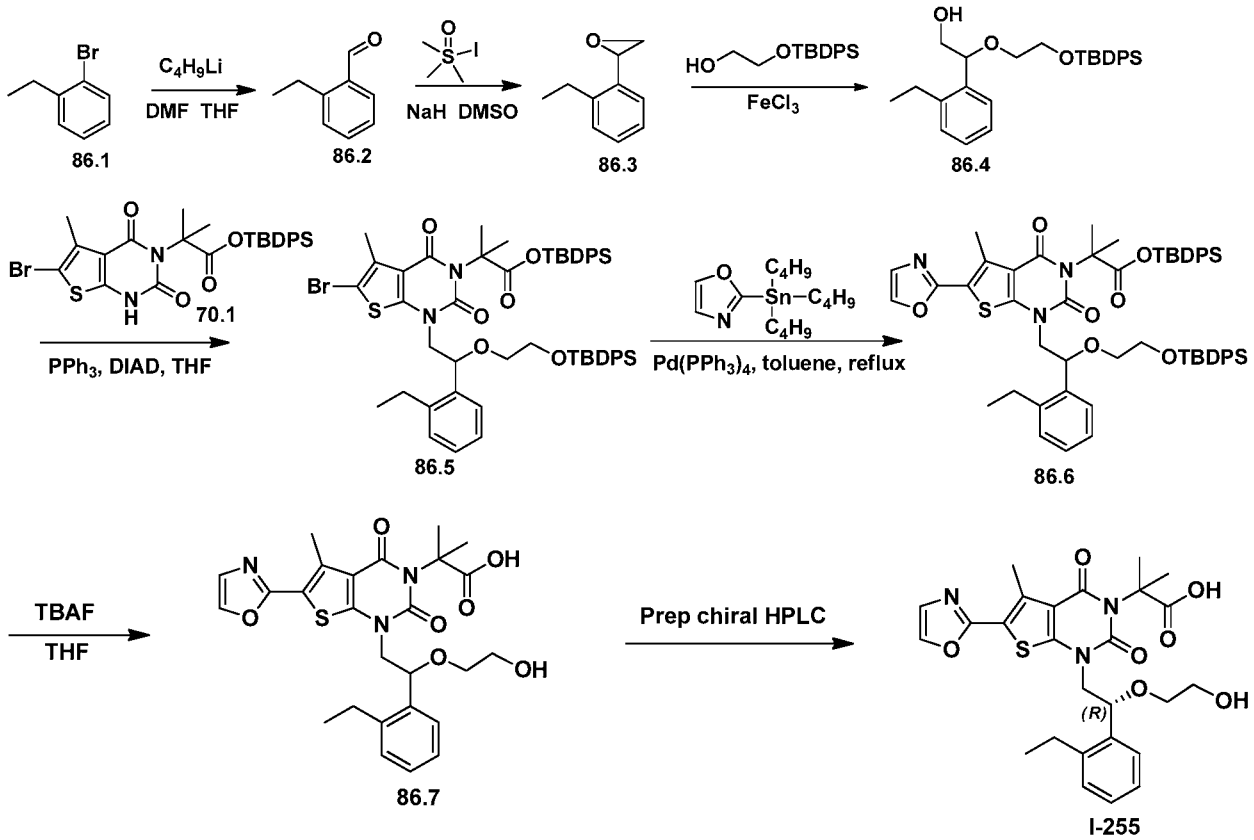
[00552] **Synthesis of compound 85.3.** Compound **85.3** was prepared according to the method used for the synthesis of **57.3**, substituting **85.2** for isopropanol. Isolated a yellow oil in 5% yield.

[00553] **Synthesis of compound 85.4.** The enantiomers of **85.3** were separated by chiral preparative HPLC under the following conditions (Gilson Gx 281): Column: Venusil Chiral OD-H, 21.1*25 cm, 5 μm; mobile phase: hexanes and IPA (hold at 2.0% IPA for 16 min); detector: UV 220/254 nm. 270 mg (39%) of **85.4** were obtained as a yellow oil.

[00554] **Synthesis of Compound I-254.** Compound **I-254** was prepared according to the method of Example 57. Purification: The residue obtained after work-up was applied onto a

silica gel column with dichloromethane/methanol (40:1). Purification afforded 14 mg (4% from **70.1**) of Compound **I-254** as a white solid. MS (ES): *m/z* 468 $(M-C_2H_5O_2)^+$, 530 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.65-1.67 (d, 6H), 2.69 (s, 3H), 3.20-3.39 (m, 1H), 3.41-3.49 (m, 1H), 3.51-3.57 (m, 2H), 3.68 (s, 3H), 3.88-3.95 (m,1H), 4.20-4.27 (m, 1H), 5.16-5.21 (t, 1H), 6.78-6.81 (d, 1H), 6.88-6.93 (t, 1H), 7.13-7.18 (m, 2H), 7.41-7.44 (d, 1H), 7.95 (s, 1H).

[00555] Example 86: Synthesis of 2-[1-[(2R)-2-(2-ethylphenyl)-2-(2-hydroxyethoxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-255).

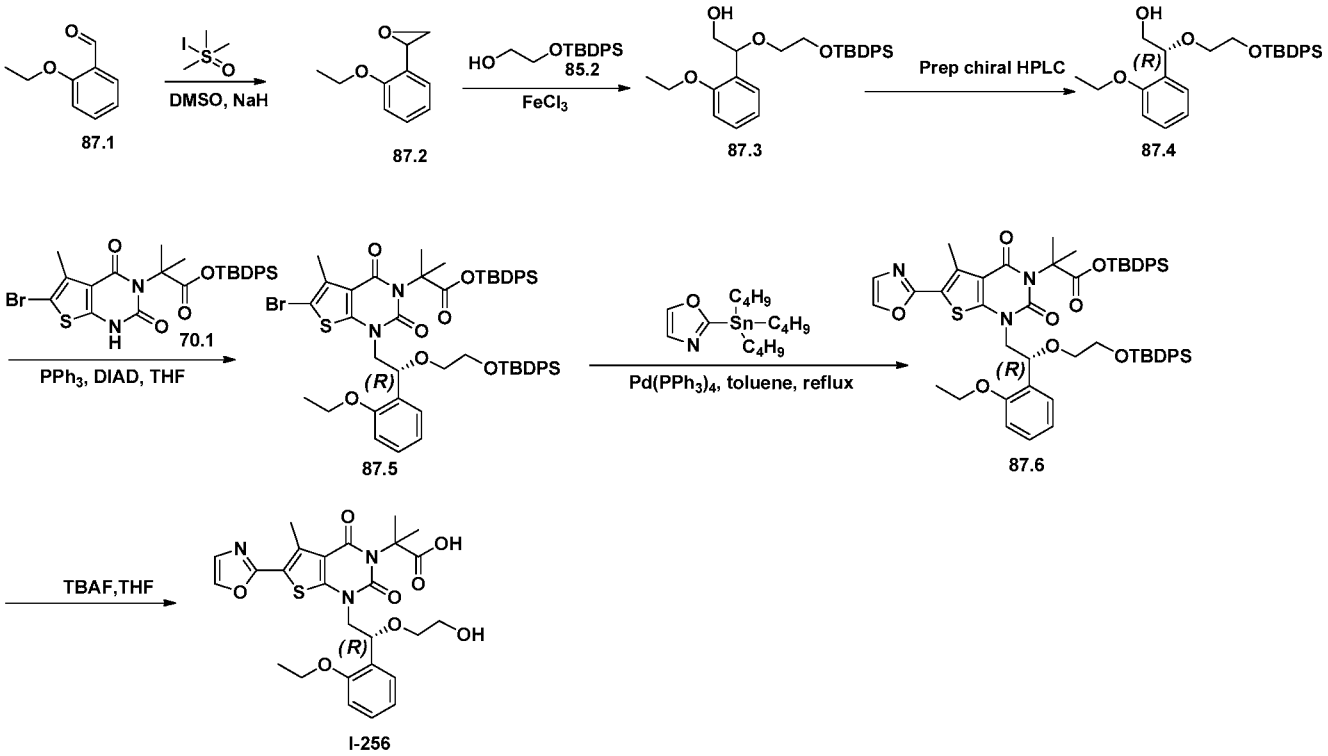


[00556] Synthesis of compound 86.5. Compound **86.5** was prepared in a manner analogous to compound **85.3**. Isolated a colorless oil in 2% yield.

[00557] Synthesis of compound 86.7. Compound **86.7** was prepared according to the method of Example 57. Purification: The residue obtained after work-up was applied onto a TLC plate with dichloromethane/methanol/HOAc (40:1:0.1). Purification afforded 406 mg (57% from **70.1**) of **86.7** as a white powder.

[00558] Synthesis of Compound I-255. The (*R*) enantiomer was isolated from 406 mg of **86.7** by chiral preparative HPLC under the following conditions: Column: CHIRALPAK IA; mobile phase: hexanes (0.1% acetic acid) : IPA = 75 : 25; detector: UV 254 nm. 44.5 mg of Compound **I-255** were obtained as a white solid. MS (ES): *m/z* 528 $(M+H)^+$. ^1H NMR (CD_3OD, 300 MHz): δ 7.98 (1H, d, J = 0.6 Hz), 7.62-7.59 (1H, m), 7.31-7.21 (4H, m), 5.19-5.15 (1H, dd, J_1 = 9 Hz, J_2 = 3.3 Hz), 4.26-4.20 (1H, dd, J_1 = 14.7 Hz, J_2 = 3.3 Hz), 3.93-3.85 (1H, dd, J_1 = 14.7 Hz, J_2 = 9 Hz), 3.57-3.53 (2H, m), 3.49-3.40 (1H, m), 2.96-2.87 (1H, m), 2.80-2.70 (4H, m), 1.81 (3H, s), 1.80 (3H, s), 1.30-1.25 (3H, t, J = 7.5 Hz).

[00559] Example 87: Synthesis of 2-[1-[(2R)-2-(2-ethoxyphenyl)-2-(2-hydroxyethoxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-256).

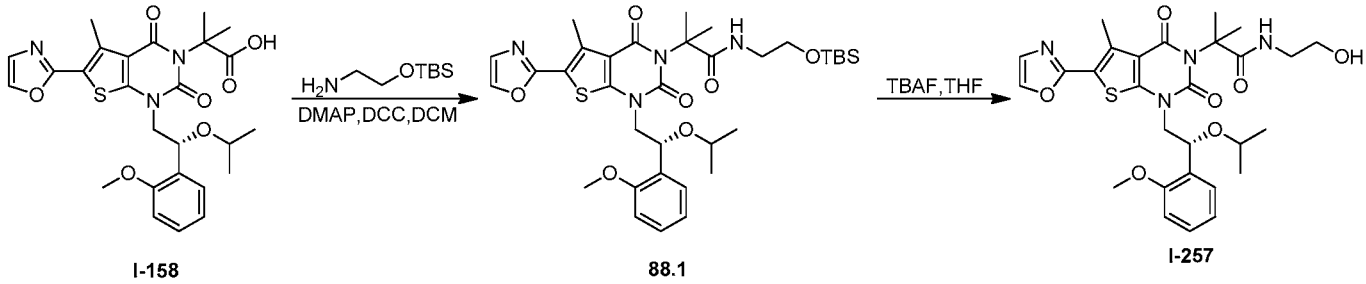


[00560] Synthesis of compound 87.4. Compound **87.4** was prepared from **87.1** in a manner analogous to compound **57.5**. Isolated a yellow oil in 2% overall yield.

[00561] Synthesis of Compound I-256. Compound **I-256** was prepared from **87.4** and **70.1** in a manner analogous to the synthesis of compound **I-158** (Example 57). MS (ES): *m/z* 482 $(M-C_2H_5O_2)^+$, 544 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.31-1.41 (t, 3H), 1.72-1.74 (d, 2H),

2.77-2.81 (s, 3H), 3.32-3.68 (m, 4H), 4.02-4.11 (m, 2H), 4.21-4.23 (m, 2H), 5.30-5.35 (t, 1H), 6.93-7.31 (m, 2H), 7.24-7.30 (m, 2H), 7.52-7.54 (d, 1H), 7.98 (s, 1H).

[00562] Example 88: Synthesis of N-(2-hydroxyethyl)-2-[1-[(2R)-2-(2-methoxyphenyl)-2-(propan-2-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanamide (I-257).

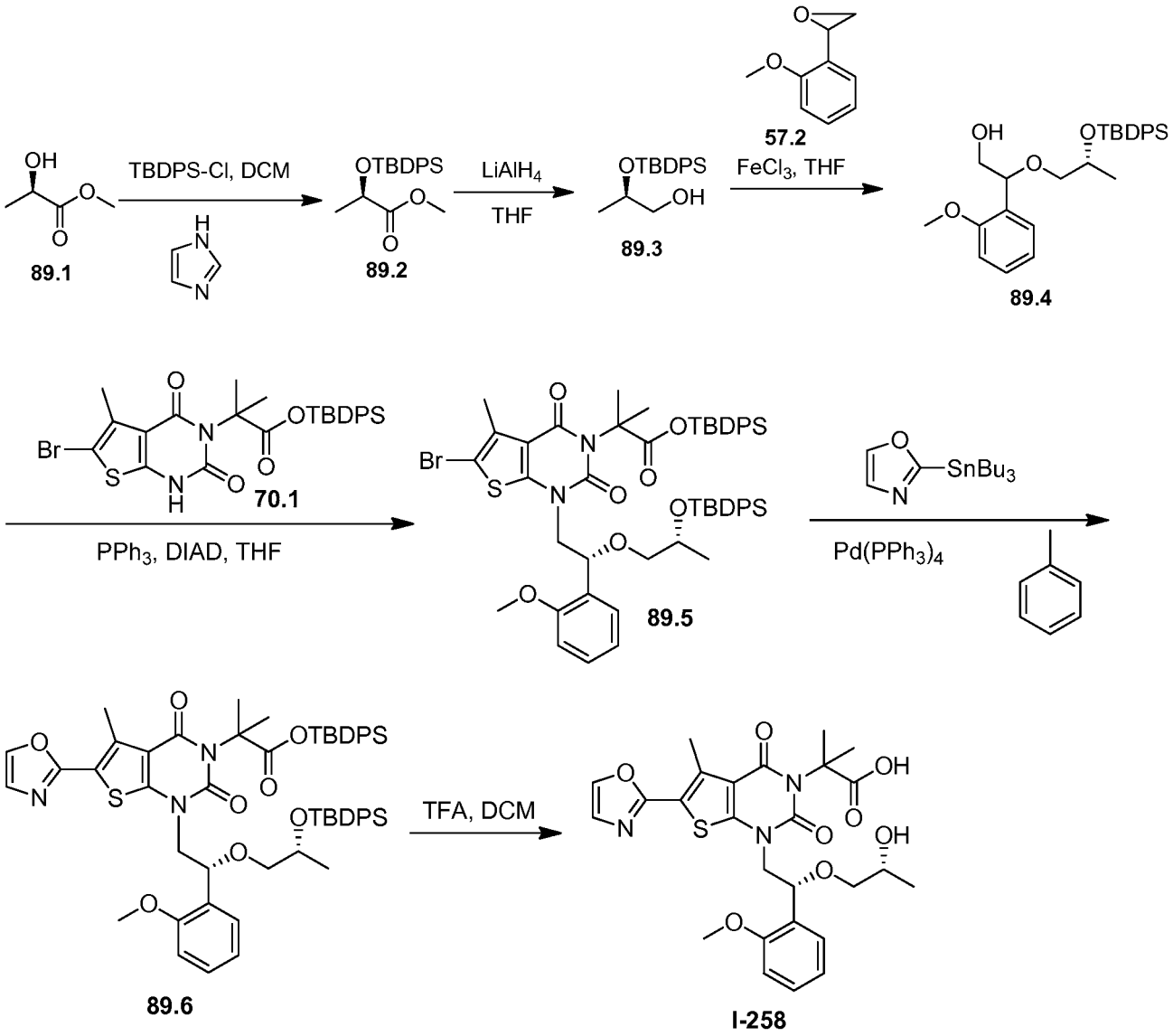


I-158 88.1 I-257

[00563] Synthesis of 88.1. Compound **88.1** was prepared from Compound **I-158** (Example 57) in a manner analogous to Example 4. Isolated a white solid in 48% yield.

[00564] Synthesis of Compound I-257. Into a 50-mL round-bottom flask was placed **88.1** (50 mg, 0.07 mmol, 1.00 equiv), TBAF (20 mg, 0.08 mmol, 1.05 equiv) and tetrahydrofuran (5 mL). The resulting solution was stirred for 3 h at room temperature and then concentrated under vacuum. The residue was purified by TLC with ethyl acetate/petroleum ether (1:1) to afford 8 mg (19%) of Compound **I-257** as a light yellow solid. MS (ES): *m/z* 571 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.14-1.15 (m, 6H), 1.71-1.96 (m, 6H), 2.41 (s, 3H), 3.33 (m, 1H), 3.46 (m, 1H), 3.56 (m, 1H), 3.74 (m, 4H), 3.93 (s, 3H), 5.13 (s, 1H), 7.00 (t, J = 7.6 Hz, 2H), 7.19 (s, 1H), 7.28-7.33 (t, J = 7.2 Hz, 1H), 7.46-7.48 (d, J = 7.6 Hz, 1H), 7.87 (s, 1H).

[00565] Example 89: Synthesis of 2-[1-[(2R)-2-[(2R)-2-hydroxypropoxy]-2-(2-methoxyphenyl)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-258).



[00566] **Synthesis of compound 89.2.** Into a 250-mL 3-necked round-bottom flask was placed dichloromethane (100 mL), methyl (2R)-2-hydroxypropanoate (10 g, 96.06 mmol, 1.00 equiv) and 1H-imidazole (9.8 g, 143.95 mmol, 1.50 equiv). This was followed by the addition of TBDPSCl (29.1 g, 112.45 mmol, 1.17 equiv) dropwise with stirring at 0 °C. The resulting solution was stirred for 2 h at room temperature and then concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:50). Purification afforded 32 g (97%) of **89.2** as a colorless oil.

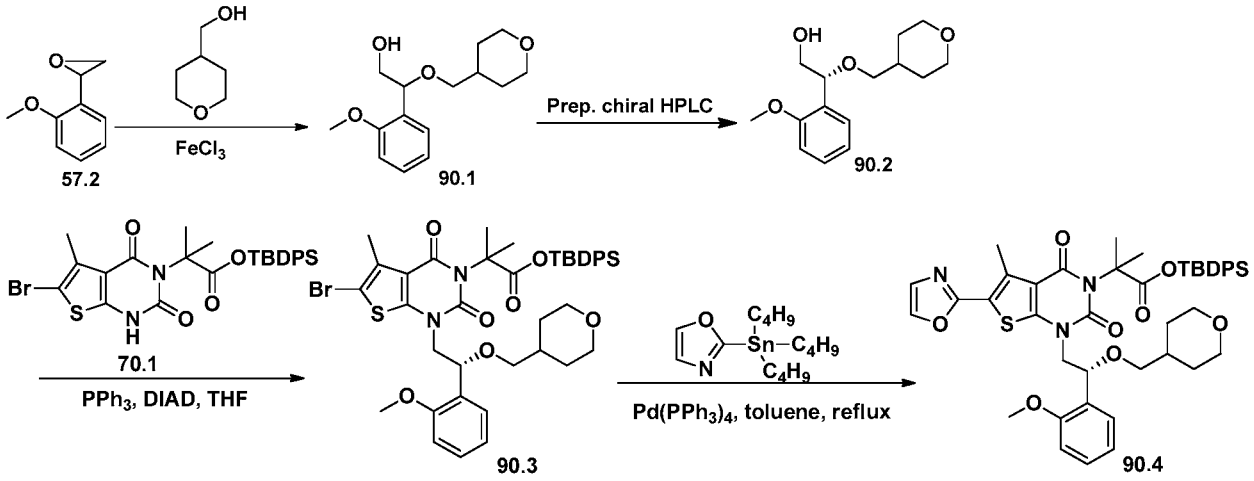
[00567] **Synthesis of compound 89.3.** Into a 500-mL 3-necked round-bottom flask was placed tetrahydrofuran (200 mL) and **89.2** (28 g, 81.75 mmol, 1.00 equiv). This was followed by the addition of $LiAlH_4$ (1.56 g, 41.11 mmol, 0.50 equiv) in portions at -30 °C. The resulting

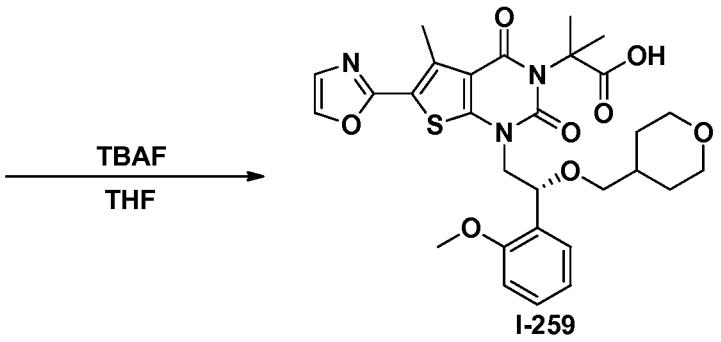
solution was stirred for 30 min at -30 °C. The reaction was then quenched by the addition of 100 mL of NH_4Cl (sat., aq.). The resulting solution was extracted with 3x200 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:30). This resulted in 11.8 g (46%) of (2R)-2-[(tert-butyldiphenylsilyl)oxy]propan-1-ol (**89.3**) as a colorless oil.

[00568] Synthesis of compound 89.4. Compound **89.4** was prepared from **57.2** and compound **89.3** in a manner analogous to compound **57.3**. Isolated a colorless oil in 1% yield.

[00569] Synthesis of Compound I-258. Compound **I-258** was prepared from **89.4** and **70.1** in a manner analogous to the preparation of compound **14.5**. Isolated a white solid in 22% yield from **70.1**. MS (ES): *m/z* 544 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.05 (d, *J* = 7.2 Hz, 3H), 1.79-1.80 (m, 6H), 2.81 (s, 3H), 3.13-3.18 (m, 1H), 3.83-3.87 (m, 4H), 4.01-4.06 (m, 1H), 4.28-4.34 (m, 1H), 5.27-5.31 (m, 1H), 6.94 (d, *J* = 8.4, 1H), 7.03 (t, *J* = 7.6, 1H), 7.26-7.30 (m, 2H), 7.54 (d, *J* = 7.6, 1H), 7.98 (s, 1H).

[00570] Example 90: Synthesis of 2-[1-[(2R)-2-(2-methoxyphenyl)-2-(oxan-4-ylmethoxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-259).



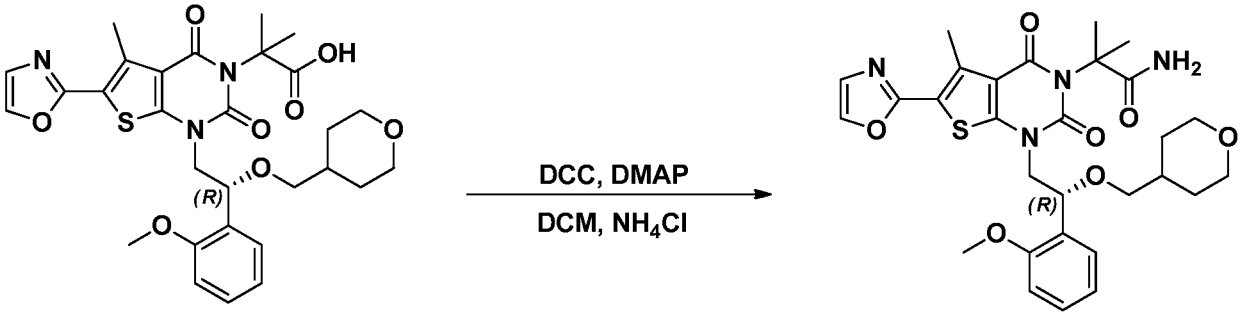


I-259

[00571] **Synthesis of compound 90.2.** Compound **90.2** was prepared from **57.2** and (tetrahydro-2H-pyran-4-yl)methanol in a manner analogous to the synthesis of **57.5**. Chiral separation: Gilson Gx 281; Column: Venusil Chiral OD-H, 0.46*25 cm, 5 μm; mobile phase: hexanes and EtOH (hold at 5.0% EtOH for 18 min); detector: UV 254 nm. Isolated 970 mg (12%) of a colorless oil.

[00572] **Synthesis of Compound I-259.** Compound **I-259** was prepared from **90.2** and **70.1** in a manner analogous to the preparation of Compound **I-158**, Example 57. MS (ES): *m/z* 584 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.13-1.46 (m, 2H), 1.51-1.57 (m, 2H), 1.62-1.80 (m, 7H), 2.76-2.81 (s, 3H), 3.07-3.12 (t, 1H), 3.25-3.56 (m, 3H), 3.82-3.92 (m, 5H), 4.09-4.21 (m, 2H, 5.21-5.26 (t, 1H), 6.95-7.05 (m, 2H), 7.32-7.32 (m, 2H), 7.44-7.47 (m, 1H), 8.00 (s, 1H).

[00573] **Example 91: Synthesis of 2-[1-[(2R)-2-(2-methoxyphenyl)-2-(oxan-4-ylmethoxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanamide (I-260).**

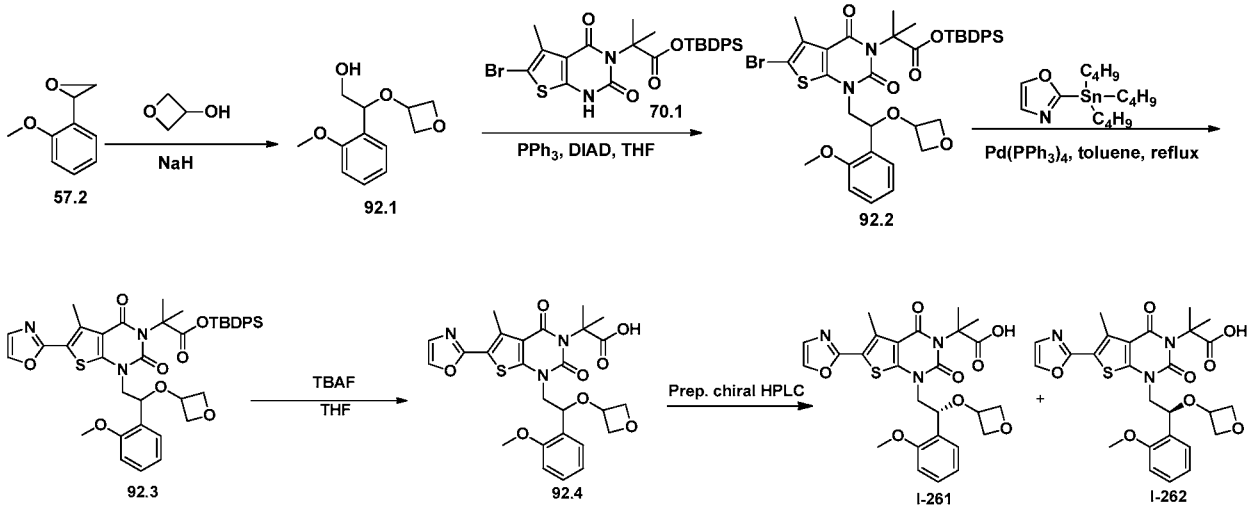


I-259 I-260

[00574] Compound **I-260** was prepared from Compound **I-259** (Example 90) according to the method of Example 4. Isolated a white solid in 43% yield. MS (ES): *m/z* 583 $(M+H)^+$, 605 $(M+Na)^+$. ^1H NMR (DMSO-d_6, 300 MHz): δ 8.22 (1H, s), 7.39-7.26 (3H, m), 7.05-6.97 (3H,

m), 6.70 (1H, br s), 5.12-5.08 (1H, m), 4.07-3.94 (2H, m), 3.78-3.70 (5H, m), 3.19-3.00 (4H, m), 2.73 (3H, s), 1.65-1.64 (7H, m), 1.44-1.36 (2H, m), 1.20-0.99 (2H, m).

[00575] Example 92: Synthesis of (R)-2-(1-(2-(2-methoxyphenyl)-2-(oxetan-3-yloxy)ethyl)-5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)-2-methylpropanoic acid (I-261) and Example 93: Synthesis of (S)-2-(1-(2-(2-methoxyphenyl)-2-(oxetan-3-yloxy)ethyl)-5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)-2-methylpropanoic acid (I-262).



[00576] Synthesis of compound 92.1. Compound **92.1** was prepared from **57.2** in a manner analagous to the preparation of **73.2**. Isolated a yellow oil in 8% yield.

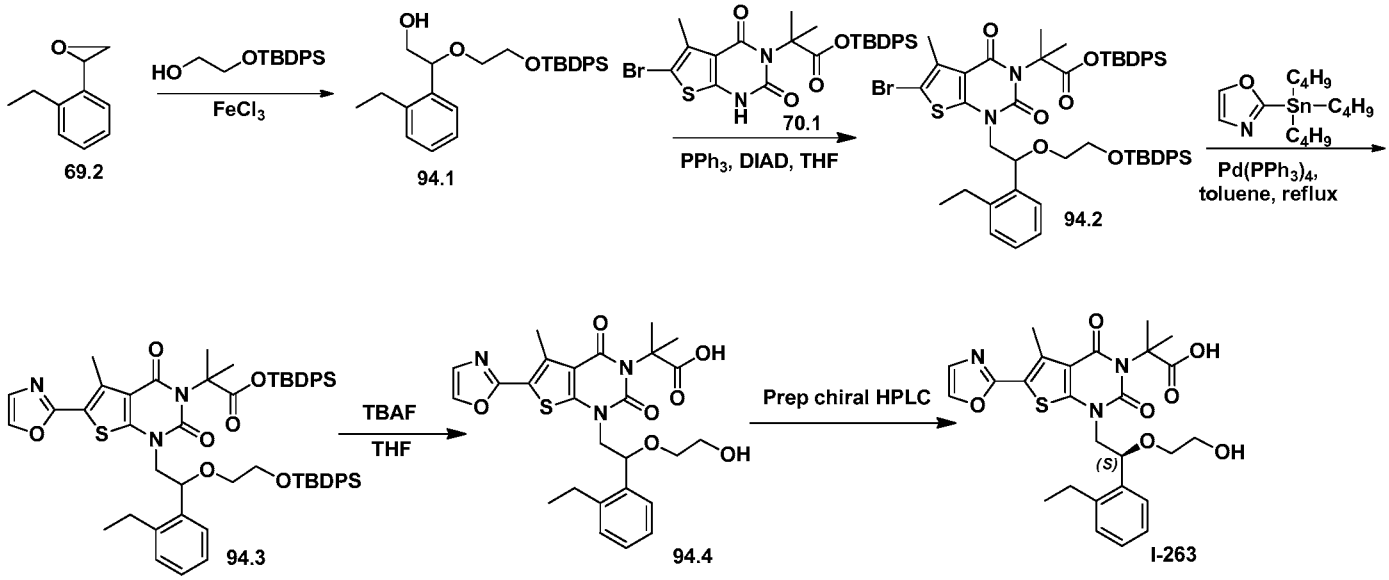
[00577] Synthesis of compound 92.4. Compound **92.4** was prepared from **92.1** and **70.1** in a manner analogous to the synthesis of Compound **I-158**, Example 57. Isolated a white solid in 15% yield from **70.1**.

[00578] Synthesis of Compounds I-261 and I-262. The enantiomers of **92.4** (100 mg) were separated by chiral preparative HPLC under the following conditions (Gilson Gx 281): Column: Chiralpak IC, 2*25 cm, 5 μm; mobile phase: hexanes (0.1% DEA) and ethanol (0.2% DEA) (hold at 25.0% ethanol (0.2% DEA) for 8 min); detector: UV 220/250 nm. 11.1 mg of Compound **I-261** and 10.2 mg of Compound **I-262** were obtained.

Analytical data for Compound **I-261**: MS (ES): *m/z* 542 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.68-1.69 (d, 6H), 2.73 (s, 3H), 3.70 (s, 3H), 4.10-4.16 (m, 1H), 4.26-4.38 (m, 3H), 4.61-4.71 (m, 3H), 6.02 (br s, 1H), 7.00-7.08 (m, 2H) , 7.32 (s, 1H), 7.37-7.40 (m, 1H), 7.42-7.56 (m, 1H), 8.17 (s, 1H), 12.4 (br s, 1H).

Analytical data for Compound **I-262**: MS (ES): *m/z* 542 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.68-1.69 (d, 6H), 2.73 (s, 3H), 3.70 (s, 3H), 4.10-4.16 (m, 1H), 4.26-4.38 (m, 3H), 4.61-4.71 (m, 3H), 6.01 (br s, 1H), 7.00-7.08 (m, 2H), 7.32 (s, 1H), 7.37-7.40 (m, 1H), 7.42-7.56 (m, 1H), 8.17 (s, 1H), 12.40 (br s, 1H).

[00579] Example 94: Synthesis of 2-[1-[(2S)-2-(2-ethylphenyl)-2-(2-hydroxyethoxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-263).

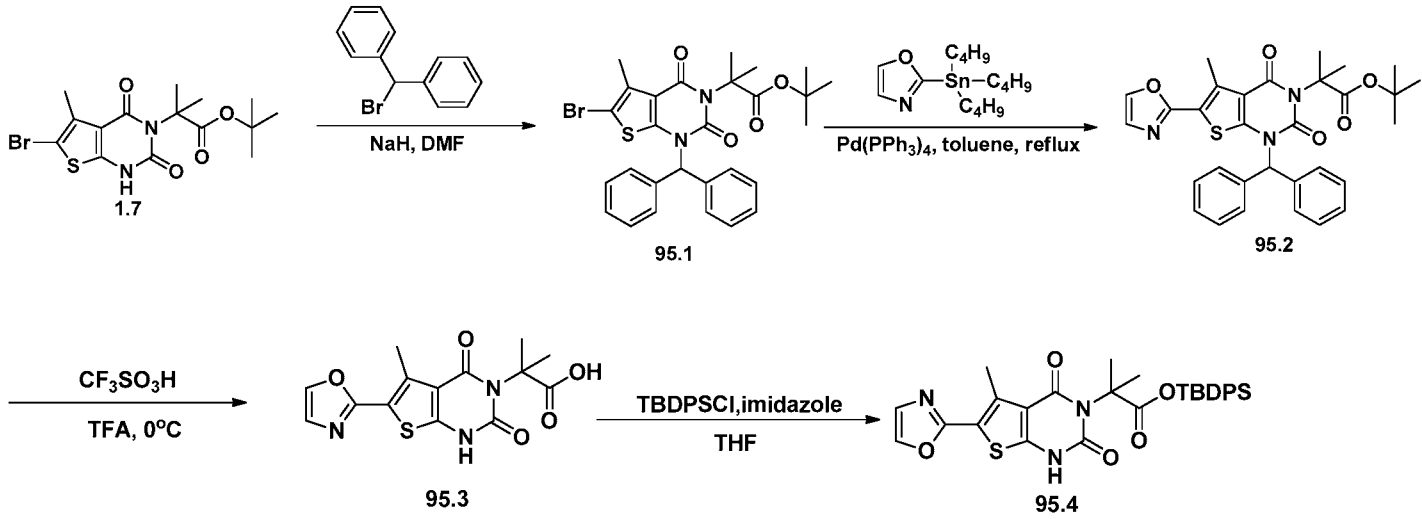


[00580] Synthesis of compound 94.1. Compound **94.1** was prepared from **69.2** using the same method as for **57.3**. Isolated a colorless oil in 2% yield.

[00581] Synthesis of compound 94.4. Compound **94.4** was prepared from **94.1** and **70.1** using the same procedure as for Compound **I-158**, Example 57. Isolated a white powder in 57% yield.

[00582] Isolation of Compound I-263. The enantiomers of **94.4** (406 mg) were separated by chiral preparative HPLC under the following conditions: Column: CHIRALPAK IA; mobile: hexanes (0.1% acetic acid):IPA = 75:25; detector: UV 254 nm. 34.2 mg of Compound **I-263** were obtained as a white solid. MS (ES): *m/z* 528 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): 7.98 (1H, d, *J*=0.6 Hz), 7.62-7.59 (1H, m), 7.31-7.21 (4H, m), 5.19-5.15 (1H, dd, J_1=9 Hz, J_2=3.3 Hz), 4.26-4.20 (1H, dd, J_1=14.7 Hz, J_2=3.3 Hz), 3.93-3.85 (1H, dd, J_1=14.7 Hz, J_2=9 Hz), 3.57-3.53 (2H, m), 3.49-3.40 (1H, m), 2.96-2.87 (1H, m), 2.80-2.70 (4H, m), 1.81 (3H, s), 1.80 (3H, s), 1.30-1.25 (3H, t, *J*=7.5 Hz).

[00583] Example 95: Synthesis of Intermediate 95.4.



[00584] Synthesis of compound 95.1. Into a 250-mL 3-necked round-bottom flask was placed **1.7** (5 g, 12.40 mmol, 1.00 equiv), N,N-dimethylformamide (60 mL), [bromo(phenyl)methyl]benzene (3.966 g, 16.05 mmol, 1.29 equiv) and sodium hydride (644.8 mg, 16.12 mmol, 1.30 equiv, 60%). The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 300 mL of water. The resulting solution was extracted with 4x200 mL of ethyl acetate and the organic layers combined, washed with 200 mL of brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:30). Purification afforded 1.93 g (27%) of **95.1** as a yellow solid.

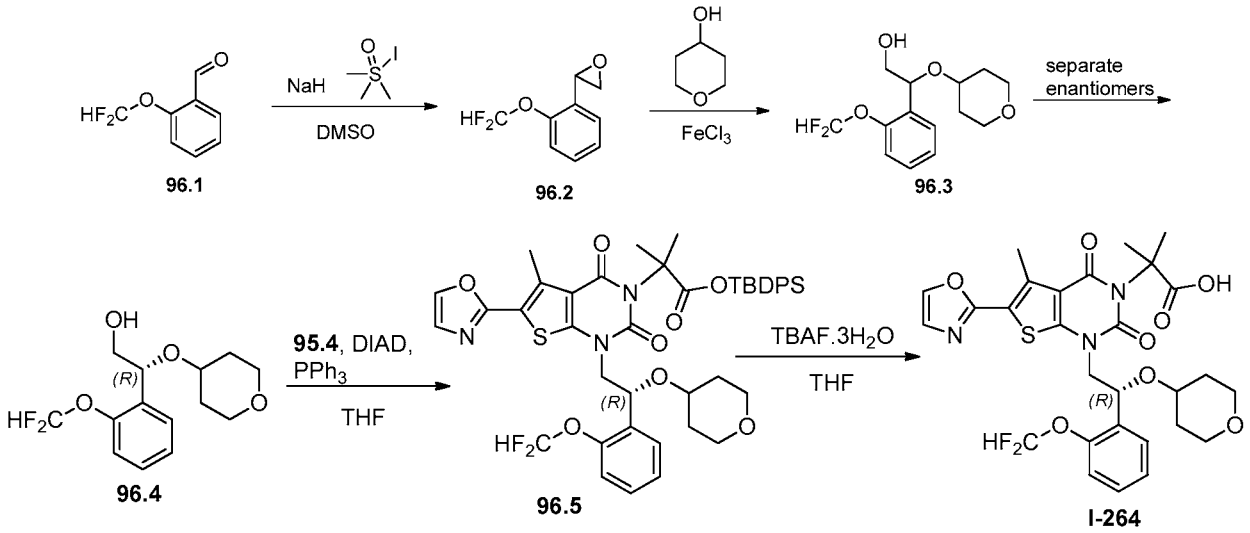
[00585] Synthesis of compound 95.2. Into a 250-mL 3-necked round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed **95.1** (8.15 g, 14.31 mmol, 1.00 equiv), toluene (40 mL), 2-(tributylstannyl)-1,3-oxazole (10.024 g, 27.99 mmol, 1.96 equiv) and $Pd(PPh_3)_4$ (2.426 g, 2.10 mmol, 0.15 equiv). The resulting solution was stirred under N_2 atmosphere overnight at 110 °C in an oil bath and then concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:20). Purification afforded 5.5 g (69%) of **95.2** as a brown solid.

[00586] Synthesis of compound 95.3. Into a 250-mL 3-necked round-bottom flask was placed **95.2** (5.5 g, 9.86 mmol, 1.00 equiv), trifluoroacetic acid (30 mL) and CF_3SO_3H (2.97 g). The resulting solution was stirred for 3 h at 0 °C in a water/ice bath and then diluted with 300 mL of water. The solids were collected by filtration and then dissolved in 100 mL of ethanol. The

resulting mixture was concentrated under vacuum. The solids were collected by filtration to afford 2.5 g (76%) of **95.3** as a white solid.

[00587] Synthesis of compound 95.4. Into a 100-mL 3-necked round-bottom flask was placed **95.3** (2.556 g, 7.58 mmol, 1.00 equiv), tetrahydrofuran (20 mL), tert-butyl(chloro)diphenylsilane (4.181 g, 15.21 mmol, 2.00 equiv) and imidazole (1.038 g, 15.26 mmol, 2.01 equiv). The resulting solution was stirred overnight at room temperature and then concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:30). Purification afforded 4 g (92%) of **95.4** as a white solid.

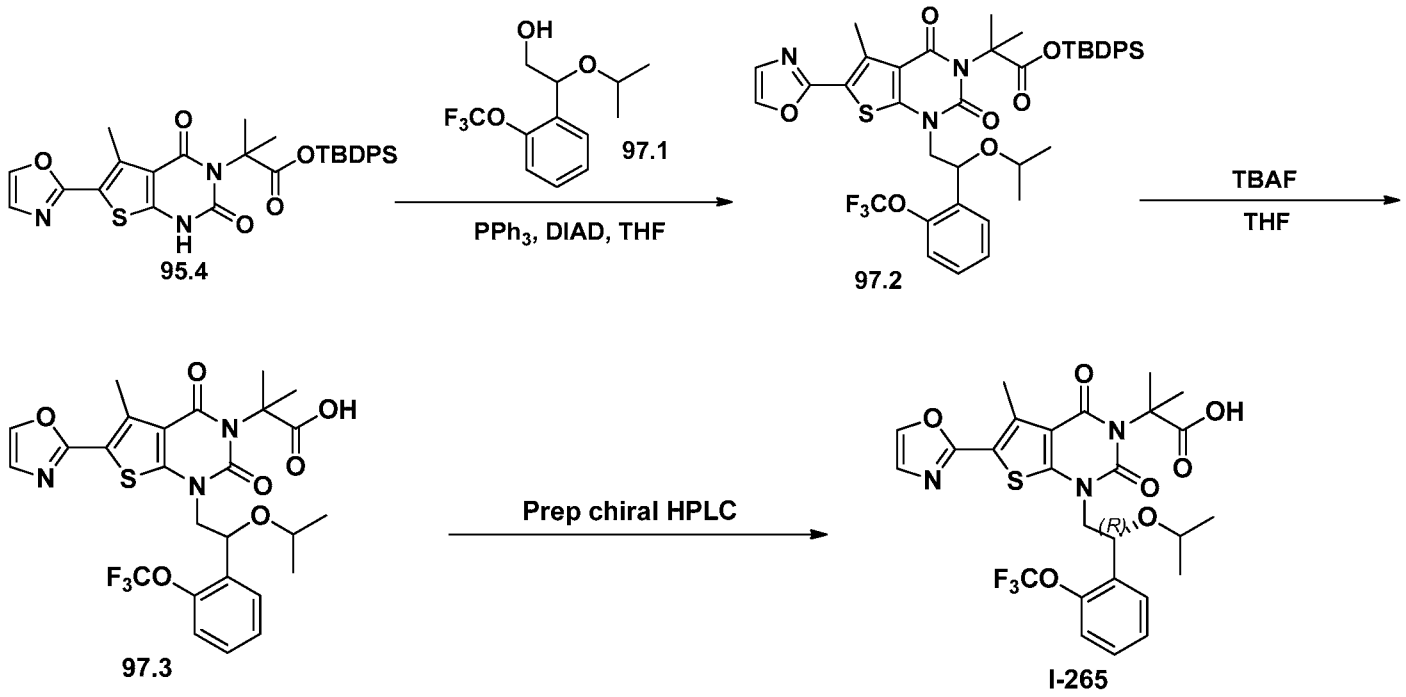
[00588] Example 96: Synthesis of 2-[1-[(2R)-2-[2-(difluoromethoxy)phenyl]-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-264).



[00589] Synthesis of compound 96.4. Compound **96.4** was prepared from 2-(difluoromethoxy)benzaldehyde according to the procedure for the synthesis of **57.5**. Chiral separation: Gilson Gx 281; column: Venusil Chiral OD-H, 21.1*25 cm, 5 μm; mobile phase: hexanes and ethanol (hold at 2% ethanol for 13 min); detector: UV 254/220 nm. Isolated 248 mg (2% overall yield from **96.1**) of a colorless oil.

[00590] Synthesis of Compound I-264. Compound I-264 was prepared from intermediate **95.4** and **96.4** in a manner analogous to compound **67.8**. Isolated a white solid in 20% yield from **95.4**. MS (ES): *m/z* 607 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 1.23-1.30 (m, 2H), 1.65 (m, 8H), 2.75 (s, 3H), 3.24-3.27 (m, 2H), 3.50-3.53 (m, 2H), 3.96-4.18 (m, 2H), 5.26-5.27 (m,1H), 7.00-7.65 (m,5H), 8.24 (s,1H), 12.42 (s,1H).

[00591] Example 97: Synthesis of (R)-2-(1-(2-isopropoxy-2-(2-(trifluoromethoxy)phenyl)ethyl)-5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)-2-methylpropanoic acid (I-265).

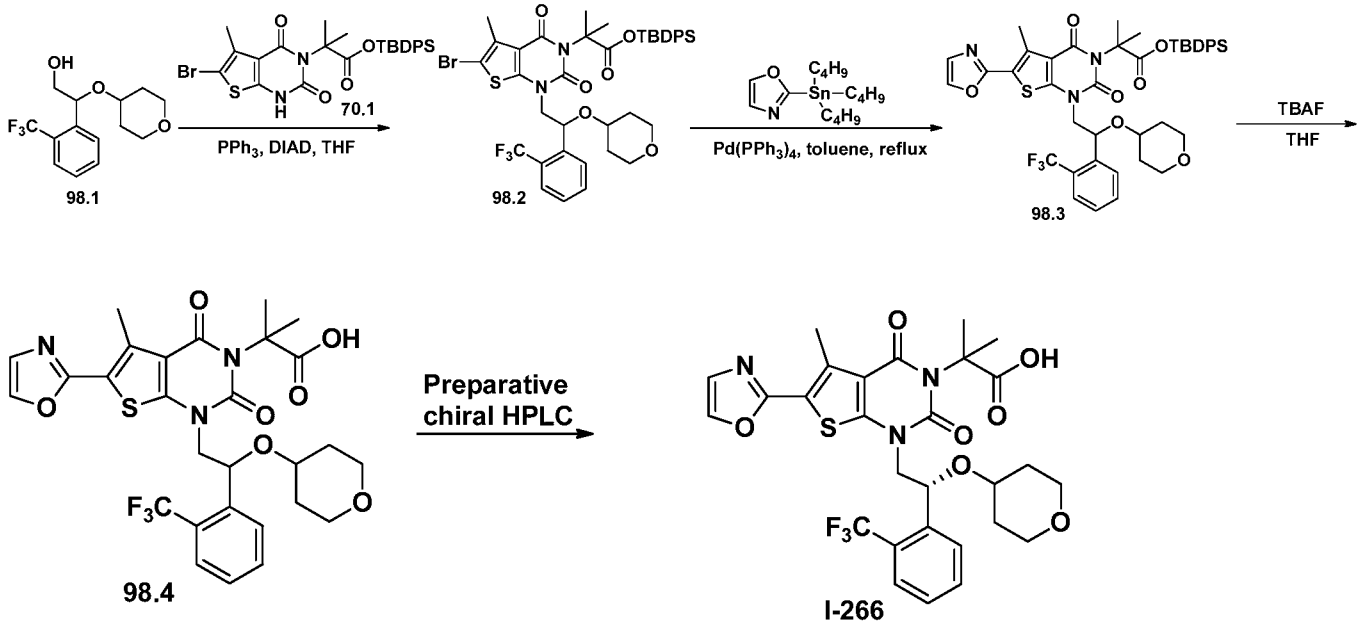


[00592] Synthesis of compound 97.1. Compound **97.1** was prepared from 2-(trifluoromethoxy)benzaldehyde and isopropanol using the same method as for compound **57.3**. Isolated a colorless oil in 17% overall yield.

[00593] Synthesis of compound 97.3. Compound **97.3** was prepared **95.4** and **97.1** in a manner analogous to Example 96. Isolated a white solid in 23% yield from **95.4**.

[00594] Synthesis of Compound I-265. The *R* enantiomer was isolated from 390 mg of **97.3** by chiral preparative HPLC under the following conditions: Gilson Gx 281; column: Chiralpak IC, 2*25 cm, 5 μm; mobile phase: hexanes (0.1% TFA) and IPA (0.1% TFA) (hold at 4% IPA (0.1%TFA) in 10 min); detector: UV 254/220 nm. 56.2 mg of a white solid were obtained. MS (ES): *m/z* 582 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ 8.23 (s, 1 H), 7.72-7.68 (m, 1 H), 7.52-7.45 (m, 2 H), 7.38-7.34 (m, 2 H), 5.16 (t, 1 H, *J* = 6.6 Hz), 4.06-3.97 (m, 2 H) , 3.46-3.32 (m, 1 H), 2.74 (s, 3H) , 1.65 (d, 6 H, *J* = 1.2 Hz), 0.95 (t, 6 H, *J* = 6.0 Hz).

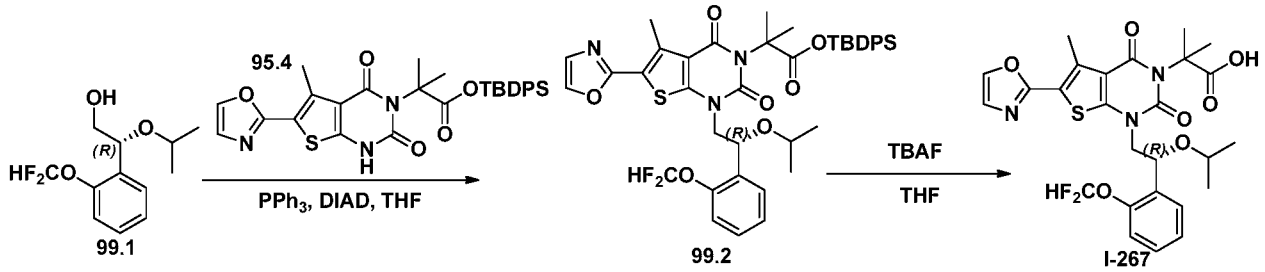
[00595] Example 98: Synthesis of 2-methyl-2-[5-methyl-1-[(2R)-2-(oxan-4-yloxy)-2-[2-(trifluoromethyl)phenyl]ethyl]-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-266).



[00596] **Synthesis of compound 98.1.** Compound **98.1** was prepared from 2-(trifluoromethoxy)benzaldehyde and oxan-4-ol using the same method as for compound **57.3**. Isolated a colorless oil in 5% yield from 2-(trifluoromethoxy)benzaldehyde.

[00597] **Synthesis of Compound I-266.** Compound **I-266** was prepared from **98.1** and **70.1** in a manner analogous to Example 97. MS (ES): *m/z* 608 $(M+H)^+$. ^1H NMR (CD_3OD, 300 MHz): 7.90 (2H, m), 771-7.63 (2H, m), 7.48-7.43 (1H, m), 7.20 (1H, s), 5.35-5.34 (1H, m), 4.30-4.24 (1H, m), 3.89-3.70 (1H, m), 3.55-3.34 (2H, m), 3.33-3.20 (2H, m), 2.73 (3H, s), 1.71-1.50 (8H, m), 1.37-1.20 (2H, m).

[00598] **Example 99: Synthesis of 2-[1-[(2R)-2-[2-(difluoromethoxy)phenyl]-2-(propan-2-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-267).**

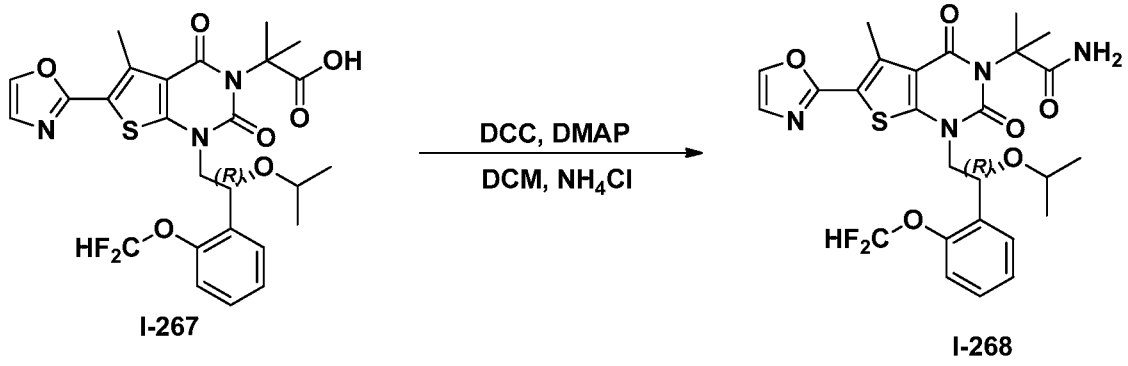


[00599] **Synthesis of compound 99.1.** Compound **99.1** was prepared from 2-(difluoromethoxy)benzaldehyde and isopropanol using the same method as for compound **57.5**.

Purification: Venusil chiral OD-H column, 0.46*25 cm, 5 μm; mobile phase: hexanes:IPA = 98:2; detector: UV 220 nm. Isolated a white solid in 13% yield from 2-(difluoromethoxy)benzaldehyde.

[00600] Synthesis of Compound I-267. Compound **I-267** was prepared from **99.1** and **95.4** in a manner analogous to compound **I-264** (Example 96). Isolated a white solid in 37% yield from **95.4**. MS (ES): *m/z* 564 $(M+H)^+$. ^1H NMR (DMSO-d_6, 300 MHz): δ 12.38 (1H, br s), 8.23 (1H, s), 7.62-7.61 (1H, d, *J* = 1.8 Hz), 7.60-7.22 (3H, m), 7.20-6.97 (2H, m), 5.20-5.16 (1H, t), 4.04 (2H, m), 3.47-3.33 (1H, m), 2.74 (3H, s), 1.65-1.64 (6H, d, *J* = 2.1 Hz), 0.98-0.93 (6H, m).

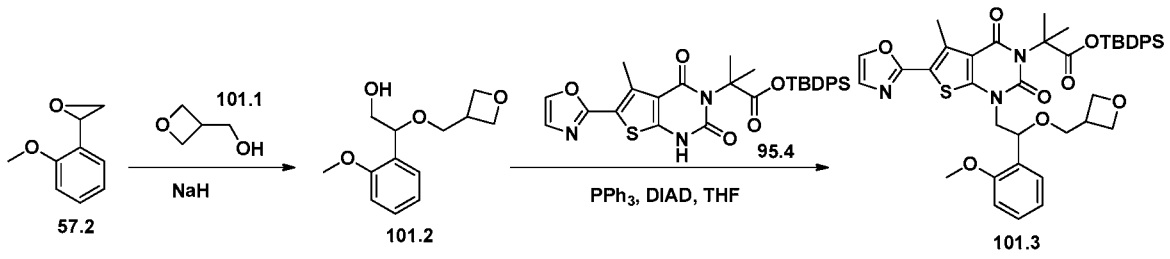
[00601] Example 100: Synthesis of 2-[1-[(2R)-2-[2-(difluoromethoxy)phenyl]-2-(propan-2-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanamide (I-268).



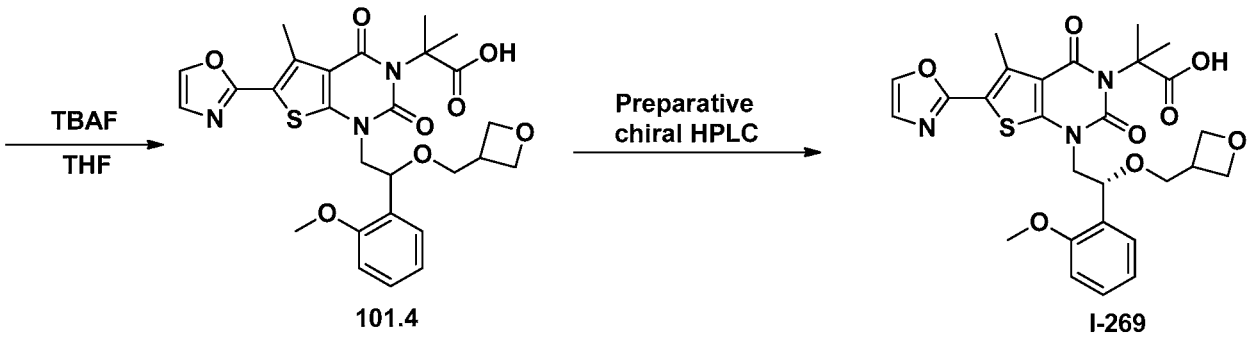
I-267 I-268

[00602] Compound **I-268** was prepared from **I-267** and ammonium chloride using the same method as Example 4. Isolated a white solid in 80% yield. MS (ES): *m/z* 563 $(M+H)^+$. ^1H NMR (DMSO-d_6, 300 MHz): δ 8.22 (1H, s), 7.62-7.60 (1H, m), 7.31 (1H, m), 7.39-7.32 (3H, m), 7.21-6.96 (3H, m), 5.18 (1H, m), 4.03 (2H, m), 3.45-3.41 (1H, m), 2.73 (3H,s), 1.63 (6H, d), 0.96 (6H, d).

[00603] Example 101: Synthesis of (R)-2-(1-(2-(2-methoxyphenyl)-2-(oxetan-3-ylmethoxy)ethyl)-5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)-2-methylpropanoic acid (I-269).



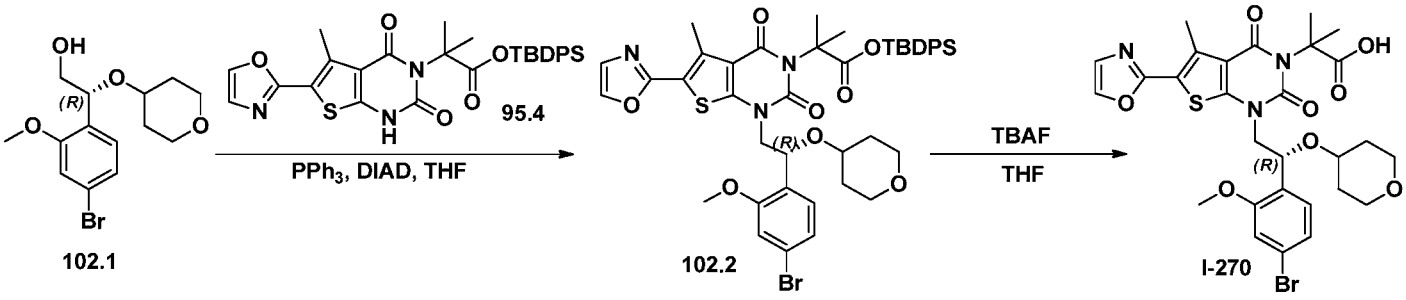
57.2 101.2 101.3



[00604] **Synthesis of compound 101.2.** Compound **101.1** was prepared from **57.2** and commercially-available **101.1** in a manner analogous to **73.2**. Isolated a colorless oil in 38% yield.

[00605] **Synthesis of Compound I-269.** Compound **I-269** was prepared from **95.4** and **101.2** in a manner analogous to **I-265** (Example 97). Isolated a white solid in 2% overall yield from **95.4**. MS (ES): *m/z* 556 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 1.70 (d, 6H), 2.69 (s, 3H), 3.08-3.12 (m, 1H), 3.62-3.81 (m, 5H), 4.16-4.23 (m, 3H), 4.32-4.28 (m, 1H), 4.48-4.54 (m, 2H) , 6.09 (m, 1H) , 6.99-7.09 (m, 2H) , 7.32 (s, 1H), 7.38-7.40 (m, 1H), 7.43-7.57 (m, 1H), 8.17 (s, 1H).

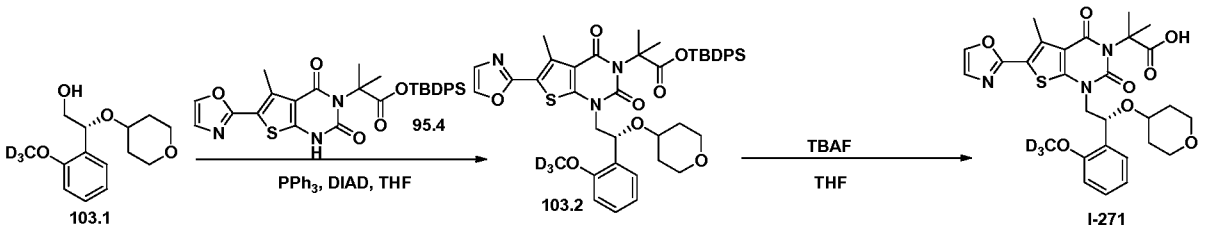
[00606] **Example 102: 2-[1-[(2R)-2-(4-bromo-2-methoxyphenyl)-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-270).**



[00607] **Synthesis of compound 102.1.** Compound **102.1** was prepared from 4-bromo-2-methoxybenzaldehyde and oxan-4-ol in a manner analogous to **57.5**. The *R* enantiomer was isolated by chiral preparative HPLC under the following conditions: Column: Chiralcel OJ-H: 0.46*25 cm, 5 μm; mobile phase, hexanes:EtOH = 75:25; detector: 254 nm. Isolated a white solid in 2% overall yield.

[00608] Synthesis of Compound I-270. Compound **I-270** was prepared from **95.4** and **102.1** in a manner analogous to **I-264** (Example 96). Isolated a white solid in 27% overall yield from **95.4**. MS (ES): *m/z* 650 $(M+H)^+$. ^1H NMR (DMSO-d_6, 300 MHz): δ 8.24 (1H, s), 7.43-7.39 (2H, m), 7.25-7.21 (2H, m), 5.23-5.19 (1H, m), 4.07-3.95 (2H, m), 3.83 (3H, s), 3.59-3.49 (2H, m), 3.32-3.20 (2H, m), 2.75 (3H, s), 1.67-1.64 (8H, m), 1.35-1.31 (2H, m).

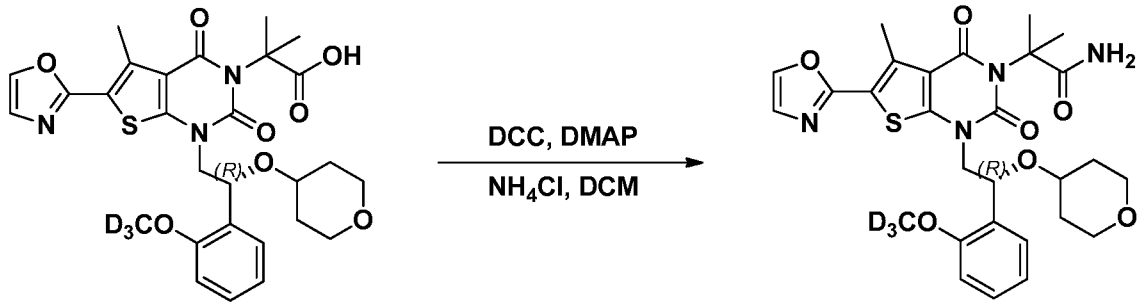
[00609] Example 103: Synthesis of 2-[1-[(2R)-2-[2-(d_3)methoxyphenyl]-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-271).



[00610] Synthesis of compound 103.1. Compound **103.1** was prepared from 2-(d_3)methoxybenzaldehyde and oxan-4-ol in a manner analogous to **57.5**. The *R* enantiomer was isolated by chiral preparative HPLC under the following conditions (Gilson Gx 281): Column: Venusil Chiral OD-H: 21.1*25 cm, 5 μm; mobile phase, hexanes and EtOH (5% EtOH for 12 min); detector: 220/254 nm. Isolated a white solid in 9% overall yield.

[00611] Synthesis of Compound I-271. Compound **I-271** was prepared from **95.4** and **103.1** in a manner analogous to Example 96. Isolated a white solid in 42% overall yield from **95.4**. MS (ES): *m/z* 573 $(M+H)^+$. ^1H NMR (DMSO-d_6, 300 MHz): δ 12.4 (1H, br s), 8.25 (1H, s), 7.50-7.49 (1H, d), 7.39 (1H, m), 7.34-7.28 (1H, m), 7.06-6.99 (2H, m), 5.30-5.26 (1H, m), 4.07-3.80 (2H, m), 3.59-3.48 (2H, m), 3.39-3.32 (1H, m), 3.27-3.20 (2H, m), 2.75 (3H, s), 1.69-1.67 (8H, m), 1.38-1.21 (2H, m).

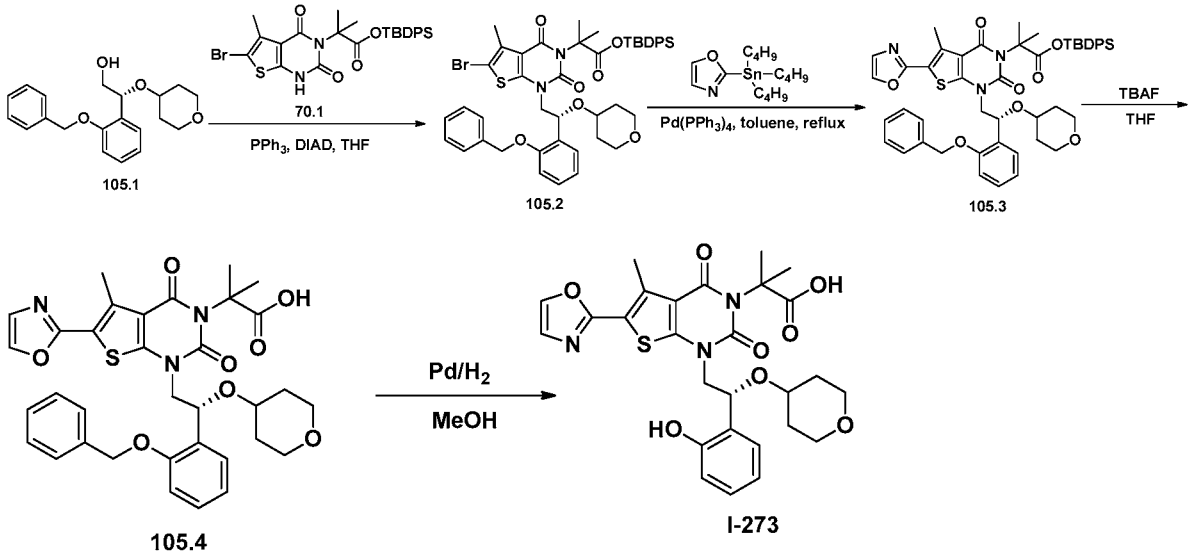
[00612] Example 104: Synthesis of 2-[1-[(2R)-2-[2-(d_3)methoxyphenyl]-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanamide (I-272).



I-271 I-272

[00613] Compound **I-272** was prepared from **I-271** (Example 103) and ammonium chloride using the same method as for Example 4. Isolated a white solid in 57% yield. MS (ES): *m/z* 594 $(M+Na)^+$. ^1H NMR (DMSO-d_6, 300 MHz): δ1.20-1.33 (m, 2H), 1.65-1.67 (m, 8H), 2.75 (s, 3H), 3.20-3.26 (m, 2H), 3.33-3.37 (m, 1H), 3.50-3.58 (m, 2H), 3.94-4.04 (m, 2H), 5.26-5.31 (s, 1H), 6.99-7.06 (m, 4H), 7.27-7.29 (m, 1H), 7.32 (s, 1H), 7.47-7.50 (d, 1H), 8.22 (s, 1H).

[00614] Example 105: Synthesis of 2-[1-[(2R)-2-(2-hydroxyphenyl)-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-273).



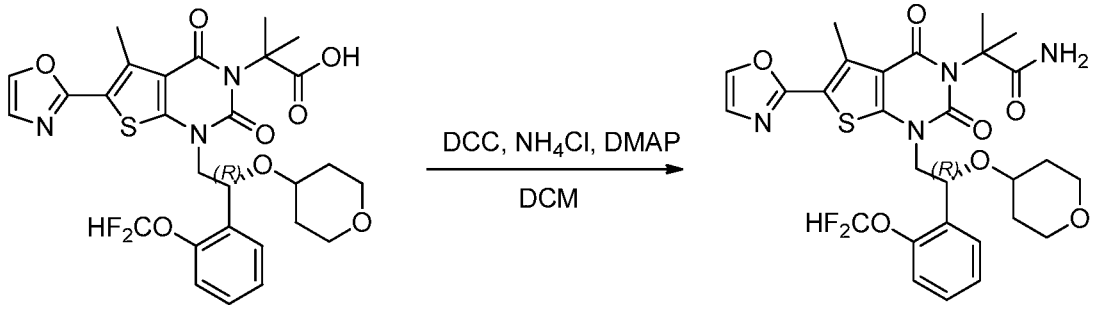
105.1 105.2 105.3 105.4 I-273

[00615] Synthesis of compound 105.1. Compound **105.1** was prepared from 2-(benzyloxy)benzaldehyde and oxan-4-ol in a manner analogous to **57.5**. The *R* enantiomer was isolated by preparative SFC under the following conditions: Column: Chiralpak AD-H, 2*25 cm; mobile phase: CO_2 (75%), ethanol (25%); detector: UV 254 nm. Isolated the product in 10% overall yield from 2-(benzyloxy)benzaldehyde.

[00616] **Synthesis of compound 105.4.** Compound **105.4** was prepared from **70.1** and **105.1** in a manner analogous to Example 57. Isolated a white solid in 25% overall yield from **70.1**.

[00617] **Synthesis of Compound I-273.** Into a 100-mL round-bottom flask was placed **105.4** (100 mg, 0.15 mmol, 1.00 equiv) and methanol (20 mL). This was followed by the addition of palladium on carbon (20 mg). The flask was evacuated and flushed three times with nitrogen, followed by flushing with hydrogen. The mixture was stirred overnight at room temperature under an atmosphere of hydrogen. The solids were collected by filtration. The filtrate was concentrated under vacuum. The residue was purified by thin layer chromatography developed with dichloromethane/MeOH/HOAc (30:1:0.15). 35.7 mg (41%) of **I-273** were obtained as a white solid. MS (ES): *m/z* 556 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 1.18-1.34 (m, 2H), 1.57-1.62 (m, 2H), 1.62 (s, 3H), 1.70 (s, 3H), 2.75 (s, 3H), 3.12-3.35 (m, 3H), 3.50-3.70 (m, 2H), 3.78 (m, 1H), 4.11-4.14 (m, 1H), 5.23-5.28 (m, 1H), 6.81-6.85 (m, 2H), 7.06-7.11 (m, 1H), 7.36-7.37 (m, 1H).

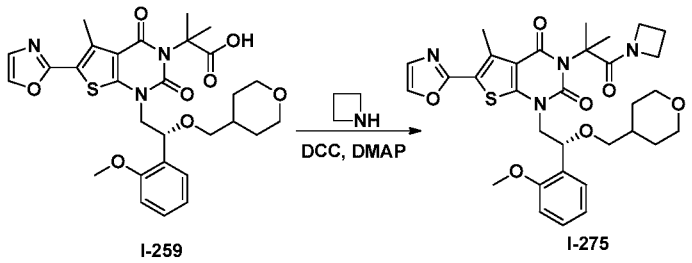
[00618] **Example 106: Synthesis of 2-[1-[(2R)-2-[2-(difluoromethoxy)phenyl]-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanamide (I-274).**



I-264 **I-274**

[00619] Compound **I-274** was prepared from **I-264** (Example 96) and ammonium chloride in a manner analogous to Example 4. Isolated 63.4 mg of a white solid in 57% yield. MS (ES): *m/z* 627 $(M+Na)^+$. ^1H NMR (DMSO-d_6, 300 MHz): δ 1.24-1.34 (m, 2H), 1.63-1.65 (m, 8H), 2.74 (s, 3H), 3.20-3.26 (m, 2H), 3.32 (m, 1H), 3.53 (m, 2H), 4.01-4.10 (m, 2H), 5.27 (m, 1H), 6.98 (br s,1H), 6.98 (br s,1H), 7.18 (br s,1H), 7.21-7.32 (m, 1H), 7.34-7.47 (m, 3H), 7.62-7.64 (m, 1H), 8.22 (s, 1H).

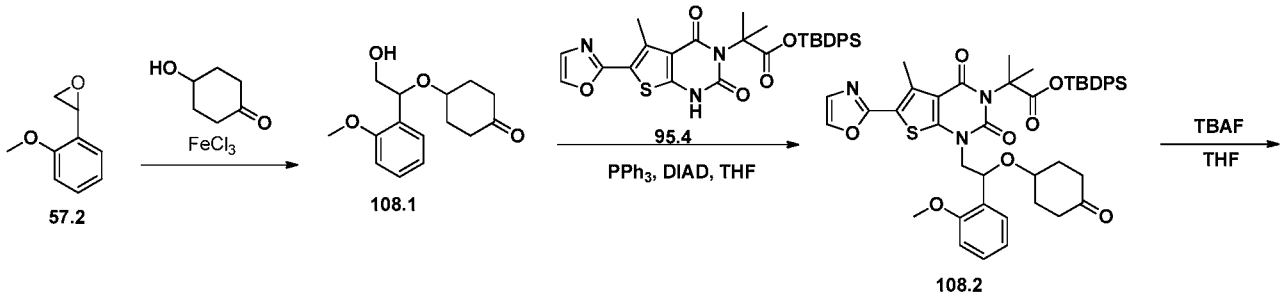
[00620] Example 107: Synthesis of 3-[1-(azetidin-1-yl)-2-methyl-1-oxopropan-2-yl]-1-[(2R)-2-(2-methoxyphenyl)-2-(oxan-4-ylmethoxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-2,4-dione (I-275).



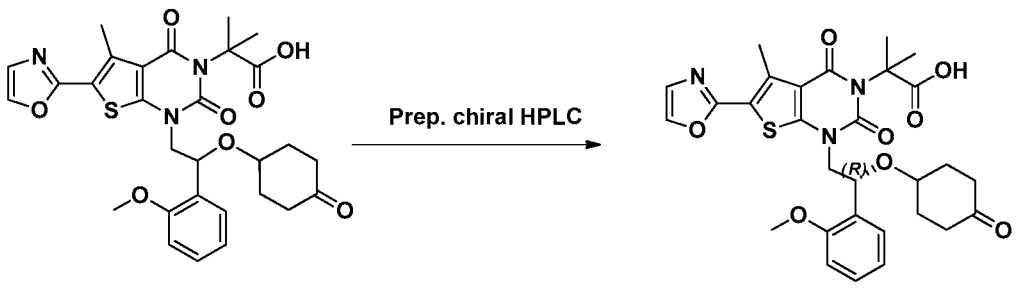
I-259 I-275

[00621] Compound **I-275** was prepared from **I-259** (Example 90) and azetidine in a manner analogous to Example 4. A sealed tube was used rather than a round-bottom flask. Isolated 46.8 mg of a white solid in 44% yield. MS (ES): *m/z* 623 $(M+H)^+$. ^1H NMR (DMSO-d_6, 300 MHz): δ 8.23 (1H, s), 7.40-7.28 (3H,m), 7.06-7.00 (2H, m), 5.14-5.09 (1H, t), 4.09 (1H, m), 3.87-3.84 (4H, m), 3.80 (3H, s), 3.78-3.69 (2H, m), 3.19-3.11 (3H, m), 3.06-3.00 (1H, m), 2.76 (3H, s), 2.14-2.09 (2H, m),1.63-1.61 (6H, d), 1.44-1.35 (2H, m), 1.10-1.03 (2H, m).

[00622] Example 108: Synthesis of (R)-2-(1-(2-(2-methoxyphenyl)-2-((4-oxocyclohexyl)oxy)ethyl)-5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)-2-methylpropanoic acid (I-276).



57.2 108.1 108.2

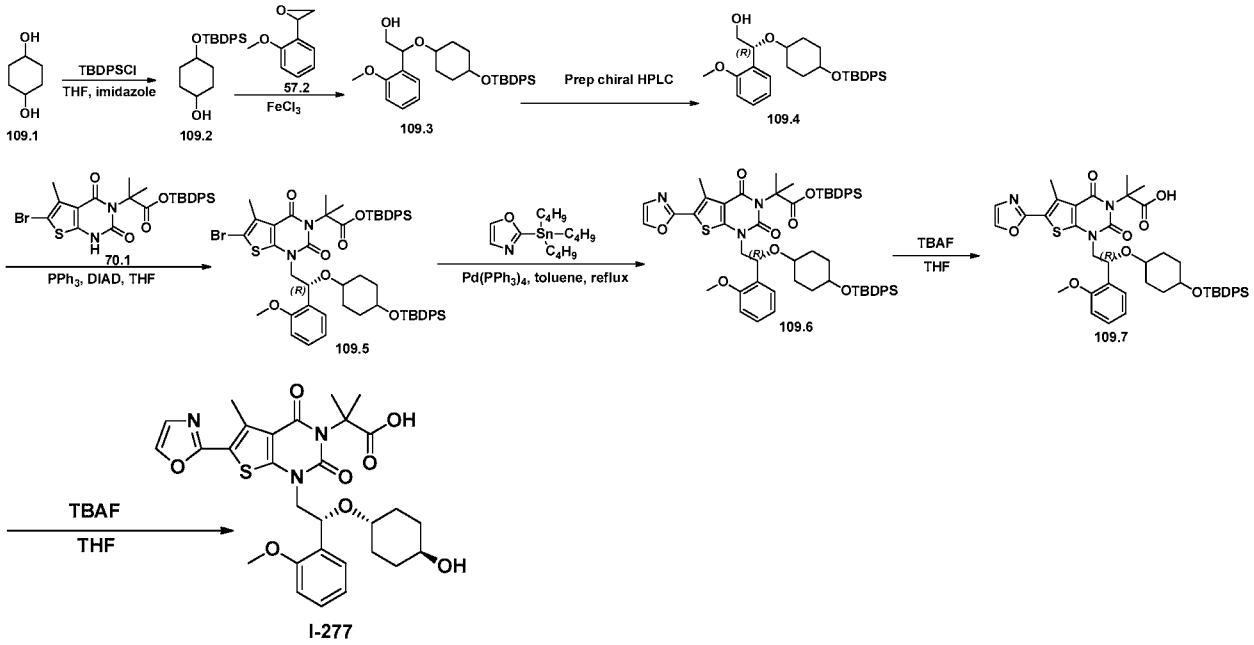


108.3 I-276

[00623] Synthesis of compound 108.1. Compound **108.1** was synthesized from **57.2** and 4-hydroxycyclohexan-1-one using the method for the synthesis of compound **57.3**. Isolated 400 mg of a colorless oil in 5% yield.

[00624] Synthesis of Compound I-276. Compound **I-276** was prepared from **108.1** and **95.4** in a manner analogous to Example 97. Isolated 7.7 mg (1% from **95.4**) of a white solid (MS (ES): *m/z* 582 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 1.64-1.78 (m, 10H), 2.06-2.20 (m, 3H), 2.22-2.27 (m, 1H), 2.73 (s, 3H), 3.56 (m, 1H), 3.83 (s, 3H), 4.09 (m, 2H), 5.31-5.35 (m, 1H), 7.02-7.09 (m, 2H), 7.30-7.39 (m, 2H), 7.52-7.42 (d, 1H), 8.23 (s, 6H), 12.42 (s, 1H).

[00625] Example 109: 2-[1-[(2R)-2-[(4-hydroxycyclohexyl)oxy]-2-(2-methoxyphenyl)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-277).



[00626] Synthesis of compound 109.2. Into a 1000-mL 3-necked round-bottom flask was placed cyclohexane-1,4-diol (20 g, 172.18 mmol, 1.00 equiv), 1,4-dioxane (500 mL) and 1H-imidazole (17.58 g, 258.24 mmol, 1.50 equiv). This was followed by the addition of a solution of tert-butyl(chloro)diphenylsilane (49.69 g, 180.78 mmol, 1.05 equiv) in dioxane (100 mL) dropwise with stirring at 15 °C. The resulting solution was stirred for 15 h at 15-20 °C. The solids were filtered out. The filtrate was diluted with 200 mL of water. The resulting solution was extracted with 3x200 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum

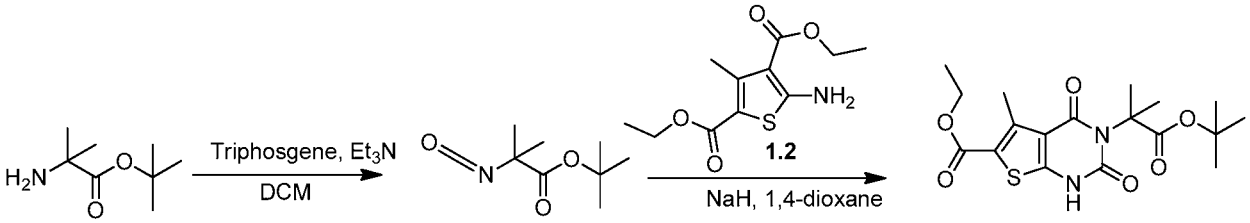
ether (0:1-1:60-1:50-1:30-1:20). Purification afforded 32.98 g (54%) of **109.2** as a white semi-solid.

[00627] Synthesis of compound 109.4. Compound **109.4** was prepared from **109.2** and **57.2** using the procedure for the synthesis of **57.5**. Purification: Chiral preparative HPLC under the following conditions (Gilson): Column: Venusil Chiral OD-H, 21.1*25 cm, 5 μm; mobile phase: hexanes and ethanol (hold at 5% ethanol for 15 min); detector: UV 220/254 nm.

[00628] Synthesis of compound 109.7. Compound **109.7** was prepared from **70.1** and **109.4** in a manner analogous to Example 57. Isolated a white solid in 14% yield from **70.1**.

[00629] Synthesis of Compound I-277. Into a 10-mL round-bottom flask was placed a solution of **109.7** (100 mg, 0.12 mmol, 1.00 equiv) in tetrahydrofuran (5 mL). TBAF (127 mg) was added and the resulting solution was stirred for 3 days at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by preparative TLC, eluting with methanol/DCM/HOAc (10:200:1). 7.8 mg (11%) of Compound **I-277** were obtained as a white solid. MS (ES): *m/z* 584 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ 0.88-0.94 (m, 1H), 1.01-1.29 (m, 3H), 1.48-1.84 (m, 10H), 2.70 (s, 3H), 2.97-3.22 (m, 1H), 3.38-3.44 (m ,1H), 3.75 (m, 3H) , 3.98 (m, 1H), 5.24-5.29 (t, 1H) , 6.83-6.94 (m, 2H), 7.15-7.20 (t, 2H) , 7.41-7.44 (d, 1H) , 7.86 (s, 1H).

[00630] Example 110: Synthesis of Intermediate 110.3.

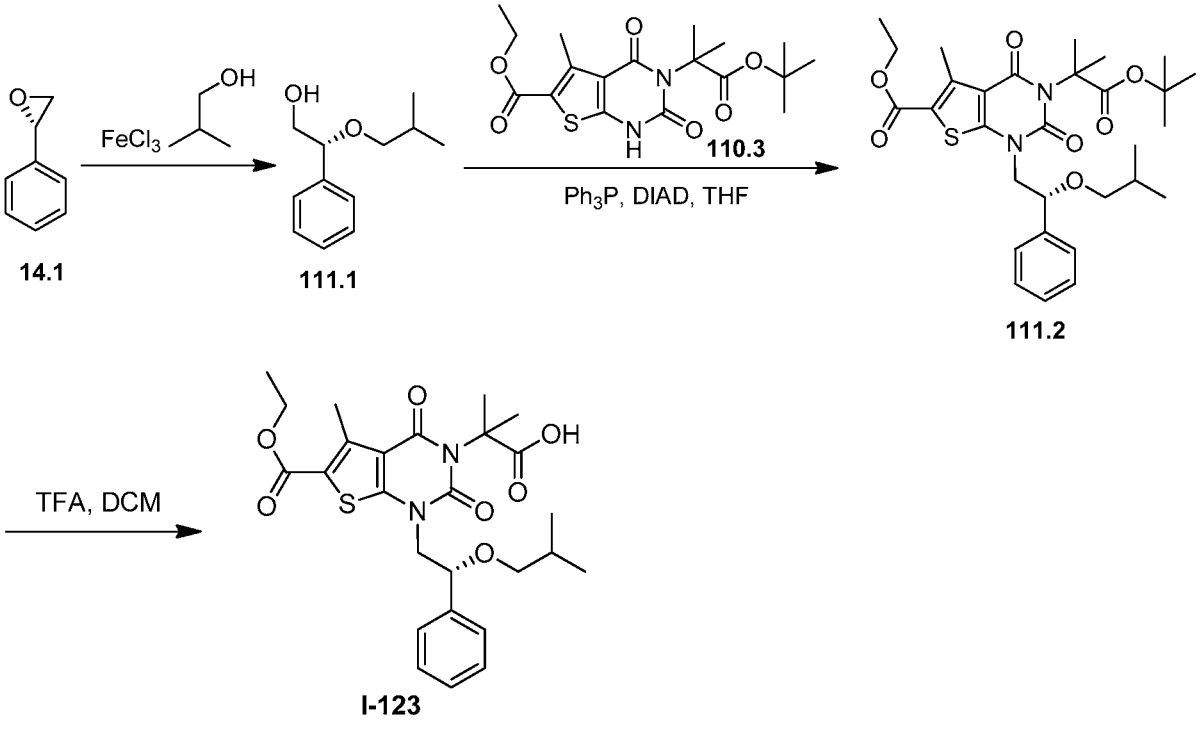


110.1 110.2 110.3

[00631] Synthesis of compound 110.2. Into a 100-mL 3-necked round-bottom flask was placed a solution of tert-butyl 2-amino-2-methylpropanoate (1.2 g, 7.54 mmol, 1.00 equiv) in dichloromethane (20 mL). This was followed by the addition of ditrichloromethyl carbonate (750 mg, 2.53 mmol, 0.34 equiv), in portions at 0 °C. After 30 min, triethylamine (2.3 g, 22.73 mmol, 3.02 equiv) was added dropwise with stirring. The resulting solution was stirred for 5 h at room temperature and then concentrated under vacuum. The residue was diluted with 20 mL of ethyl ether. The solids were filtered out. The filtrate was concentrated under vacuum. Purification afforded 1.4 g (crude) of tert-butyl 2-isocyanato-2-methylpropanoate (**110.2**) as a yellow oil.

[00632] **Synthesis of intermediate 110.3.** Into a 100-mL 3-necked round-bottom flask was placed a solution of **1.2** (1.62 g, 6.30 mmol, 1.00 equiv) in 1,4-dioxane (20 mL). This was followed by the addition of sodium hydride (280 mg, 7.00 mmol, 1.11 equiv, 60%) at 10 °C, and the mixture was stirred at room temperature for 15 min. To this was added a solution of **110.2** (1.4 g, 7.56 mmol, 1.20 equiv) in 1,4-dioxane (10 mL) dropwise with stirring at 10 °C. The resulting solution was stirred at room temperature for 30 min then heated to 100 °C with stirring overnight. The reaction was then quenched by the addition of 30 mL of NH_4Cl (aq.). The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined and dried over anhydrous magnesium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). Purification afforded 0.2 g (crude) of intermediate **110.3** as a yellow oil.

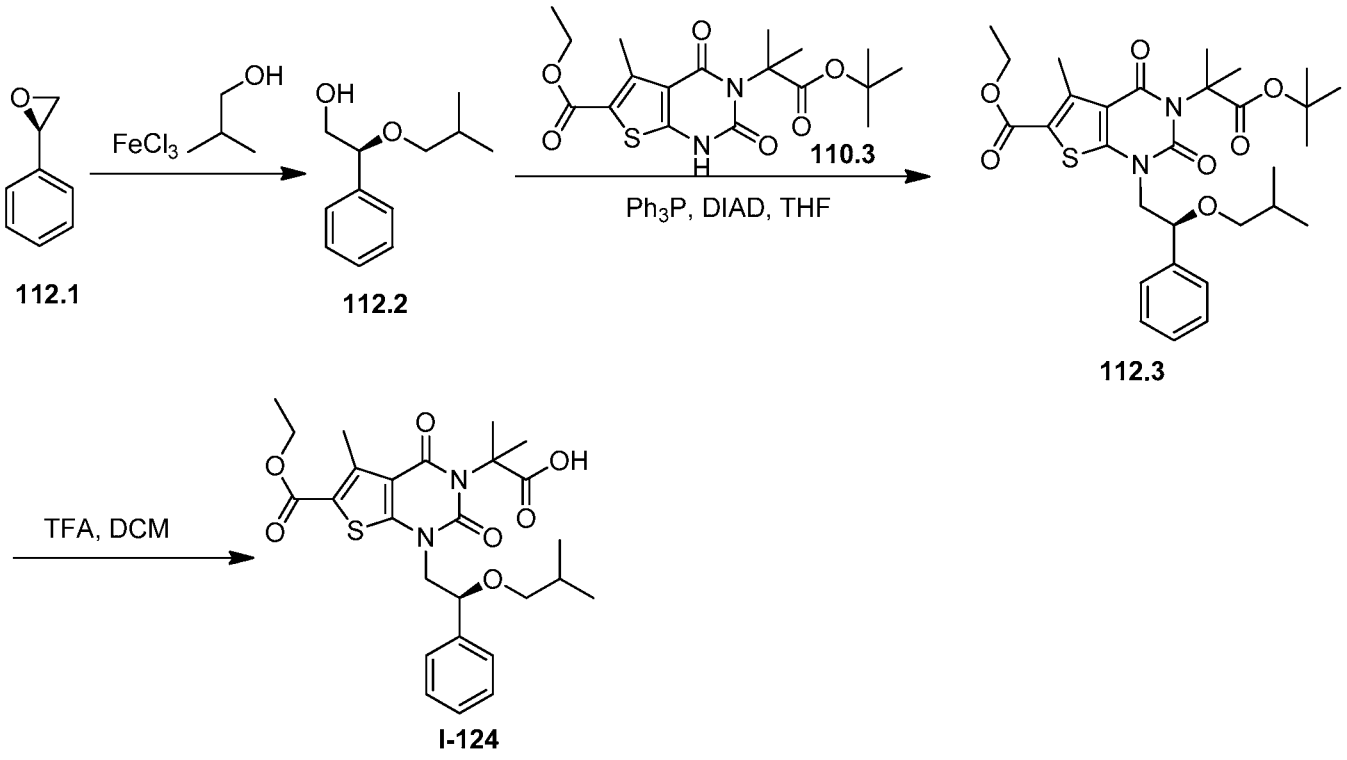
[00633] **Example 111: 2-[6-(ethoxycarbonyl)-5-methyl-1-[(2R)-2-(2-methylpropoxy)-2-phenylethyl]-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-123).**



[00634] **Synthesis of compound 111.1.** Compound **111.1** was prepared from methylpropan-1-ol and **14.1** in a manner analogous to the synthesis of compound **57.3**. Isolated **111.1** as a colorless oil in 68% yield.

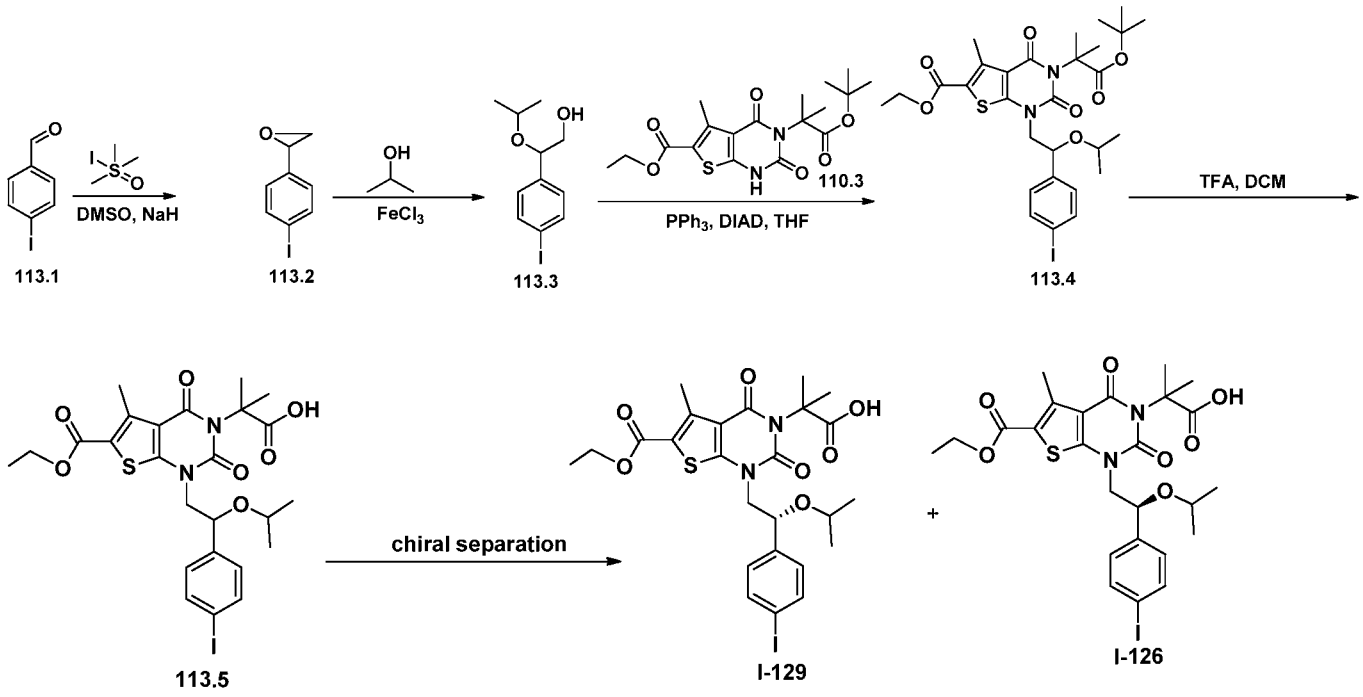
[00635] Synthesis of compound I-123. Compound **I-123** was prepared from **111.1** and **110.3** in a manner analogous to compound **2.5**. The crude product (150 mg) was purified by chiral preparative HPLC under the following conditions (Gilson Gx 281): Column: Chiralpak IC, 2*25 cm, 5 μm; mobile phase: hexanes and ethanol (0.1% TFA) (hold at 5.0% ethanol (0.1%TFA) for 15 min); detector: UV 220/254 nm. Isolated 33.7 mg of a light brown solid in 12% yield from **110.3**. MS (ES): *m/z* 517 $(M+H)^+$, 539 $(M+Na)^+$, 580 $(M+Na+CH_3CN)^+$. ^1H NMR (300 MHz, CD_3CN): δ 0.67-0.73 (m, 6H), 1.31 (t, *J* = 6.9, 3H), 1.60-1.67 (m, 1H), 1.70 (s, 6H), 2.71 (s, 3H), 2.93-3.09 (m, 2H), 3.79-3.87 (m, 1H), 4.08-4.13 (m, 1H), 4.28 (q, *J* = 7.2, 2H), 4.69-4.73 (m, 1H), 7.32-7.39 (m, 5H).

[00636] Example 112: 2-[6-(ethoxycarbonyl)-5-methyl-1-[(2S)-2-(2-methylpropoxy)-2-phenylethyl]-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-124).



[00637] Compound **I-124** was prepared from **112.1** and **110.3** in a manner analogous to Example 111. Isolated 22.2 mg (10% from **110.3**) as a light brown solid. MS (ES): *m/z* 517 $(M+H)^+$, 539 $(M+Na)^+$, 580 $(M+Na+CH_3CN)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 0.64-0.72 (m, 6H), 1.31 (t, *J* = 6.9, 3H), 1.65 (s, 6H), 2.68 (s, 3H), 2.89-3.03 (m, 2H), 3.80-3.88 (m, 1H), 4.05-4.11 (m, 1H), 4.25 (q, *J* = 7.2, 2H), 4.64-4.68 (m, 1H), 7.31-7.41 (m, 5H).

[00638] Example 113: Synthesis of (R)-2-(6-(ethoxycarbonyl)-1-(2-(4-iodophenyl)-2-isopropoxyethyl)-5-methyl-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)-2-methylpropanoic acid (I-129) and Example 114: Synthesis of (S)-2-(6-(ethoxycarbonyl)-1-(2-(4-iodophenyl)-2-isopropoxyethyl)-5-methyl-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)-2-methylpropanoic acid (I-126).



[00639] Synthesis of compound 113.3. Compound **113.3** was prepared in a manner analogous to compound **57.3**. Isolated 1.036 g (59% from **113.1**) as a colorless oil.

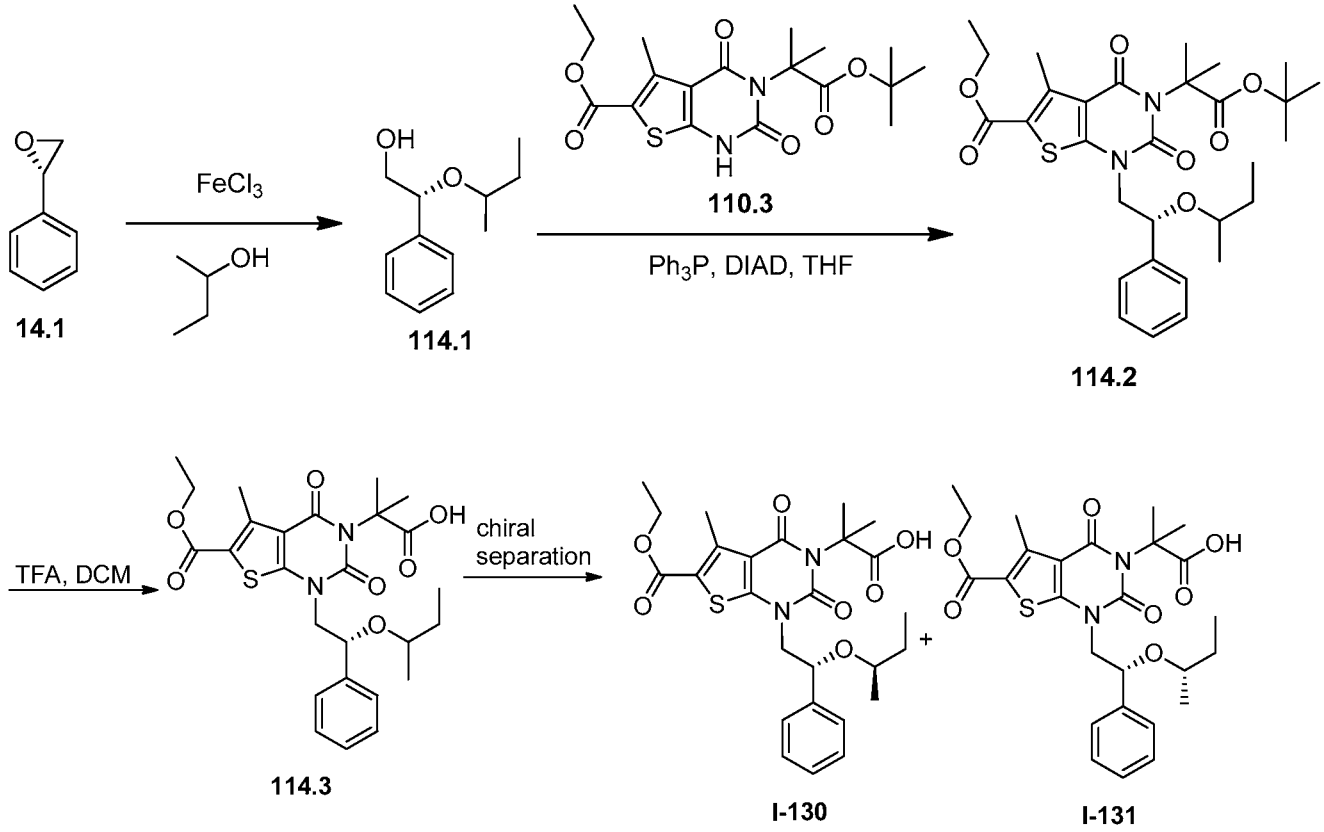
[00640] Synthesis of compound 113.5. Compound **113.5** was prepared in a manner analogous to compound **2.5**. Isolated 1.2 g of a white solid in 79% yield from **110.3**.

[00641] Synthesis of Compounds I-129 and I-126. The enantiomers of **113.5** (1.2 g) were separated by chiral preparative HPLC under the following conditions (Gilson Gx 281): Column: Chiralpak IC, 2*25 cm, 5 μm; mobile phase: hexanes and ethanol (hold at 15.0% ethanol for 23 min); detector: UV 220/254nm. 325.8 mg of **I-129** (tR = 18.56 min) and 325.7 mg of **I-126** (tR = 13.09 min) were obtained as white solids.

Analytical data for Compound **I-129**: MS (ES): *m/z* 629 $(M+H)^+$, 692 $(M+Na+CH_3CN)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 0.89 (d, 3H), 0.91(d, 3H), 1.28 (t, 3H), 1.62 (s, 6H), 2.68 (s, 3H), 3.41 (m, 1H), 3.76 (m, 1H), 4.01 (d, 1H) , 4.26 (q, 2H), 4.73 (m, 1H), 7.19 (d, 2H), 7.73 (d, 2H), 12.3 (br s, 1H).

Analytical data for Compound **I-126**: MS (ES): *m/z* 629 $(M+H)^+$, 692 $(M+Na+CH_3CN)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 0.89 (d, 3H), 0.91(d, 3H), 1.28 (t, 3H), 1.62 (s, 6H), 2.68 (s, 3H), 3.41 (m, 1H), 3.76 (m, 1H), 4.0 (d, 1H) , 4.26 (q, 2H), 4.73 (m, 1H), 7.18 (d, 2H), 7.73 (d, 2H), 12.3 (br s, 1H).

[00642] Example 114: Synthesis of 2-[1-[(2R)-2-[(2R)-butan-2-yloxy]-2-phenylethyl]-6-(ethoxycarbonyl)-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-130) and Example 115: Synthesis of 2-[1-[(2R)-2-[(2R)-butan-2-yloxy]-2-phenylethyl]-6-(ethoxycarbonyl)-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-131).



[00643] Synthesis of compound 114.1. Compound **114.1** was prepared from **14.1** in a manner analogous to compound **57.3**. Isolated 1.3 g (40%) of a colorless oil.

[00644] Synthesis of compound 114.3. Compound **114.3** was prepared in a manner analogous to compound **2.5**. Isolated 320 mg of a white solid in 77% yield from **110.3**.

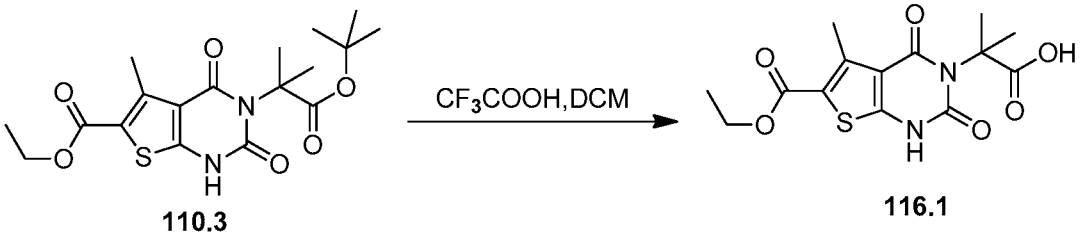
[00645] Synthesis of Compounds I-130 and I-131. The enantiomers of **114.3** were separated by chiral preparative HPLC under the following conditions (Gilson): Column: Phenomenex Lux 5u Cellulose-4, 2.12*25, 5 μm; mobile phase: hexanes (0.1%TFA) and ethanol (hold at 5.0%

ethanol in 22 min); detector: UV 220/254nm. Compound **I-130** was the first compound to elute and was isolated in 65% yield (117.4 mg) as a white solid. Compound **I-131** was the second to elute and was isolated in 54% yield (97.2 mg) as a white solid.

Analytical data for Compound **I-130**: MS (ES): *m/z* 517 $(M+H)^+$, 539 $(M+Na)^+$, 580 $(M+Na+CH_3CN)^+$. ^1H NMR (300 MHz, CD_3OD): δ 0.66 (t, *J* = 6.9, 3H), 0.91 (d, *J* = 6.3, 3H), 1.26-1.35 (m, 2H), 1.40 (t, *J* = 7.5, 3H), 1.75-1.77 (m, 6H), 2.75 (s, 3H), 3.28-3.34 (m, 1H), 3.80-3.83 (m, 1H), 4.09-4.15 (m, 1H), 4.31 (q, *J* = 7.2, 2H), 7.29-7.43 (m, 5H).

Analytical data for Compound **I-131**: MS (ES): *m/z* 517 $(M+H)^+$, 539 $(M+Na)^+$, 580 $(M+Na+CH_3CN)^+$. ^1H NMR (300 MHz, CD_3OD): δ 0.66 (t, *J* = 6.9, 3H), 0.91 (d, *J* = 6.3, 3H), 1.26-1.35 (m, 2H), 1.40 (t, *J* = 7.5, 3H), 1.75-1.77 (m, 6H), 2.75 (s, 3H), 3.28-3.34 (m, 1H), 3.80-3.83 (m, 1H), 4.09-4.15 (m, 1H), 4.31 (q, *J* = 7.2, 2H), 7.29-7.43 (m, 5H).

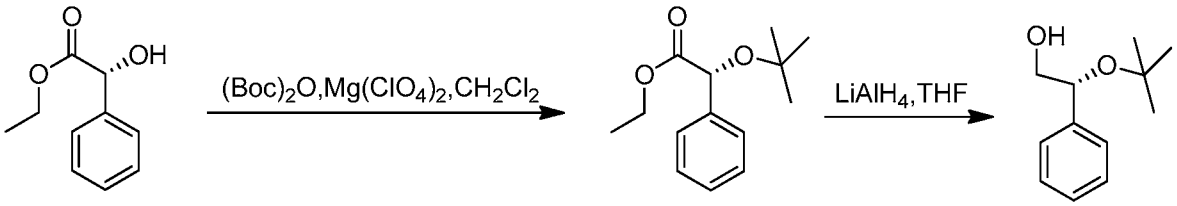
[00646] Example 116: Synthesis of Intermediate 116.1.



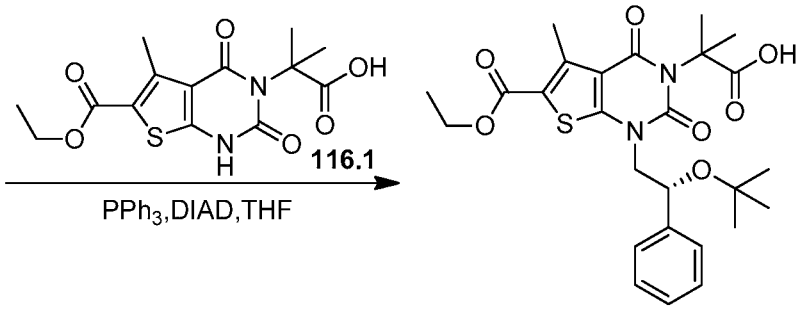
110.3 116.1

[00647] Into a 25-mL round-bottom flask was placed **110.3** (500 mg, 1.26 mmol, 1.00 equiv), dichloromethane (10 mL) and CF_3COOH (3 mL). The resulting solution was stirred for 3 h at room temperature and then concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:20). Purification afforded 0.409 g (95%) of intermediate **116.1** as a white solid.

[00648] Example 117: Synthesis of 2-[1-[(2R)-2-(tert-butoxy)-2-phenylethyl]-6-(ethoxycarbonyl)-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-127).



117.1 117.2 117.3



I-127

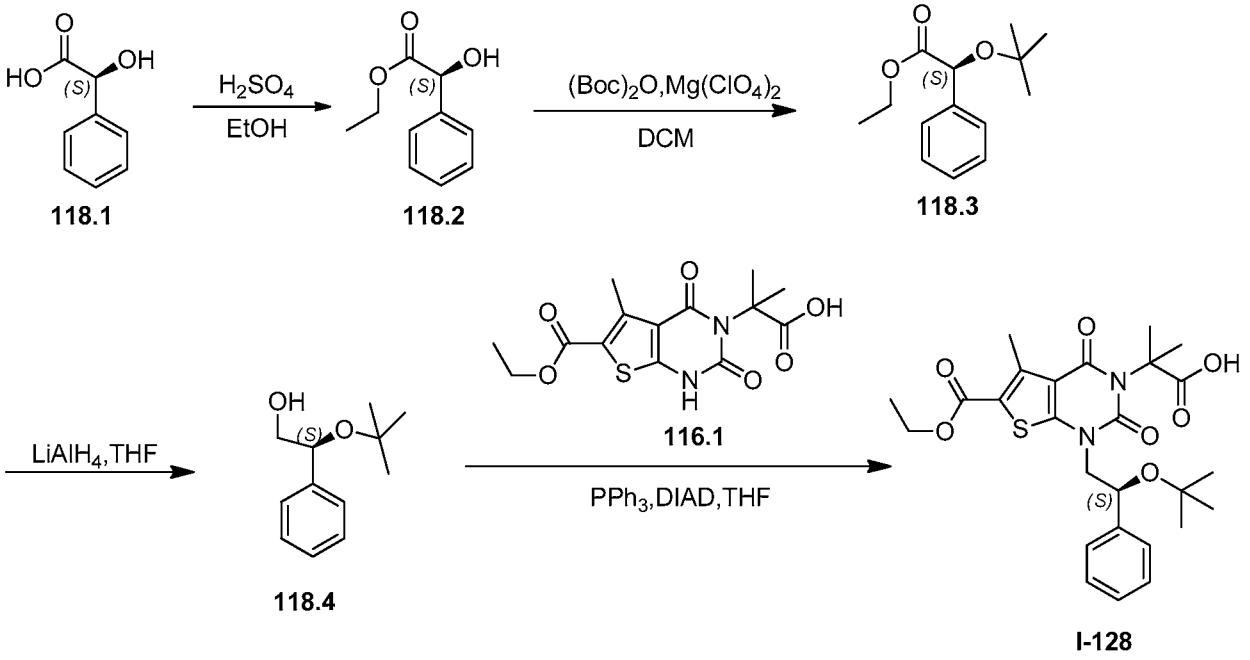
[00649] **Synthesis of compound 117.2.** Into a 100-mL 3-necked round-bottom flask was placed ethyl (2R)-2-hydroxy-2-phenylacetate (**117.1**, 5 g, 27.75 mmol, 1.00 equiv), dichloromethane (50 mL), $Mg(ClO_4)_2$ (0.619 g, 0.10 equiv) and $(Boc)_2O$ (13.912 g, 63.74 mmol, 2.30 equiv). The resulting solution was stirred overnight at 40 °C. The reaction was then quenched by the addition of water. The resulting solution was extracted with ethyl acetate and the organic layers combined, dried, and concentrated under vacuum. The residue was applied onto a silica gel column with EA/PE (1:25). Purification afforded 2.5 g (38%) of ethyl (2R)-2-(tert-butoxy)-2-phenylacetate (**117.2**) as a light yellow liquid.

[00650] **Synthesis of compound 117.3.** Into a 50-mL round-bottom flask was placed tetrahydrofuran (10 mL), **117.2** (500 mg, 2.12 mmol, 1.00 equiv) and $LiAlH_4$ (81 mg, 2.13 mmol, 1.01 equiv). The resulting solution was stirred for 2 h at 0 °C in a water/ice bath. The reaction was then quenched by the addition of 20 mL of ethyl acetate. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). Purification afforded 0.38 g (92%) of (2R)-2-(tert-butoxy)-2-phenylethan-1-ol (**117.3**) as a white solid.

[00651] **Synthesis of Compound I-127.** Into a 100-mL 3-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed **116.1** (200 mg, 0.59 mmol, 1.00 equiv), tetrahydrofuran (30 mL), DIAD (238 mg, 1.18 mmol, 2.00 equiv), PPh_3 (309 mg, 1.18 mmol, 2.00 equiv) and **117.3** (114 mg, 0.59 mmol, 1.00 equiv). The resulting solution was stirred overnight at room temperature and then concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/hexane (1:25). The product thus obtained (100 mg) was purified by preparative HPLC under the following conditions (Waters): Column: Xbridge Prep Phenyl 5 μm, 19*150 mm; mobile phase: water (0.05% NH_4HCO_3) and CH_3CN (6.0% CH_3CN up to 50.0% in 10 min); detector: 220/254 nm. 24.9 mg (8%) of Compound **I-127** were

obtained as a white solid. MS (ES): *m/z* 517 $(M+H)^+$; 443 $(M-C_4H_9O)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 0.94 (s, 9H), 1.22-1.27 (t,3H), 1.58-1.61 (d, 6H), 2.61 (s,3H), 3.80-3.86 (q, 2H), 4.19-4.24 (m, 2H), 4.66-4.70 (m, 1H), 7.09-7.46 (m, 5H), 12.38-12.51 (s, 1H).

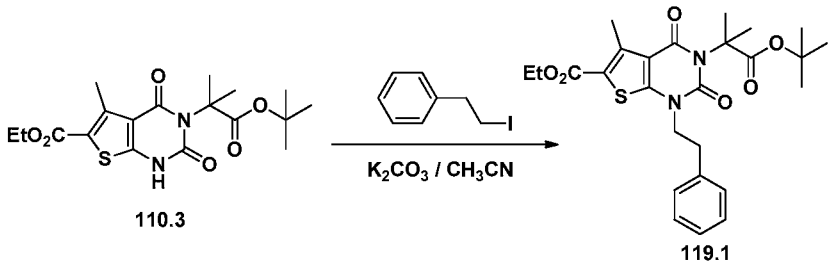
[00652] Example 118: Synthesis of 2-[1-[(2S)-2-(tert-butoxy)-2-phenylethyl]-6-(ethoxycarbonyl)-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-128).



[00653] Synthesis of compound 118.4. Compound **118.4** was prepared from **118.1** in a manner analogous to compound **117.3**. Isolated 220 mg of a white solid in 16% overall yield.

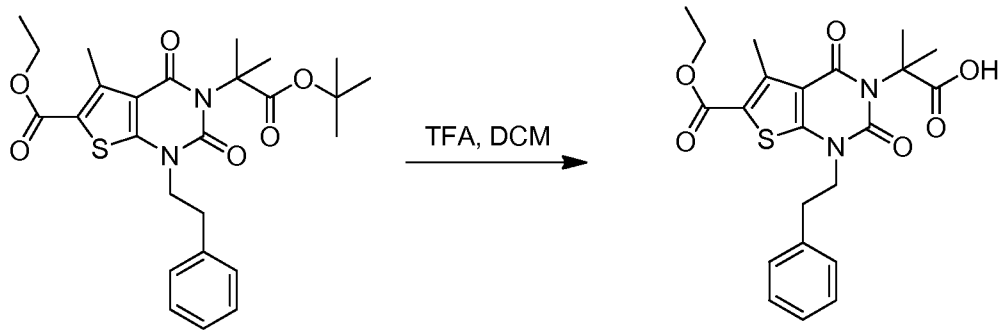
[00654] Synthesis of Compound I-128. Compound **I-128** was prepared from **118.4** and **116.1** in a manner analogous to Example 117. MS (ES): *m/z* 517 $(M+H)^+$, 443 $(M-C_4H_9O)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 0.94 (s, 9H), 1.22-1.27 (t, 3H), 1.59-1.61 (d, 6H), 2.61 (s, 3H), 3.79-3.82 (q, 2H), 4.19-4.26 (q, 2H), 4.66-4.70 (m, 1H), 7.09-7.43 (m, 5H), 12.382 (s,1H).

[00655] Example 119: Synthesis of Intermediate 119.1.



[00656] Synthesis of compound 119.1. Into a 100-mL 3-necked round-bottom flask was placed **110.3** (1 g, 2.52 mmol, 1.00 equiv), CH_3CN (50 mL), potassium carbonate (1.045 g, 7.56 mmol, 3.00 equiv) and (2-iodoethyl)benzene (1.172 g, 5.05 mmol, 2.00 equiv). The resulting solution was stirred for 4 h at 80 °C. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with EA/PE (1:100-1:15). Purification afforded 1.24 g (98%) of **119.1** as a white solid.

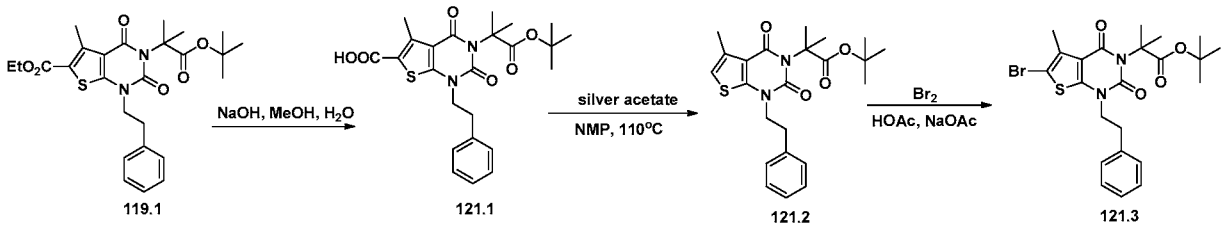
[00657] Example 120: Synthesis of 2-[6-(ethoxycarbonyl)-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-70).



119.1 **I-70**

[00658] Compound **I-70** was synthesized following the procedure of intermediate **116.1**. Isolated 50 mg of a white solid in 38% yield. MS (ES): *m/z* 445 $(M+H)^+$. ^1H NMR (DMSO-d_6, 300 MHz): δ 1.29 (t, *J* = 9.6 Hz, 3H), 1.63 (s, 6H), 2.70 (s, 3H), 2.98 (t, *J* = 9.6 Hz, 2H), 4.07 (t, *J* = 9.6 Hz, 2H), 4.27 (q, *J* = 9.6 Hz, 2H), 7.19-7.31 (m, 5H), 12.40 (s, 1H).

[00659] Example 121: Synthesis of Intermediate 121.3.



119.1 121.1 121.2 121.3

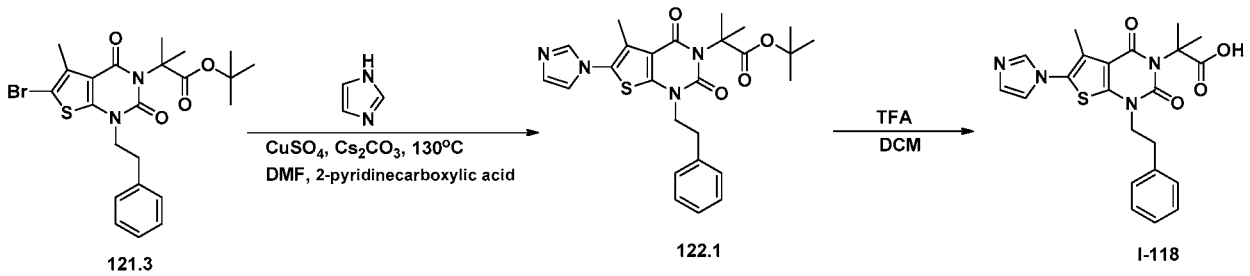
[00660] Synthesis of compound 121.1. Into a 100-mL 3-necked round-bottom flask was placed **119.1** (1.017 g, 2.03 mmol, 1.00 equiv) and methanol (40 mL). Then a solution of sodium hydroxide (162 mg, 4.05 mmol, 2.00 equiv) in water (5 mL) was added dropwise. The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the

addition of HCl (aq.). The resulting solution was extracted with ethyl acetate and the organic layers combined and concentrated under vacuum. The crude product was purified by re-crystallization from EA/PE in the ratio of 1:4. 0.578 g (60%) of **121.1** were obtained as a white solid.

[00661] Synthesis of compound 121.2. Into a 100-mL 3-necked round-bottom flask was placed **121.1** (578 mg, 1.22 mmol, 1.00 equiv), NMP (40 mL), potassium carbonate (169 mg, 1.22 mmol, 1.00 equiv) and AgOAc (0.204 g). The resulting solution was stirred for 2 h at 110 ^{0}C. The reaction was then quenched by the addition of water. The resulting solution was extracted with ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with EA/PE (1:25). Purification afforded 0.445 g (85%) of **121.2** as a white solid.

[00662] Synthesis of compound 121.3. Into a 50-mL round-bottom flask was placed **121.2** (445 mg, 1.04 mmol, 1.00 equiv), acetic acid (5 mL) and CH_3COONa (0.170 g). Then Br_2 (167 mg, 1.04 mmol, 1.01 equiv) was added dropwise. The resulting solution was stirred for 15 min at room temperature and then concentrated under vacuum. The residue was applied onto a silica gel column with EA/PE (1:25). Purification afforded 0.502 g (95%) of intermediate **121.3** as a white solid.

[00663] Example 122: Synthesis of 2-[6-(1H-imidazol-1-yl)-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-118).



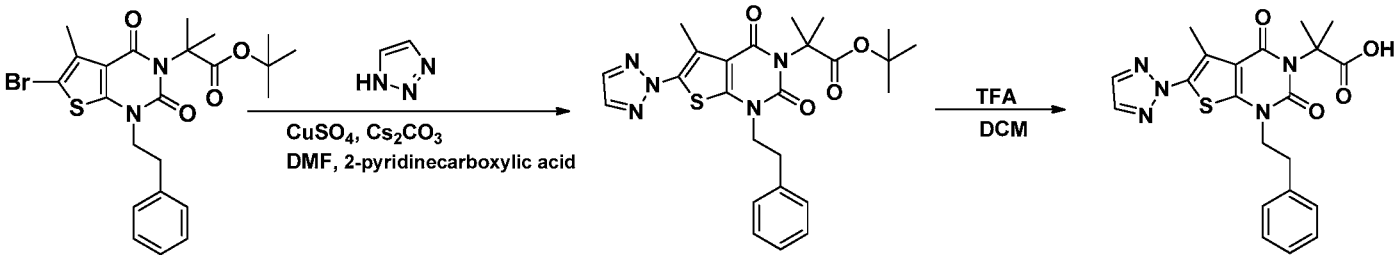
121.3 122.1 I-118

[00664] Synthesis of compound 122.1. Into a 10-mL sealed tube, purged and maintained with an inert atmosphere of nitrogen, was placed a solution of **121.3** (200 mg, 0.39 mmol, 1.00 equiv) in N,N-dimethylformamide (5 mL), 1H-imidazole (200 mg, 2.94 mmol, 7.45 equiv), pyridine-2-carboxylic acid (50 mg, 0.41 mmol, 1.03 equiv), $CuSO_4$ (100 mg, 0.63 mmol, 1.60 equiv) and Cs_2CO_3 (400 mg, 1.23 mmol, 3.11 equiv). The resulting solution was stirred overnight at 140 ^{o}C. The reaction was then quenched by the addition of 5 mL of NH_4Cl (aq.).

The resulting solution was extracted with 3x5 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:2). Purification afforded 166 mg (85%) of **122.1** as a brown oil.

[00665] Synthesis of Compound I-118. Into a 100-mL round-bottom flask was placed **122.1** (166 mg, 0.34 mmol, 1.00 equiv), dichloromethane (10 mL) and trifluoroacetic acid (2 mL). The resulting solution was stirred for 4 h at room temperature and then concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (50:1). Purification afforded 121.7 mg (83%) of **I-118** was a yellow solid. MS (ES): *m/z* 439 $(M+H)^+$. ^1H NMR (DMSO-d_6, 300 MHz): δ 1.61 (s, 6 H), 2.13 (s, 3 H), 2.95 (t, J = 7.2 Hz, 2H), 4.00 (t, J = 7.2 Hz, 2 H), 7.47-7.16 (m, 5 H), 7.47 (s, 1 H), 8.09 (s, 1 H), 12.38 (br s, 1 H).

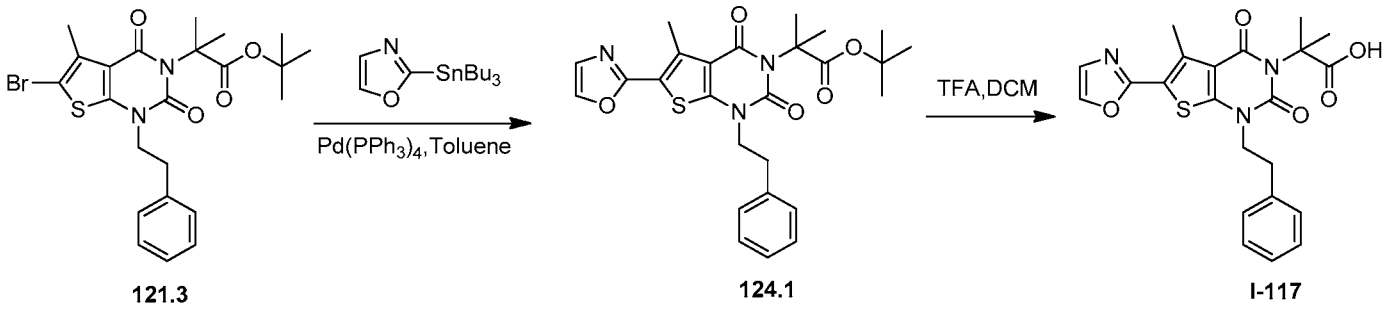
[00666] Example 123: Synthesis of 2-methyl-2-[5-methyl-2,4-dioxo-1-(2-phenylethyl)-6-(2H-1,2,3-triazol-2-yl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-122).



121.3 123.1 I-YY

[00667] Compound **I-122** was prepared from 1H-1,2,3-triazole and intermediate **121.3** following the procedure of Example 122. Isolated 20.6 mg of a white solid in 5% yield from **123.1**. MS (ES): *m/z* 440 $(M+H)^+$. ^1H NMR (CD_3OD, 300 MHz): δ 1.75 (s, 6H), 2.51 (s, 3H), 3.05 (t, J = 7.2 Hz, 2H), 4.08 (t, J = 7.2 Hz, 2H), 7.26-7.12 (m, 5H), 7.91 (s, 1H).

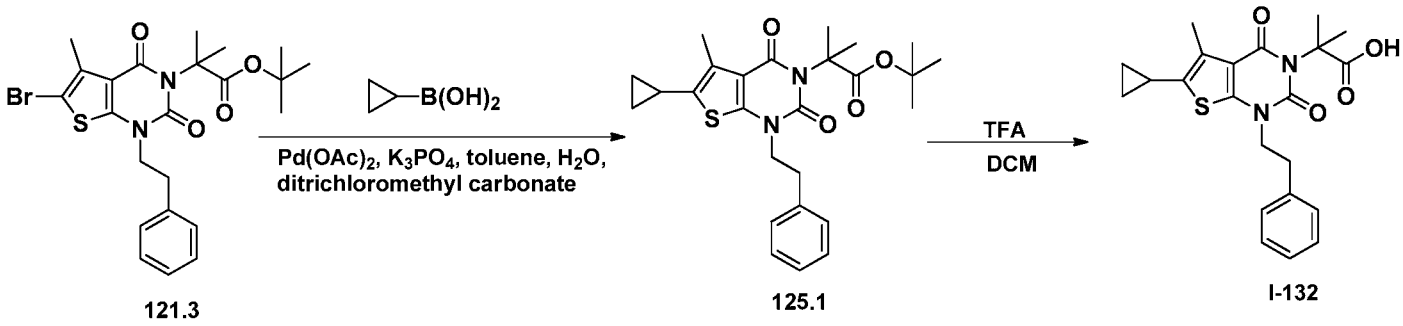
[00668] Example 124: Synthesis of 2-methyl-2-[5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-117).



121.3 124.1 I-117

[00669] Compound **I-117** was prepared from **121.3** in a manner analogous to the procedure of Example 7. MS (ES): *m/z* 440 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.79 (s, 6 H), 2.78 (s, 3 H), 3.11 (t, *J* = 7.2 Hz, 2 H), 4.15 (t, *J* = 7.2 Hz , 2 H), 7.19-7.23 (m, 1 H), 7.25-7.31 (m, 5 H) , 7.96 (s, 1 H).

[00670] Example 125: Synthesis of 2-[6-cyclopropyl-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-132).



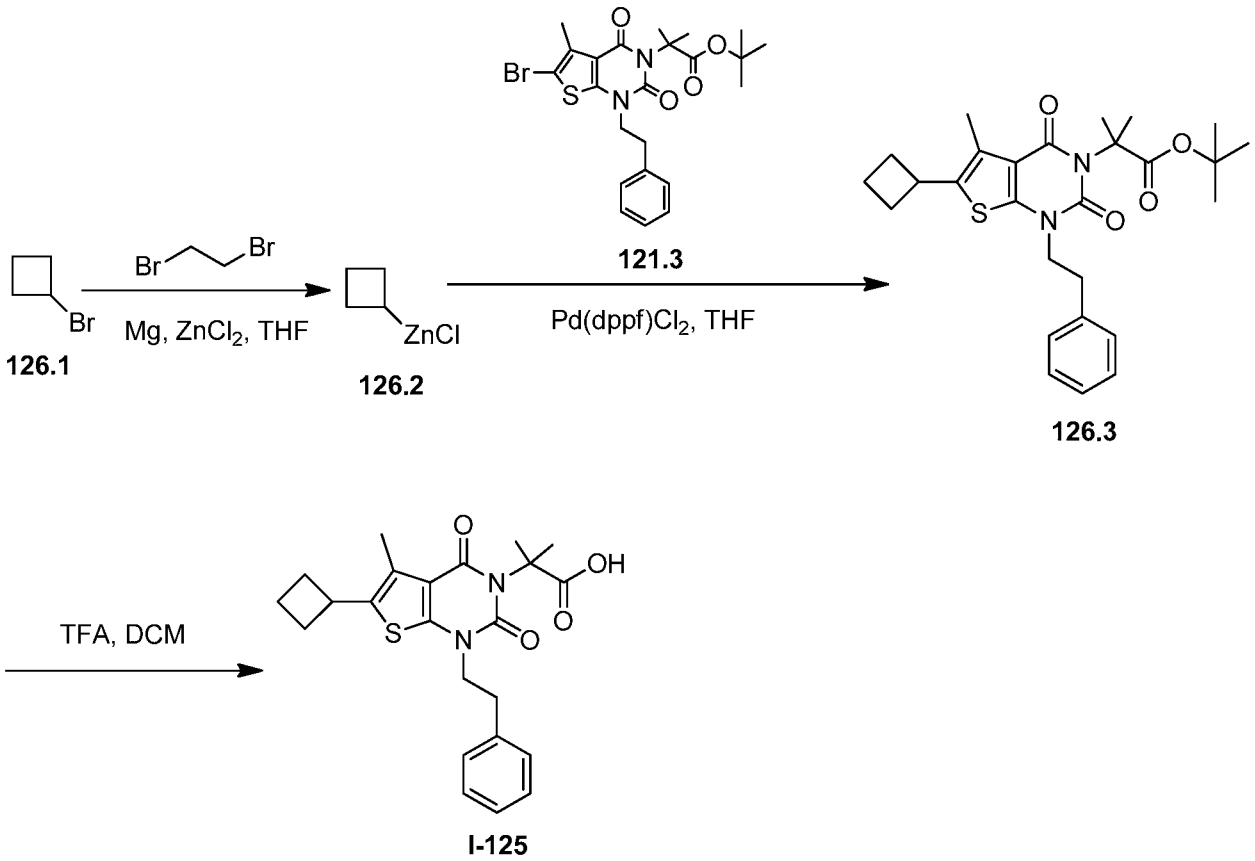
121.3 125.1 I-132

[00671] Synthesis of compound 125.1. Into a 100-mL 3-necked round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed **121.3** (200 mg, 0.39 mmol, 1.00 equiv), cyclopropylboronic acid (200 mg, 2.33 mmol, 5.91 equiv), ditrichloromethyl carbonate (20 mg, 0.07 mmol, 0.17 equiv), K_3PO_4 (300 mg, 1.41 mmol, 3.59 equiv), $Pd(OAc)_2$ (10 mg, 0.04 mmol, 0.11 equiv), water (0.5 mL) and toluene (20 mL). The resulting solution was heated to reflux for 2 hr and then concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). Purification afforded 170 mg of a white solid.

[00672] Synthesis of compound I-132. Into a 50-mL round-bottom flask was placed **125.1** (170 mg, 0.36 mmol, 1.00 equiv), trifluoroacetic acid (1 mL) and dichloromethane (5 mL). The resulting solution was stirred overnight at room temperature and then concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol

(20:1). Purification afforded 22 mg (15%) of **I-132** as a white solid. MS (ES): *m/z* 413 $(M+H)^+$. ^1H NMR (CD_3OD, 400 MHz): δ 0.67 (t, *J* = 5.2 Hz, 2H), 0.97 (t, *J* = 8 Hz, 2H), 1.80 (s, 6H), 1.90-2.00 (m, 1H), 2.41 (s, 3H), 3.03 (t, *J* = 6.8 Hz, 2H), 4.08 (t, *J* = 6.8 Hz, 2H), 7.29-7.18 (m, 5H).

[00673] Example 126: Synthesis of 2-[6-cyclobutyl-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-125).

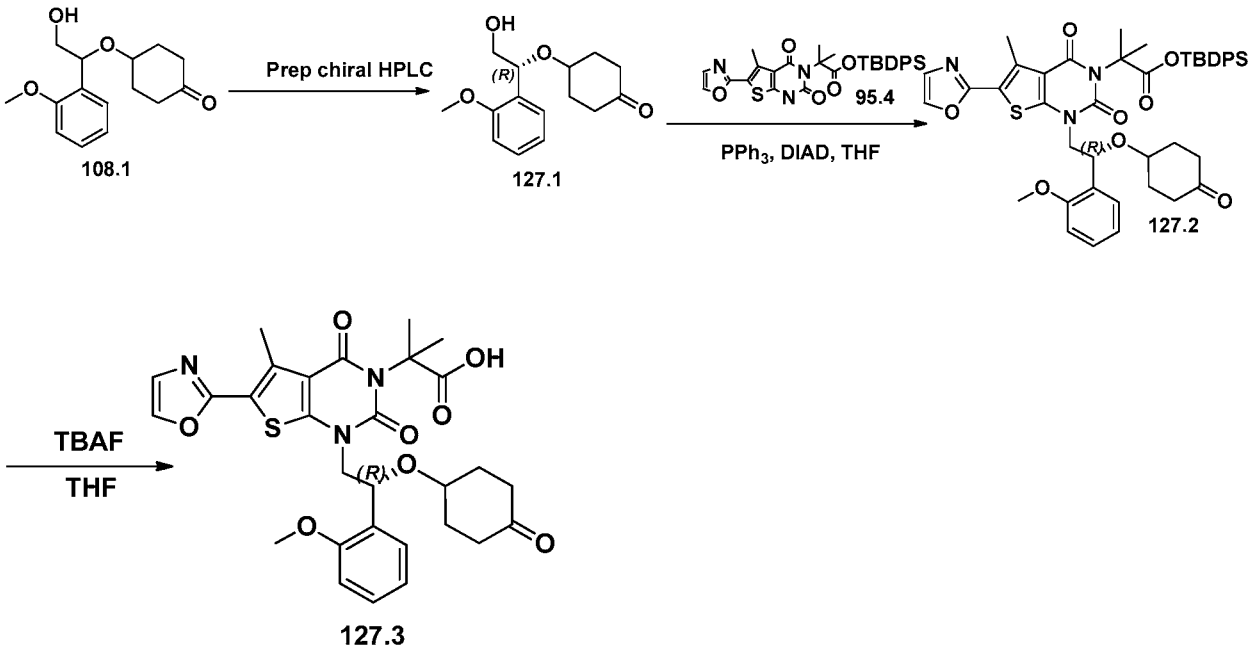


[00674] Synthesis of compound 126.2. Into a 100-mL 3-necked round-bottom flask was placed a suspension of Mg (0.46 g) in tetrahydrofuran (10 mL), followed by a roughly 10% portion of a 2-g batch of bromocyclobutane (14.81 mmol, 1.00 equiv). Then several drops of 1,2-dibromoethane were added to initiate the reaction. This was followed by the addition of a solution of the remaining bromocyclobutane (2 g, 14.81 mmol, 1.00 equiv) in THF dropwise. The resulting solution was stirred for 2 h at room temperature. After cooling to 0 °C, $ZnCl_2$ (2.22 g, 16.29 mmol, 1.10 equiv) was added in portions. The resulting solution was stirred for 2 h at room temperature and directly used for the next step.

[00675] **Synthesis of compound 126.3**. A solution of $Pd(dppf)Cl_2$ (72 mg, 0.10 mmol, 0.10 equiv) and **121.3** (500 mg, 0.99 mmol, 1.00 equiv) in tetrahydrofuran (5 mL) was added to a flask of chloro(cyclobutyl)zinc (**126.2**, crude solution). The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 50 mL of NH_4Cl (aq.). The resulting solution was extracted with 3x100 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:40). Purification afforded 240 mg (50%) of **126.3** as a colorless oil.

[00676] **Synthesis of Compound I-125.** Into a 50-mL round-bottom flask was placed dichloromethane (5 mL), **126.3** (240 mg, 0.50 mmol, 1.00 equiv) and trifluoroacetic acid (2 mL). The resulting solution was stirred for 2 h at room temperature and then concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (50:1). Purification afforded 43.5 mg (21%) of Compound **I-125** as a white solid. MS (ES): *m/z* 426 $(M+H)^+$, 449 $(M+Na)^+$, 490 $(M+Na+CH_3CN)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 1.59 (s, 6H), 1.77-1.81 (m, 1H), 1.90-2.00 (m, 3H), 2.18 (s, 3H), 2.31-2.34 (m, 2H), 2.93 (t, J = 7.5, 2H), 3.71-3.77 (m, 1H), 3.99 (t, J = 7.5, 2H), 7.15-7.28 (m, 5H).

[00677] **Example 127: Synthesis of intermediate 127.3.**

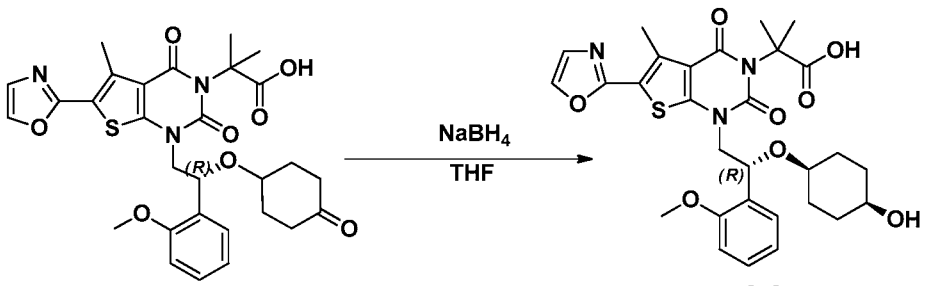


[00678] **Synthesis of compound 127.1.** The enantiomers of racemic **108.1** (400 mg) were separated by chiral preparative HPLC under the following conditions (Gilson Gx 281): Column:

Venusil Chiral OD-H, 21.1*25 cm, 5 μm; mobile phase: hexanes and IPA (hold at 5% IPA for 36 min); detector: UV 254/220 nm. 180 mg of **127.1** were obtained.

[00679] Synthesis of compound 127.3. Compound **127.3** was prepared from **95.4** and **127.1** in a manner analogous to the procedure Example 96. Isolated a white solid in 53% yield from **95.4**.

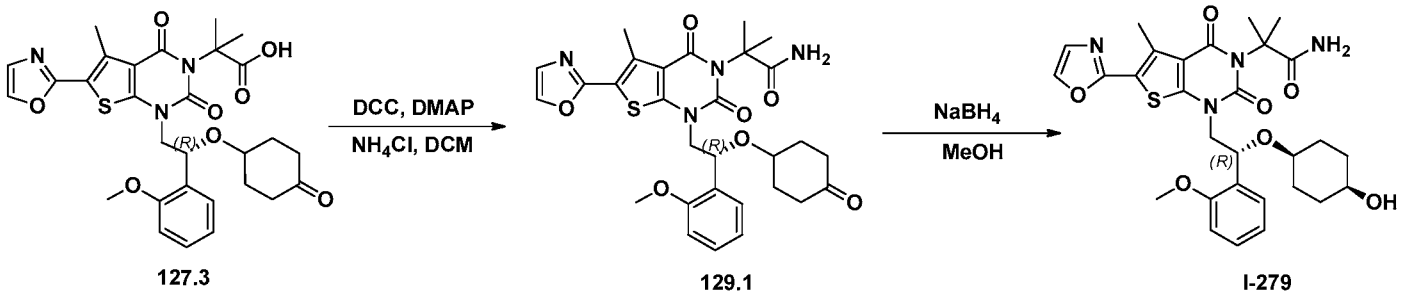
[00680] Example 128: Synthesis of 2-[1-[(2R)-2-[(4-hydroxycyclohexyl)oxy]-2-(2-methoxyphenyl)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-278).



127.3 I-278

[00681] Into a 25-mL round-bottom flask was placed **127.3** (600 mg, 1.03 mmol, 1.00 equiv) and methanol (5 mL). Then sodium borohydride (40 mg, 1.09 mmol, 1.00 equiv) was added at 0 °C. The resulting solution was stirred overnight at room temperature and then concentrated under vacuum. The crude product (400 mg) was purified by preparative HPLC under the following conditions (Waters): Column: Xbridge Prep Phenyl 5 μm, 19*150 mm; mobile phase: water (50 mM NH_4HCO_3) and CH_3CN (40.0% CH_3CN up to 60.0% in 20 min); detector: UV 254/220 nm. 93.5 mg (16%) of Compound **I-278** were obtained as a white solid. MS (ES): *m/z* 584 $(M+H)^+$, 606 $(M+Na)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 1.21-1.40 (m, 6H), 1.56 (m, 2H), 1.68 (d, 6H), 2.74 (s, 3H), 3.17 (m, 2H), 3.78 (s, 3H), 3.89-4.03 (m,2H), 5.24 (t, 1H), 6.99 (m,2H) , 7.26 (m,1H), 7.38 (s,1H), 7.47 (m,1H), 8.21 (s, 1H).

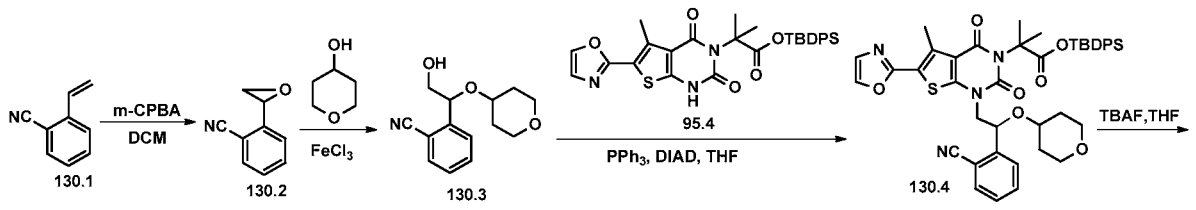
[00682] Example 129: Synthesis of 2-[1-[(2R)-2-[(4-hydroxycyclohexyl)oxy]-2-(2-methoxyphenyl)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanamide (I-279).

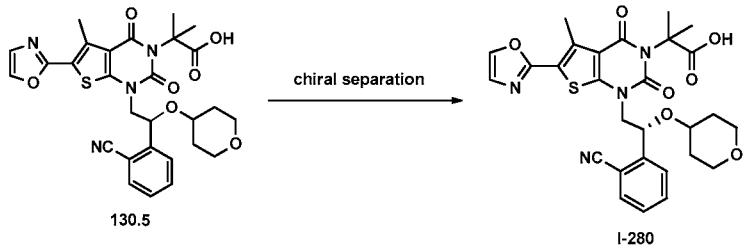


[00683] Synthesis of compound 129.1. Compound **129.1** was prepared from **127.3** and ammonium chloride following the procedure of Example 4. Isolated 530 mg of a white solid in quantitative yield.

[00684] Synthesis of Compound I-279. Into a 50-mL round-bottom flask was placed **129.1** (530 mg, 0.91 mmol, 1.00 equiv), methanol (10 mL) and sodium borohydride (35 mg, 0.95 mmol, 1.04 equiv). The resulting solution was stirred overnight at room temperature and concentrated under vacuum. The crude product (150 mg) was purified by preparative HPLC under the following conditions (Waters): Column: HPrepC-012(T) Xbridge Prep Phenyl 5 μm, 19*150 mm; mobile phase: Water (50 mM NH_4HCO_3) and CH_3CN (30.0% CH_3CN up to 70.0% in 15 min); detector: 254/220 nm. Purification afforded 39.1 mg (7%) of Compound **I-279** (tR = 8.21 min) as a white solid. MS (ES): *m/z* 605 $(M+Na)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 1.17-1.30 (m, 6H), 1.53 (m, 2H), 1.66 (d, 6H), 2.74 (s, 3H), 3.17 (m, 1H), 3.31 (m, 1H), 3.78 (s, 3H), 3.99 (m, 2H), 4.29 (s, 1H), 5.28 (t, 1H), 6.79-7.28 (m, 4H), 7.30 (m, 1H), 7.37 (s, 1H), 7.47 (m, 1H), 8.21 (s, 1H).

[00685] Example 130: Synthesis of 2-[1-[(2R)-2-(2-cyanophenyl)-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-280).



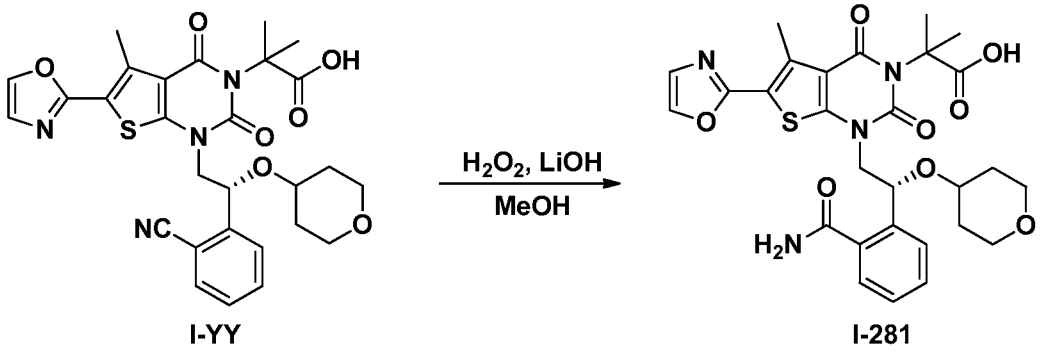


[00686] Synthesis of compound 130.2. Into a 100-mL round-bottom flask was placed 2-ethenylbenzonitrile (2.73 g, 21.14 mmol, 1.00 equiv), sodium bicarbonate (1.77 g, 21.07 mmol, 4.61 equiv), dichloromethane (20 mL) and water (20 mL). Then m-CPBA (10.9 g, 63.16 mmol, 2.25 equiv) was added at 0 °C in several batches. The resulting solution was stirred overnight at room temperature and then concentrated under vacuum. The residue was applied onto a silica gel column with PE/EA (50:1). Purification afforded 400 mg (13%) of 2-(oxiran-2-yl)benzonitrile as a yellow oil.

[00687] Synthesis of compound 130.3. Compound **130.3** was prepared from **130.2** in a manner analogous to the synthesis of **57.3**. Isolated a yellow oil in 59% yield.

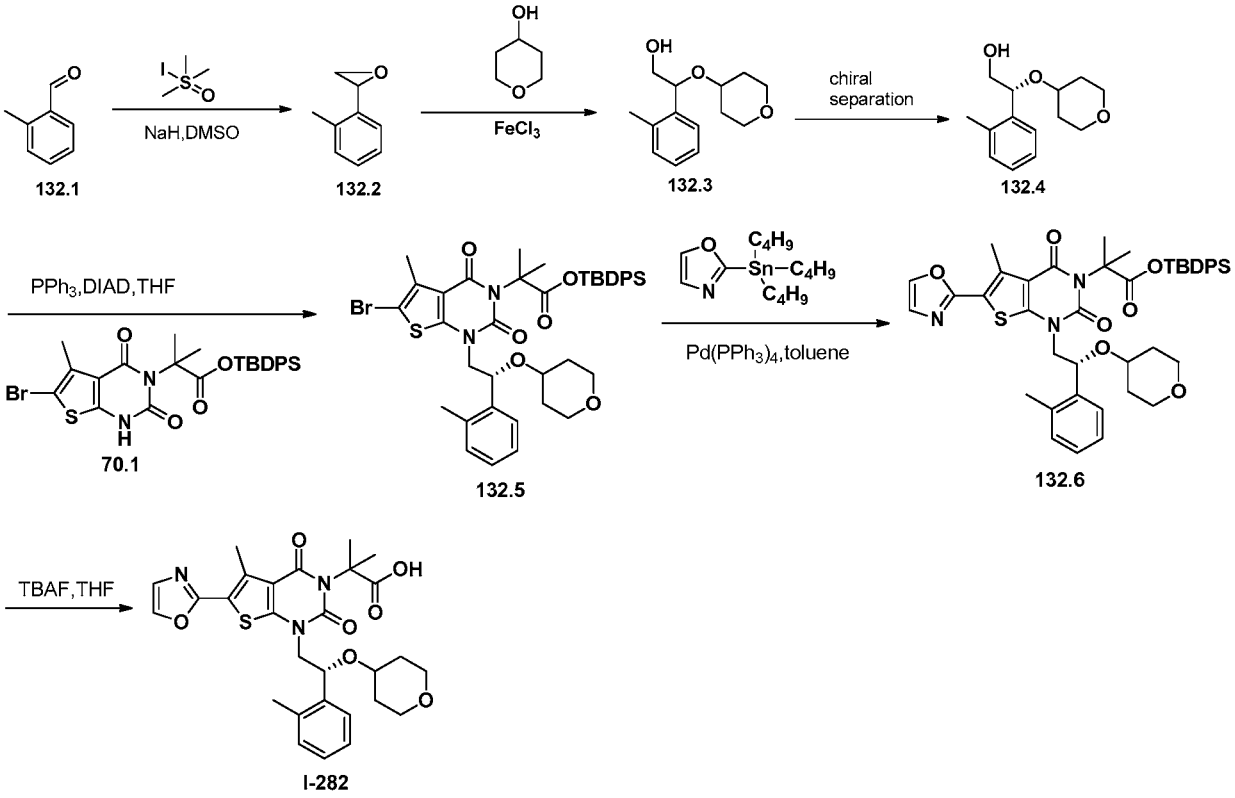
[00688] Synthesis of Compound I-280. Compound **I-280** was prepared from **95.4** and **130.3** according to the procedure for Example 97. Purification: The enantiomers of **130.5** were separated by chiral preparative HPLC under the following conditions: Gilson Gx 281; column: Chiralpak IA, 2*25 cm, 5 μm; mobile phase: hexanes and IPA (hold at 20.0% IPA for 4 min); detector: UV 254/220 nm. MS (ES): *m/z* 565 $(M+H)^+$, 587 $(M+Na)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.41-1.45 (m, 2H), 1.61-1.72 (m, 8H), 2.70 (s, 3H), 3.20-3.33 (m, 3H), 3.43-3.59 (m, 1H), 3.60-3.62 (m, 2H), 4.08-4.19 (m, 2H), 5.19-5.24 (m,1H), 7.17-7.17 (s, 1H), 7.42-7.45 (m, 1H), 7.63-7.68 (m, 3H), 7.87 (s, 1H).

[00689] Example 131: Synthesis of 2-[1-[(2R)-2-(2-carbamoylphenyl)-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-281).



[00690] Into a 50-mL round-bottom flask was placed **I-280** (30 mg, 0.05 mmol, 1.00 equiv), $LiOH \cdot H_2O$ (7 mg, 0.17 mmol, 5.50 equiv), H_2O_2 (8 mg, 30%) and methanol (10 mL). The resulting solution was stirred overnight at 35 °C. The resulting mixture was concentrated under vacuum. The residue was purified by thin layer chromatography developed with dichloromethane/methanol (30:1). 2.8 mg (9%) of Compound **I-281** were obtained as a white solid. MS (ES): *m/z* 583 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.24-1.25 (m, 2H), 1.57-1.67 (m, 8H), 2.76 (s, 3H), 3.22-3.34 (m, 3H), 3.44-3.48 (m, 2H), 4.09-4.25 (m, 2H), 5.36-5.37 (m, 1H), 7.38-7.42 (m, 3H), 7.54 (s, 2H), 7.65-7.66 (m, 1H), 7.92 (s, 1H), 8.24 (s, 1H).

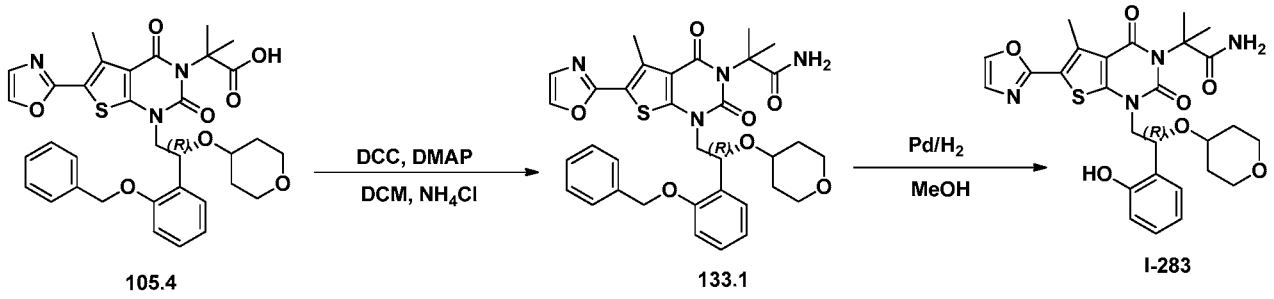
[00691] Example 132: Synthesis of 2-methyl-2-[5-methyl-1-[(2R)-2-(2-methylphenyl)-2-(oxan-4-yloxy)ethyl]-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-282).



[00692] Synthesis of compound 132.4. Compound **132.4** was synthesized from 2-methylbenzaldehyde in a manner analogous to the synthesis of compound **57.5**. Isolated 680 mg of a yellow oil in 5% yield from **132.1**.

[00693] Synthesis of Compound I-282. Compound **I-282** was prepared from **70.1** and **132.4** in a manner analogous to the procedure for Example 57. Isolated 173 mg of a white solid in 14% yield from **70.1**. MS (ES): *m/z* 554 $(M+H)^+$, 576 $(M+Na)^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.30-1.33 (m, 2H), 1.62-1.72 (m, 8H), 2.44-2.51 (s, 3H), 2.77 (s, 3H), 3.20-3.24 (m, 2H), 3.33-3.39 (m, 2H), 3.41-3.64 (m, 2H), 4.21-4.24 (m, 1H), 5.10-5.13 (m, 1H), 7.21-7.32 (m, 3H), 7.41 (s, 1H), 7.54-7.56 (m, 1H), 8.25 (s, 1H), 12.49 (s, 1H).

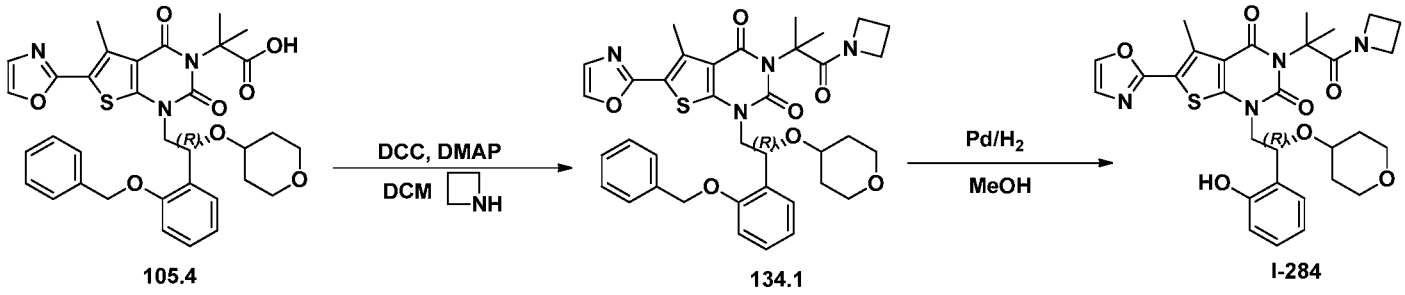
[00694] Example 133: Synthesis of 2-[1-[(2R)-2-(2-hydroxyphenyl)-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanamide (I-283).



[00695] Synthesis of compound 133.1. Compound **133.1** was prepared from **105.4** according to the procedure for Example 4. Isolated a white solid in 70% yield.

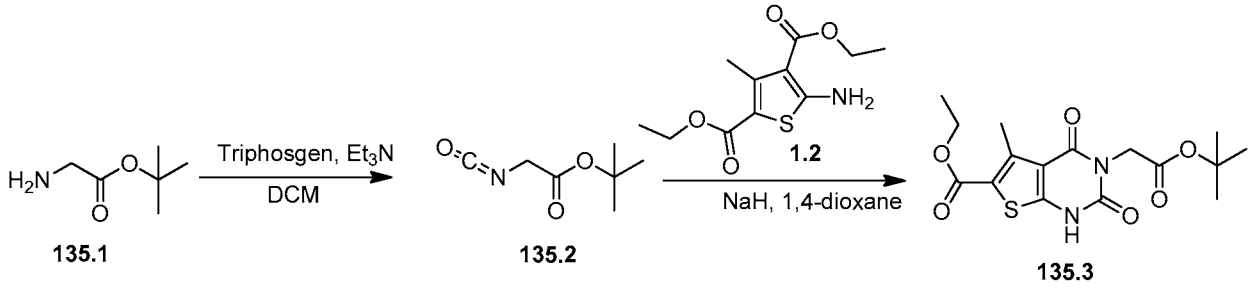
[00696] Synthesis of Compound I-283. Into a 100-mL round-bottom flask was placed **133.1** (290 mg, 0.45 mmol, 1.00 equiv) and methanol (30 mL). This was followed by the addition of palladium on carbon (50 mg). The flask was evacuated and flushed three times with nitrogen, followed by flushing with hydrogen. The mixture was stirred overnight at room temperature under an atmosphere of hydrogen. The solids were filtered out. The filtrate was concentrated under vacuum. The residue was purified by thin layer chromatography developed with dichloromethane/MeOH/HOAc (30:1:0.15). 91.6 mg (37%) of Compound **I-283** were obtained as a white solid. MS (ES): *m/z* 577 $(M+Na)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 1.23 (m, 2H), 1.65-1.68 (m, 8H), 2.75 (s, 3H), 3.21 (m, 2H), 3.50 (m, 2H), 3.90 (m, 1H), 4.13 (m, 1H), 5.29 (t,1H), 6.79-6.89 (m, 3H), 7.10 (m, 2H), 7.38 (m, 2H), 8.23 (s, 1H), 9.72 (s, 1H).

[00697] Example 134: Synthesis of 3-[1-(azetidin-1-yl)-2-methyl-1-oxopropan-2-yl]-1-[(2R)-2-(2-hydroxyphenyl)-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-2,4-dione (I-284).



[00698] Compound **I-284** was prepared according to the procedure for Example 133, substituting azetidine for ammonium chloride in the first step. MS (ES): *m/z* 595 $(M+H)^+$, 617 $(M+Na)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 1.18-1.32 (m, 2H), 1.63-1.70 (m, 8H), 2.08-2.16 (m, 2H), 2.77 (s, 3H), 3.20 (m, 2H), 3.50 (m, 1H), 3.50-3.60 (m, 2H), 3.76-4.13 (br m, 6H), 5.29 (t, 1H) , 6.79-6.89 (m, 2H) , 7.10 (m, 1H), 7.37 (m, 2H), 8.23 (s, 1H) , 9.74 (s, 1H).

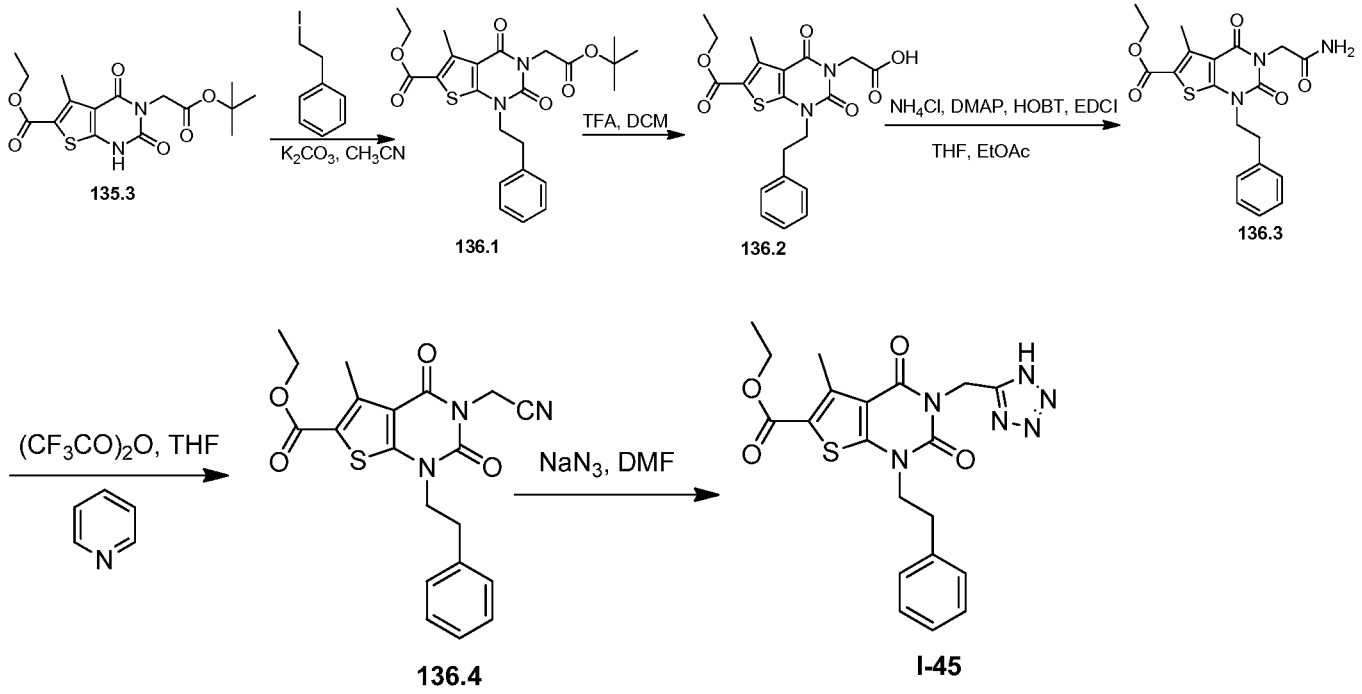
[00699] Example 135: Synthesis of intermediate 135.3.



[00700] Synthesis of compound 135.2. Into a 500-mL 3-necked round-bottom flask was placed tert-butyl 2-aminoacetate (**135.1**, 5.9 g, 44.98 mmol, 1.00 equiv). Then dichloromethane (180 mL) and ditrichloromethyl carbonate (4.43 g, 14.93 mmol, 0.33 equiv) were added at 0 °C. After 30 min triethylamine (13.65 g, 134.89 mmol, 3.00 equiv) was added to the above mixture. The resulting solution was stirred for 4 h at 5-10 °C in a water/ice bath. The solids were filtered out. The filtrate was concentrated under vacuum. The resulting solution was diluted with 50 mL of ethyl ether. The solids were filtered out. The resulting mixture was concentrated under vacuum. Purification afforded 7.1 g (crude) of tert-butyl 2-isocyanatoacetate (**135.2**) as a yellow oil.

[00701] **Synthesis of intermediate 135.3.** Into a 250-mL 3-necked round-bottom flask was placed **1.2** (7.9 g, 30.70 mmol, 1.00 equiv) and 1,4-dioxane (80 mL). Then sodium hydride (1.32 g, 33.00 mmol, 1.07 equiv, 60%) was added at 0 °C. The mixture was stirred for 15 min at room temperature. Then a solution of tert-butyl 2-isocyanatoacetate (7.1 g, 45.17 mmol, 1.47 equiv) in 1,4-dioxane (20 mL) was added dropwise with stirring at 0 °C in 15 min. The resulting solution was stirred for 30 min at 10-15 °C in a water/ice bath. The resulting solution was allowed to react, with stirring, overnight while the temperature was maintained at 100 °C in an oil bath. The reaction mixture was cooled to 20 °C with a water bath. The reaction was then quenched by the addition of 80 mL of NH_4Cl (aq.). The resulting solution was extracted with 3x200 mL of ethyl acetate, the organic layers combined and dried over anhydrous magnesium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:7). Purification afforded 5.1 g (45%) of intermediate **135.3** as a white solid.

[00702] **Example 136: Synthesis of ethyl 5-methyl-2,4-dioxo-1-(2-phenylethyl)-3-(1H-1,2,3,4-tetrazol-5-ylmethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-45).**



[00703] **Synthesis of compound 136.1.** Compound **136.1** was prepared from **135.3** and (2-iodoethyl)benzene in a manner analogous to the synthesis of compound **9.1**. Isolated 1.7 g (66%) of **136.1** as a white solid.

[00704] **Synthesis of compound 136.2 (I-13).** Into a 50-mL round-bottom flask was placed a solution of **136.1** (2.4 g, 5.08 mmol, 1.00 equiv) in dichloromethane (20 mL). Then CF_3COOH (3 mL) was added dropwise. The resulting solution was stirred for 30 min at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (10:1). Purification afforded 1.7 g (80%) of **136.2** (**I-13**) as a white solid. MS (ES): *m/z*: (M+H)+ calcd for $C_{20}H_{21}N_2O_6S$ 417, found 417; ^{1}H-NMR (300MHz, DMSO-d6) δ13.08 (1H, br s), 7.22-7.34 (5H, m), 4.57 (2H, s), 4.27-4.34 (2H, q), 4.13-4.18 (2H, t), 3.00-3.05 (2H, t), 2.77 (3H, s),1.27-1.34 (3H,t).

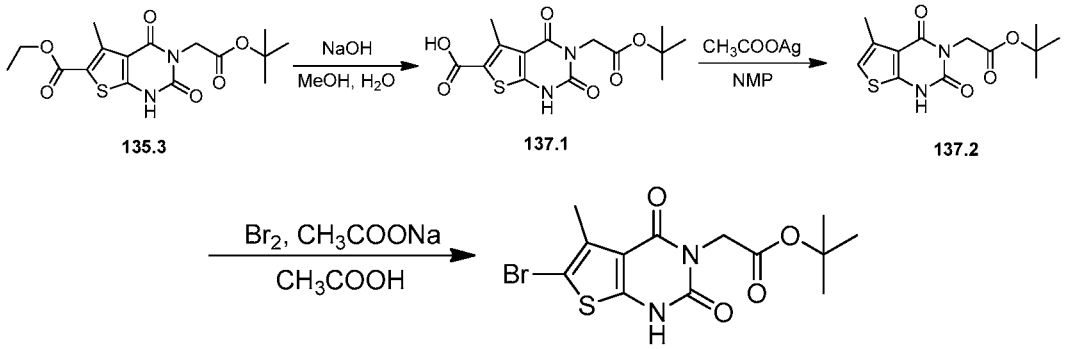
[00705] **Synthesis of compound 136.3.** Into a 250-mL 3-necked round-bottom flask was placed HOBt (220 mg, 1.63 mmol, 1.13 equiv), **136.2** (600 mg, 1.44 mmol, 1.00 equiv), NH_4Cl (1.5 g, 28.04 mmol, 19.46 equiv), EDCI (310 mg, 1.62 mmol, 1.12 equiv), CH_3CN (20 mL), ethyl acetate (20 mL) and 4-dimethylaminopyridine (200 mg, 1.64 mmol, 1.14 equiv). The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 20 mL of water. The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined and dried over anhydrous magnesium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (50:1). Purification afforded 0.3 g (50%) of **136.3** as an off-white solid.

[00706] **Synthesis of compound 136.4.** Into a 100-mL 3-necked roundbottom flask was placed **136.3** (300 mg, 0.72 mmol, 1.00 equiv), pyridine (280 mg, 3.54 mmol, 4.90 equiv) and tetrahydrofuran (10 mL). This was followed by the addition of $(CF_3CO)_2O$ (0.38 g, 1.75 mmol, 2.50 equiv) dropwise with stirring at 0-10 °C. The resulting solution was stirred for 3 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). Purification afforded 250 mg (87%) of **136.4** as a white solid.

[00707] **Synthesis of Compound I-45.** Into an 8-mL sealed tube was placed **136.4** (50 mg, 0.13 mmol, 1.00 equiv), NaN_3 (13 mg, 0.20 mmol, 1.57 equiv) and N,N-dimethylformamide (3 mL). The resulting solution was stirred overnight at 120 °C in an oil bath. The reaction was then quenched by the addition of 5 mL of water. The resulting solution was extracted with 3x20 mL of ethyl acetate and the organic layers were combined, dried over anhydrous magnesium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl

acetate/petroleum ether (1:2). Purification afforded 2.5 mg (5%) of Compound **I-45** as a white solid. MS (ES): *m/z* 441 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.43 (t, *J* = 7.2 Hz, 3H), 2.83 (s, 3H), 3.12 (t, *J* = 8.0 Hz, 2H), 4.19 (t, *J* = 8.0 Hz, 2H), 4.35 (q, *J* = 4.8 Hz, 2H), 5.43 (s, 2H), 7.23-7.33 (m, 5H).

[00708] Example 137: Synthesis of intermediate 137.3.



135.3 137.1 137.2 137.3

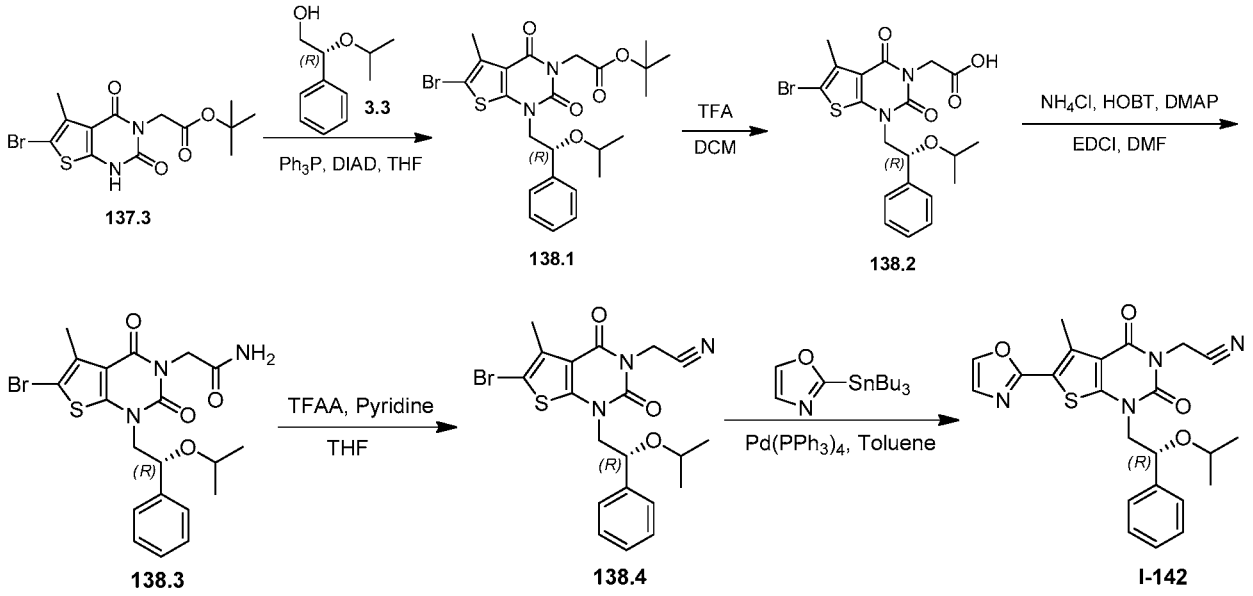
[00709] Synthesis of compound 137.1. Into a 250-mL 3-necked round-bottom flask was placed **135.3** (5 g, 13.57 mmol, 1.00 equiv), water (50 mL), sodium hydroxide (1.63 g, 40.75 mmol, 3.00 equiv) and methanol (50 mL). The resulting solution was stirred for 5 h at 50 °C. The pH value of the solution was adjusted to 4 with hydrogen chloride (10 %). The resulting mixture was concentrated under vacuum. The residue was extracted with 3x50 mL of ethyl acetate and the organic layers combined, washed with 100 mL of brine and dried over anhydrous magnesium sulfate and concentrated under vacuum. 4.6 g (crude) of **137.1** were obtained as a white solid.

[00710] Synthesis of compound 137.2. Into a 30-mL round-bottom flask was placed **137.2** (4.6 g, 13.52 mmol, 1.00 equiv), CH_3COOAg (2.48 g, 14.85 mmol, 1.10 equiv) and NMP (30 mL). The resulting solution was stirred for 2 h at 110 °C. The reaction was then quenched by the addition of 50 mL of water. The resulting solution was extracted with 3x100 mL of ethyl acetate and the organic layers were combined, washed with 150 mL of water and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). Purification afforded 1.3 g (32%) of **137.2** as a white solid.

[00711] Synthesis of intermediate 137.3. Into a 50-mL round-bottom flask, was placed CH_3COONa (720 mg, 8.78 mmol, 2.00 equiv), **137.2** (1.3 g, 4.39 mmol, 1.00 equiv) and acetic acid (20 mL). This was followed by the addition of Br_2 (780 mg, 4.88 mmol, 1.11 equiv) dropwise with stirring. The resulting solution was stirred for 30 min at room temperature and

then concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). Purification afforded 1.6 g (97%) of **137.3** as a white solid.

[00712] Example 138: Synthesis of 2-(1-((R)-2-isopropoxy-2-phenylethyl)-5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)acetonitrile (I-142).



[00713] Synthesis of compound 138.2. Compound **138.2** was prepared from **137.3** and **3.3** in a manner analogous to the synthesis of compound **2.5**. Isolated 400 mg of a yellow oil in 78% yield from **137.3**.

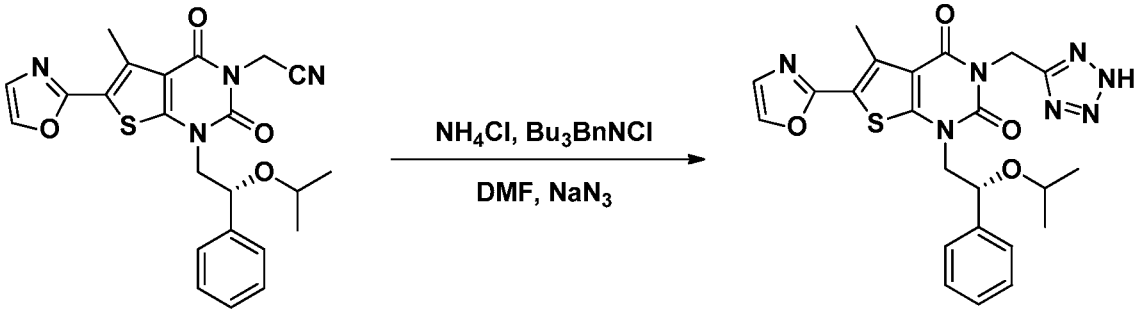
[00714] Synthesis of compound 138.3. Into a 50-mL round-bottom flask was placed **138.2** (400 mg, 0.83 mmol, 1.00 equiv), NH_4Cl (90 mg, 1.68 mmol, 2.02 equiv), HOBT (169 mg, 1.25 mmol, 1.51 equiv), 4-dimethylaminopyridine (152 mg, 1.24 mmol, 1.50 equiv), EDCI (240 mg, 1.25 mmol, 1.51 equiv) and N,N-dimethylformamide (10 mL). The resulting solution was stirred for 3 h at room temperature. The reaction was then quenched by the addition of 30 mL of water. The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (100:1). Purification afforded 390 mg (98%) of **138.3** as a white solid.

[00715] Synthesis of compound 138.4. Into a 50-mL round-bottom flask was placed a solution of **138.3** (390 mg, 0.81 mmol, 1.00 equiv) in tetrahydrofuran (10 mL) and pyridine (321 mg, 4.06 mmol, 5.00 equiv). This was followed by the addition of TFAA (426 mg, 2.03 mmol,

2.50 equiv) dropwise with stirring at 0 °C. The resulting solution was stirred for 2 h at room temperature and then concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). Purification afforded 360 mg (96%) of **138.4** as a yellow solid.

[00716] Synthesis of Compound I-142. Into a 50-mL round-bottom flask, maintained with an inert atmosphere of nitrogen, was placed **138.4** (360 mg, 0.78 mmol, 1.00 equiv), $Pd(PPh_3)_4$ (90 mg, 0.08 mmol, 0.10 equiv), 2-(tributylstannyl)-1,3-oxazole (560 mg, 1.56 mmol, 2.00 equiv) and toluene (10 mL). The resulting solution was stirred overnight at 110 °C and then concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). Purification afforded 60 mg (17%) of Compound **I-142** as a yellow solid. MS (ES): *m/z* 451 $(M+H)^+$, 473 $(M+Na)^+$, 492 $(M+H+CH_3CN)^+$. ^1H NMR (400 MHz, CD_3CN): δ 0.93-1.00 (m, 6H), 2.85 (s, 3H), 3.47-3.53 (m, 1H), 3.93-3.99 (m, 1H), 4.16-4.20 (m, 1H), 4.91 (s, 2H), 4.92-4.94 (m, 1H), 7.28 (s, 1H), 7.35-7.51 (m, 5H), 7.92 (s, 1H).

[00717] Example 139: Synthesis of 5-methyl-6-(1,3-oxazol-2-yl)-1-[(2R)-2-phenyl-2-(propan-2-yloxy)ethyl]-3-(1H-1,2,3,4-tetrazol-5-ylmethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-2,4-dione (I-153).

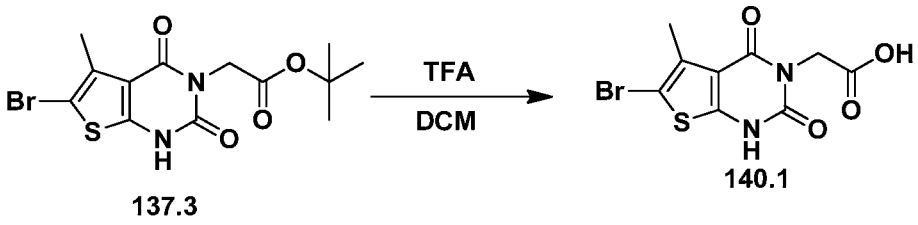


I-142 I-153

[00718] Into a 50-mL round-bottom flask was placed **I-142** (Example 138) (60 mg, 0.13 mmol, 1.00 equiv), NH_4Cl (29 mg, 0.54 mmol, 4.07 equiv), N,N-dimethylformamide (5 mL), Bu_3BnNCl (42 mg) and NaN_3 (35 mg, 0.54 mmol, 4.04 equiv). The resulting solution was stirred overnight at 135 °C. The solids were filtered out. The crude product (50 mg) was purified by flash preparative HPLC under the following conditions (IntelFlash-1): Column: C18 silica gel; mobile phase: acetonitrile:water = 0:100 increasing to acetonitrile:water = 100:0 within 29 min; detector: UV 220 nm. 16 mg (24%) of Compound **I-153** were obtained as an off-white solid. MS (ES): *m/z* 494 $(M+H)^+$, 535 $(M+H+CH_3CN)^+$. ^1H NMR (400 MHz, CD_3CN): δ 0.90-0.91 (d, *J* =

6.0, 3H), 0.97-0.99 (d, J = 6.4, 3H), 2.85 (s, 3H), 3.45-3.51 (m, 1H), 3.92-3.98 (m, 1H), 4.14-4.19 (m, 1H), 4.89-4.92 (d, 1H), 5.47 (s, 2H), 7.28 (s, 1H), 7.33-7.49 (m, 5H), 7.91 (s, 1H).

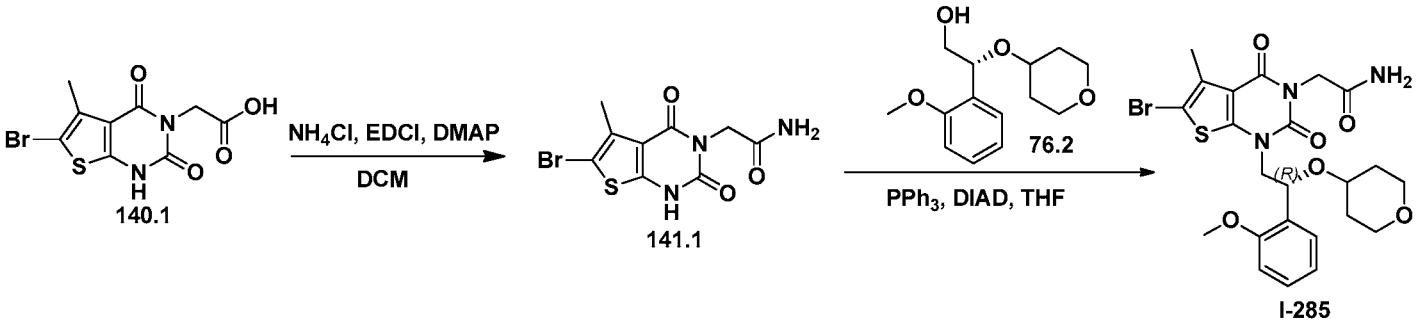
[00719] Example 140: Synthesis of intermediate 140.1.



137.3 140.1

[00720] Synthesis of compound 140.1. Into a 250-mL round-bottom flask was placed **137.3** (2.3 g, 6.13 mmol, 1.00 equiv), dichloromethane (100 mL), trifluoroacetic acid (20 mL). The resulting solution was stirred for 6 h at room temperature and then concentrated under vacuum. The crude product was re-crystallized from ethyl acetate/hexane in the ratio of 1:10 to afford 1.9 g (97%) of **140.1** as a white solid.

[00721] Example 141: Synthesis of 2-[6-bromo-1-[(2R)-2-(2-methoxyphenyl)-2-(oxan-4-yloxy)ethyl]-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetamide (I-285).

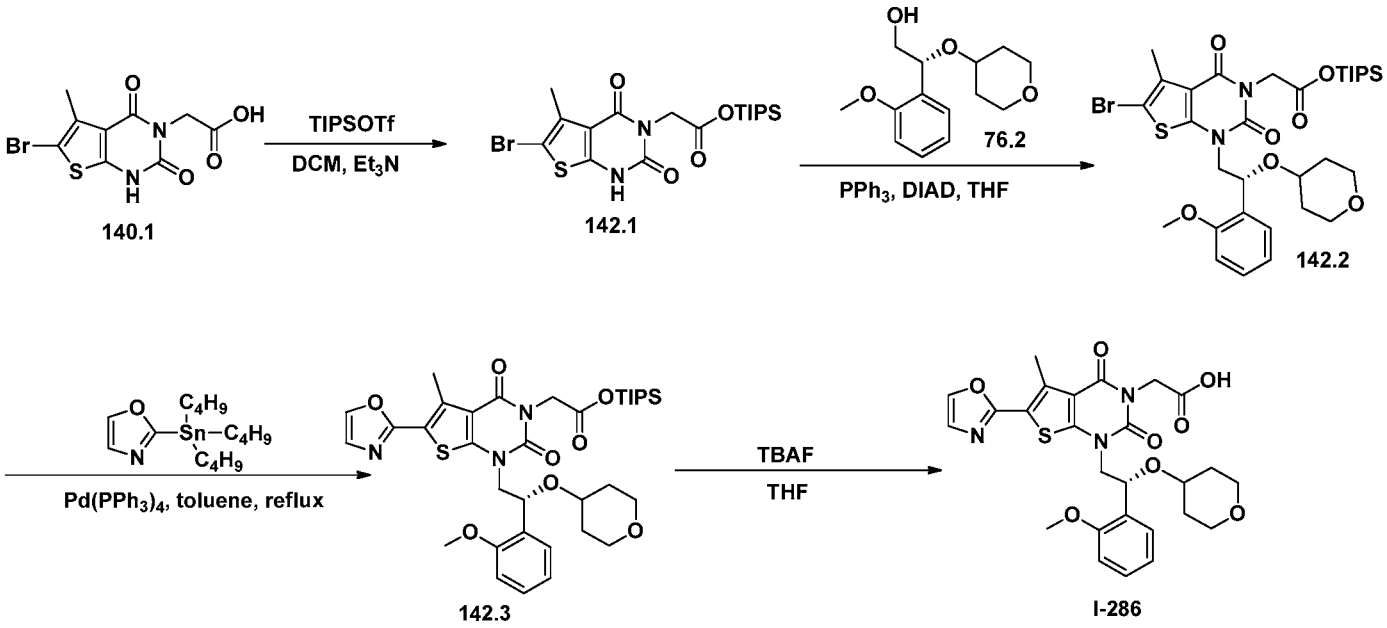


140.1 141.1 I-285

[00722] Synthesis of compound 141.1. Into a 100-mL round-bottom flask was placed **140.1** (1 g, 3.13 mmol, 1.00 equiv), NH_4Cl (500 mg, 9.35 mmol, 2.98 equiv), 4-dimethylaminopyridine (575 mg, 4.71 mmol, 1.50 equiv), EDCI (900 mg, 4.69 mmol, 1.50 equiv) and dichloromethane (25 mL). The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 10 mL of water. The resulting solution was extracted with 2x100 mL of ethyl acetate and the organic layers were combined, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (20/1/0.1). Purification afforded 320 mg (32%) of **141.1** as a white solid.

[00723] Synthesis of Compound I-285. Into a 50-mL round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed **141.1** (300 mg, 0.94 mmol, 1.00 equiv), **76.2** (303 mg, 1.20 mmol, 1.27 equiv), tetrahydrofuran (15 mL), DIAD (379 mg, 1.87 mmol, 1.99 equiv) and PPh_3 (490 mg, 1.87 mmol, 1.98 equiv). The resulting solution was stirred for 8 h at room temperature and then concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:1). Purification afforded 106 mg (20%) of Compound **I-285** as a white solid. MS (ES): *m/z* 554, 552 ($M+H^+$). ^1H NMR (DMSO-d_6, 300 MHz): δ 7.69 (1H, s), 7.46-7.44 (1H, d, J = 6.9 Hz), 7.32-7.23 (2H, m) 7.04-7.00 (2H, m), 5.18-5.13 (1H, m), 4.61-4.46 (2H, m), 4.42-4.38 (1H, m), 4.27-4.25 (1H, m), 3.81 (3H, s), 3.80-3.78 (1H, m), 3.48-3.41 (1H, m), 3.27-3.22 (1H, m), 2.38 (3H, s), 1.89-1.85 (1H, m), 1.70-1.64 (1H, m), 1.49-1.35 (2H, m).

[00724] Example 142: Synthesis of 2-[1-[(2R)-2-(2-methoxyphenyl)-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-286).

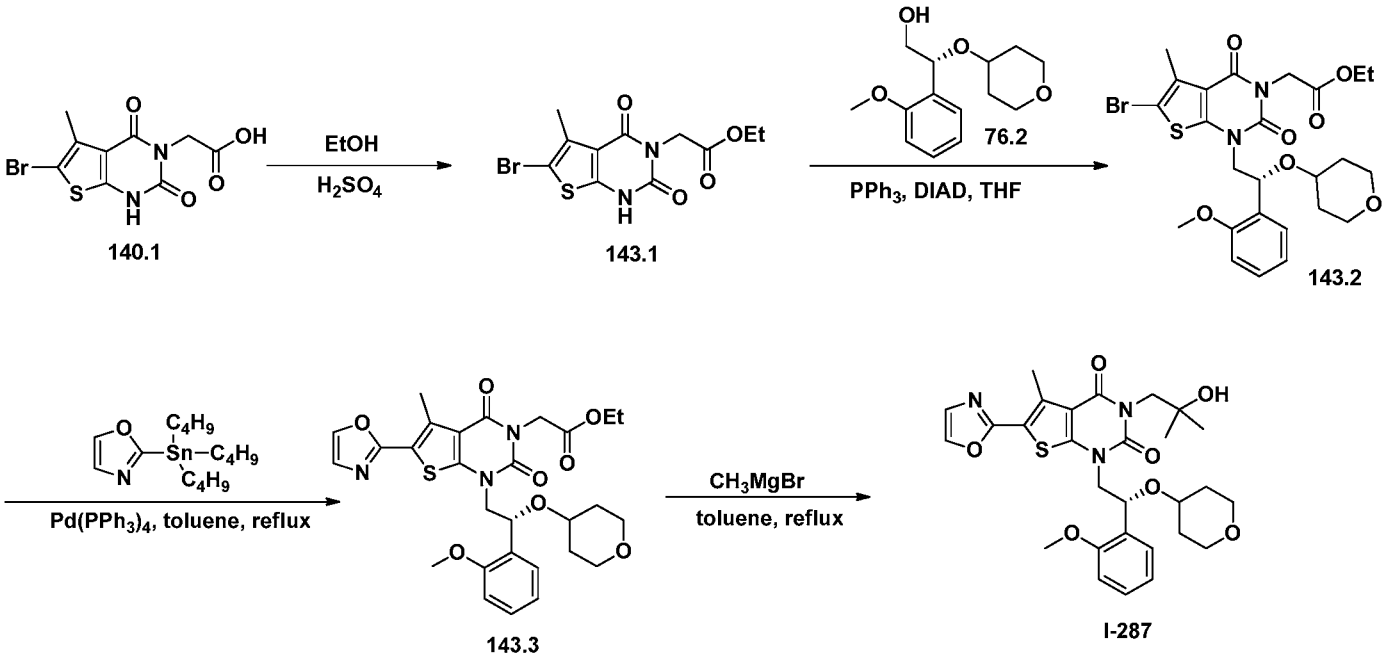


[00725] Synthesis of 142.1. Into a 100-mL 3-necked round-bottom flask was placed **140.1** (450 mg, 1.41 mmol, 1.00 equiv) and dichloromethane (10 mL). This was followed by the addition of TIPSOTf (475 mg, 1.55 mmol, 1.10 equiv) dropwise with stirring over 2 min. To this was added TEA (171 mg, 1.69 mmol, 1.20 equiv) dropwise with stirring over 2 min. The resulting solution was stirred for 2 h at room temperature. The resulting mixture was

concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). Purification afforded 235 mg (35%) of **142.1** as a white solid.

[00726] Synthesis of Compound I-286. Compound **I-286** was prepared from **142.1** and **76.2** in a manner analogous to Example 57. Isolated 3.6 mg (1.4% from **142.1**) of **I-286** as a white solid. MS (ES): *m/z* 542 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.18-1.42 (m, 2H), 1.59-1.62 (m, 2H), 2.741 (s, 3H), 3.16-3.63 (m, 4H), 3.75 (s, 3H), 3.92-4.13 (m, 2H), 4.45-4.76 (m, 1H), 5.32-5.35 (m, 1H), 6.85-6.95 (m, 2H), 7.17-7.23 (m, 2H), 7.44-7.47 (m, 1H), 7.85 (s, 1H).

[00727] Example 143: Synthesis of 3-(2-hydroxy-2-methylpropyl)-1-[(2R)-2-(2-methoxyphenyl)-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-2,4-dione (I-287).



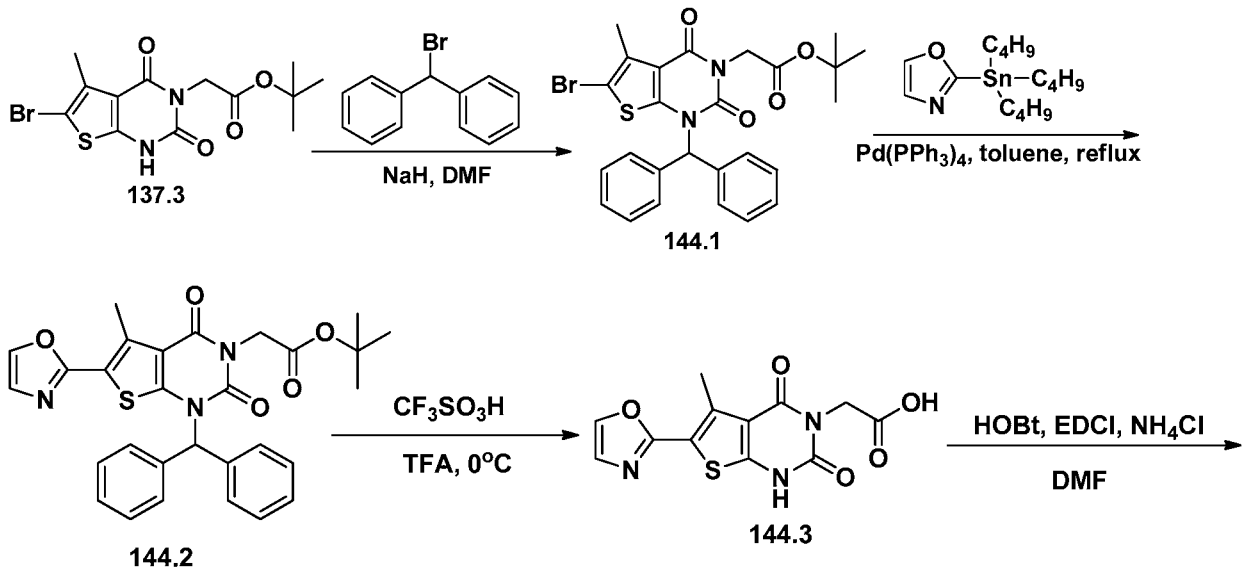
140.1 143.1 76.2 143.2 143.3 I-287

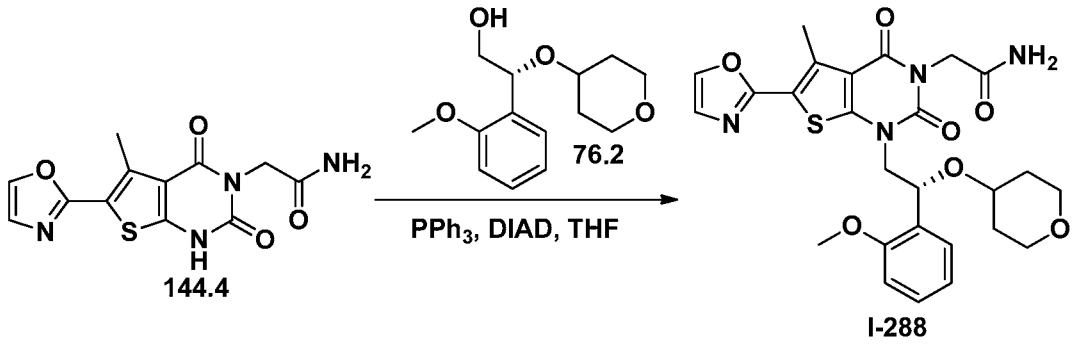
[00728] Synthesis of compound 143.1. Into a 100-mL round-bottom flask was placed **140.1** (420 mg, 1.32 mmol, 1.00 equiv), ethanol (30 mL) and sulfuric acid (conc.) (100 mg). The resulting solution was stirred overnight at 80 °C in an oil bath. The reaction was then quenched by the addition of 5 mL of sodium bicarbonate (sat.). The resulting solution was extracted with 2x150 mL of ethyl acetate and the organic layers were combined, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). Purification afforded 230 mg (50%) of **143.1** as a white solid.

[00729] **Synthesis of compound 143.3.** Compound **143.3** was prepared from **143.1** in a manner analogous to compound **13.5**. Isolated a white solid in 8% yield.

[00730] **Synthesis of Compound I-287.** Into a 10-mL sealed tube purged and maintained with an inert atmosphere of nitrogen was placed a solution of **143.3** (57 mg, 0.10 mmol, 1.00 equiv) in toluene (1 mL). This was followed by the addition of bromo(methyl)magnesium (1 M in THF, 3 mL) dropwise with stirring at room temperature. The resulting solution was heated to reflux overnight. The reaction was then quenched by the addition of 1 mL of NH_4Cl (sat., aq.). The resulting solution was extracted with 3x2 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with methanol/DCM/HOAc (7:200:1). Purification afforded 2.2 mg (4%) of **I-287** as a white solid. MS (ES): *m/z* 556 $(M+H)^+$. ^1H NMR (CD_3OD, 300 MHz): δ 7.92 (1H, s), 7.54-7.50 (1H, d), 7.30-7.24 (2H, m), 7.02-6.92 (2H, m), 5.45-5.40 (1H, m), 4.20-4.10 (4H, m), 3.80 (3H, s), 3.70-3.51 (2H, m), 3.43-3.33 (1H, m), 2.83 (3H, s), 1.73-1.67 (2H, m), 1.48-1.33 (2H, m), 1.21-1.20 (6H, d).

[00731] **Example 144: Synthesis of 2-[5-methyl-1-[(2R)-2-(oxan-4-yloxy)-2-phenylethyl]-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetamide (I-288). .**





[00732] **Synthesis of compound 144.1.** Into a 100-mL 3-necked round-bottom flask, purged and maintained under an inert atmosphere of nitrogen, was placed **137.3** (2.651 g, 7.06 mmol, 1.00 equiv) and N,N-dimethylformamide (50 mL). This was followed by the addition of sodium hydride (368 mg, 9.20 mmol, 1.30 equiv, 60%) in portions at 0 °C over 10 min. The resulting solution was stirred for 30 min at room temperature. To this was added [bromo(phenyl)methyl]benzene (2.3 g, 9.31 mmol, 1.32 equiv) in portions at 0 °C in 10 min. The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 50 mL of NH_4Cl (aq.). The resulting solution was extracted with 3x100 mL of ethyl acetate and the organic layers were combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). Purification afforded 2.26 g (59%) of **144.1** as a white solid.

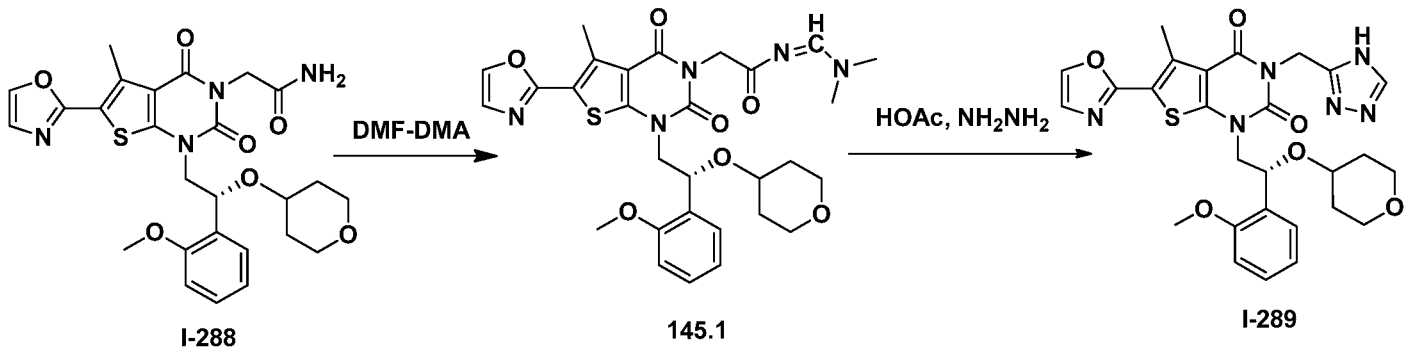
[00733] **Synthesis of compound 144.2.** To a 100-mL 3-necked round-bottom flask, purged and maintained under an inert atmosphere of nitrogen, was added **144.1** (2.26 g, 4.17 mmol, 1.00 equiv), toluene (50 mL), 2-(tributylstannyl)-1,3-oxazole (3 g, 8.38 mmol, 2.01 equiv) and $Pd(PPh_3)_4$ (728 mg, 0.63 mmol, 0.15 equiv). The resulting solution was stirred overnight at 110 °C and then concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:2). Purification afforded 1.9 g (crude) of **144.2** as a yellow solid.

[00734] **Synthesis of compound 144.3.** Into a 50-mL round-bottom flask was placed **144.2** (950 mg, 1.79 mmol, 1.00 equiv) and CF_3COOH (10 mL). This was followed by the addition of CF_3SO_3H (540 mg) dropwise with stirring at 0 °C over 2 min. The resulting solution was stirred for 20 min at room temperature. The reaction was then quenched by the addition of 50 mL of water. The solids were washed with EA (100 mL) and then collected by filtration to afford 490 mg (89%) of **144.3** as a white solid.

[00735] **Synthesis of compound 144.4.** Into a 50-mL 3-necked round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed **144.3** (490 mg, 1.59 mmol, 1.00 equiv), HOBt (432 mg, 3.20 mmol, 2.00 equiv), N,N-dimethylformamide (10 mL), 4-dimethylaminopyridine (390 mg, 3.19 mmol, 2.00 equiv) and EDCI (614 mg, 3.20 mmol, 2.01 equiv). The resulting solution was stirred for 2 hours at room temperature. Then NH_4Cl (346 mg, 6.47 mmol, 4.06 equiv) was added. The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 50 mL of water. The solids were collected by filtration and washed with EA. Purification afforded 90 mg (18%) of **144.4** as a white solid.

[00736] **Synthesis of Compound I-288.** Into a 50-mL 3-necked round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed **144.4** (90 mg, 0.29 mmol, 1.00 equiv), **76.2** (89 mg, 0.35 mmol, 1.20 equiv), DIAD (119 mg, 0.59 mmol, 2.00 equiv), tetrahydrofuran (5 mL) and PPh_3 (154 mg, 0.59 mmol, 2.00 equiv). The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (20:1). Purification afforded 11.1 mg (7%) of Compound **I-288** as a pink solid. MS (ES): *m/z* 541 $(M+H)^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.7 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.36-7.26 (m, 1H), 7.23 (s, 1H), 7.06-7.01 (m, 1H), 6.88 (d, *J* = 8.1 Hz, 1H), 5.81-5.47 (m, 2H), 5.41 (d, *J* = 8.7 Hz, 1H), 4.80-4.69 (m, 2H), 4.27 (d, *J* = 14.7 Hz, 1H), 4.01-3.93 (m, 2H), 3.88 (s, 2H), 3.75-3.63 (m, 2H), 3.42-3.28(m, 3H), 2.90 (s, 3H), 1.68-1.37 (m, 4 H).

[00737] **Example 145: 1-[(2R)-2-(2-methoxyphenyl)-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-3-(4H-1,2,4-triazol-3-ylmethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-2,4-dione (I-289).**

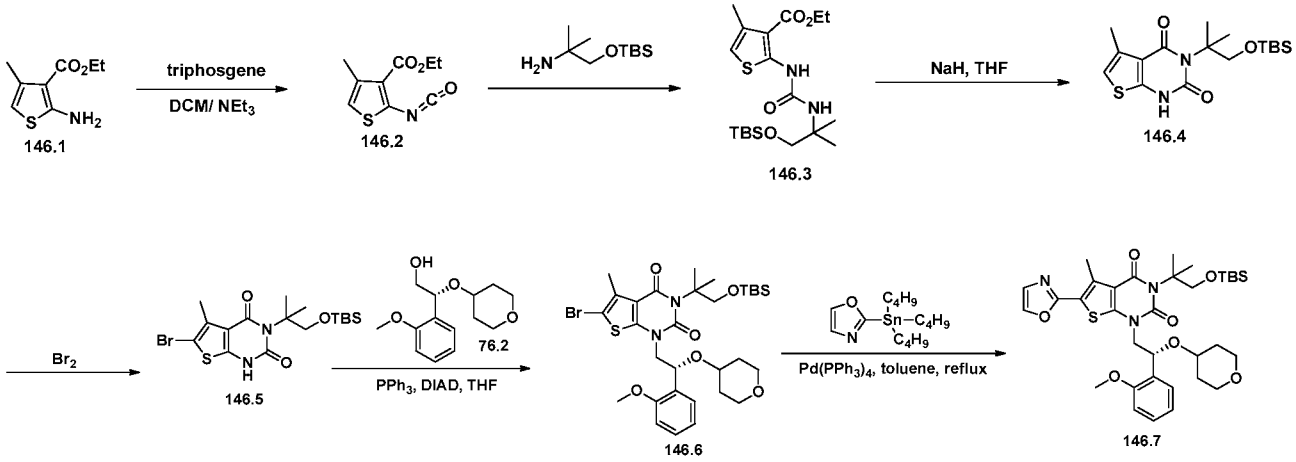


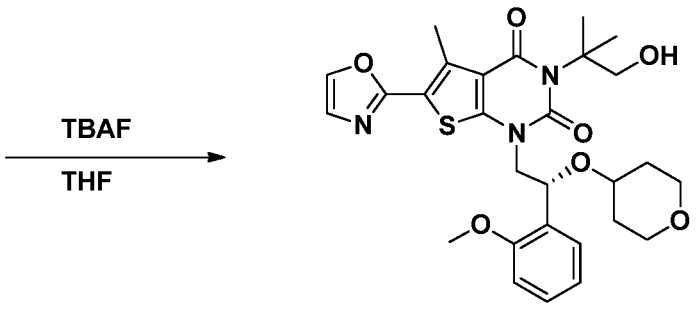
I-288 145.1 I-289

[00738] Synthesis of compound 145.1. Into a 25-mL round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed Compound **I-288** (Example 144) (20 mg, 0.03 mmol, 1.00 equiv, 90%) and (dimethoxymethyl)dimethylamine (0.5 mL). The resulting solution was stirred for 2 h at 120 °C. The resulting mixture was concentrated under vacuum to afford 20 mg (crude) of **145.1** as a yellow liquid.

[00739] Synthesis of Compound I-289. Into a 25-mL round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed **145.1** (20 mg, 0.03 mmol, 1.00 equiv), AcOH (1 mL) and NH_2NH_2 (4 mg, 0.06 mmol, 1.91 equiv, 98%). The resulting solution was stirred for 2 h at 90 °C. The resulting mixture was concentrated under vacuum. The crude product (500 mg) was purified by preparative HPLC under the following conditions (Waters): Column: SunFire Prep C18, 19*150 mm 5 μm; mobile phase: water (0.05% NH_4HCO_3) and CH_3CN (10.0% CH_3CN up to 42.0% over 11 min, up to 100.0% over 2 min, down to 10.0% over 1 min); detector: UV 220, 254 nm. Purification afforded 4.5 mg (24%) of Compound **I-289** as a white solid. MS (ES): *m/z* 565 $(M+H)^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.72 (s, 1H), 7.56 (d, *J* = 7.2 Hz, 1H), 7.33-7.22 (m, 2H), 7.03 (t, *J* = 6.0 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 5.43 (s, 3 H), 4.29-4.09 (m, 2H), 3.85 (s, 3H), 3.75-3.62 (m, 2H), 3.40-3.21 (m, 3H), 2.91 (s, 3H), 1.77-1.25 (m, 4H).

[00740] Example 146: Synthesis of 3-(1-hydroxy-2-methylpropan-2-yl)-1-[(2R)-2-(2-methoxyphenyl)-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-2,4-dione (I-290).





I-290

[00741] **Synthesis of compound 146.2.** Into a 250-mL 3-necked round-bottom flask, purged and maintained under an inert atmosphere of nitrogen, was placed ethyl 2-amino-4-methylthiophene-3-carboxylate (**146.1**, 7.4 g, 39.95 mmol, 1.00 equiv) and dichloromethane (150 mL). This was followed by the addition of ditrichloromethyl carbonate (4 g, 13.48 mmol, 0.34 equiv), in portions, at 0 °C. The mixture was stirred for 0.5 h at 0 °C. To this was added Et_3N (16.2 g) dropwise with stirring at 0 °C. The resulting solution was stirred for 5 h at room temperature. The mixture was used in the next step directly.

[00742] **Synthesis of compound 146.3.** Into a 250-mL 3-necked round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed the crude solution of **146.2** (150 mL, from the previous step). This was followed by the addition of (2-amino-2-methylpropoxy)(tert-butyl)dimethylsilane (9.2 g, 45.23 mmol, 1.00 equiv), in portions at 10 °C over 20 min. The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 200 mL of water. The resulting solution was extracted with 2x300 mL of ethyl acetate and the organic layers combined, dried over sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:20). Purification afforded 11 g (61%) of **146.3** as a yellow solid.

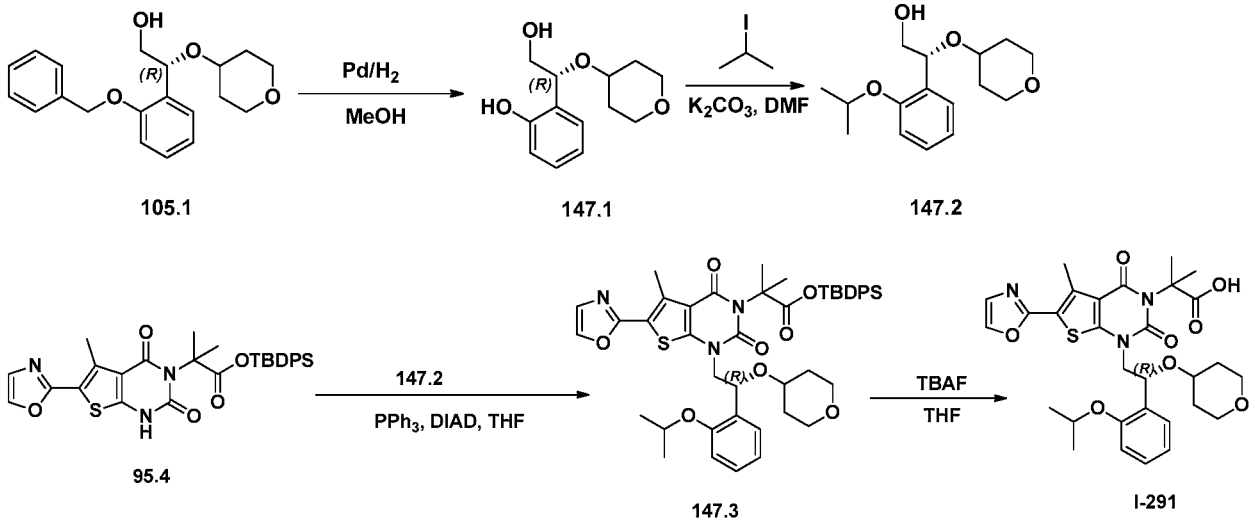
[00743] **Synthesis of compound 146.4.** Into a 250-mL 3-necked round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed a solution of **146.3** (2.07 g, 4.99 mmol, 1.00 equiv) in tetrahydrofuran (100 mL). This was followed by the addition of sodium hydride (600 mg, 15.00 mmol, 3.00 equiv) in portions at 0-10 °C. The resulting solution was stirred for 1 h at 0-10 °C and warmed to 60 °C overnight. The reaction was then quenched by the addition of 100 mL of NH_4Cl (sat., aq.). The resulting solution was extracted with 3x100 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was

applied onto a silica gel column with ethyl acetate/petroleum ether (1:20). Purification afforded 510 mg (28%) of **146.4** as a white solid.

[00744] Synthesis of compound 146.5. Into a 50-mL round-bottom flask was placed **146.4** (510 mg, 1.38 mmol, 1.00 equiv), acetic acid (10 mL) and NaOAc (227 mg). The resulting solution was stirred for 30 min at room temperature. This was followed by the addition of Br_2 (222 mg, 1.39 mmol, 1.00 equiv) dropwise with stirring at room temperature. The resulting solution was stirred for 30 min at room temperature. The reaction was then quenched by the addition of 10 mL of Na_2SO_3 (aq.). The resulting solution was diluted with 50 mL of H_2O. The resulting solution was extracted with 2x50 mL of ethyl acetate, the organic layers were combined and concentrated under vacuum. The residue was purified by preparative TLC (ethyl acetate/petroleum ether = 1:5). Purification afforded 334 mg (54%) of **146.5** as a white solid.

[00745] Synthesis of Compound I-290. Compound **I-290** was prepared from **146.5** and **76.2** in a manner analogous to Example 57. Isolated 57.8 mg of a white solid in 14% yield from **146.5**. MS (ES): *m/z* 556 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 1.23-1.35 (m, 2H), 1.57-1.65 (m, 8H), 2.74 (s, 3H), 3.20-3.27 (m, 2H), 3.39-3.59 (m, 2H), 3.79-3.96 (m, 7H), 4.72-4.76 (m, 1H), 5.25-5.29 (m, 1H), 7.00-7.05 (m, 2H), 7.27-7.37 (m, 2H) , 7.46-7.49 (d, 1H), 8.20 (s, 1H).

[00746] Example 147: Synthesis of 2-methyl-2-[5-methyl-1-[(2R)-2-(oxan-4-yloxy)-2-[2-(propan-2-yloxy)phenyl]ethyl]-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-291).



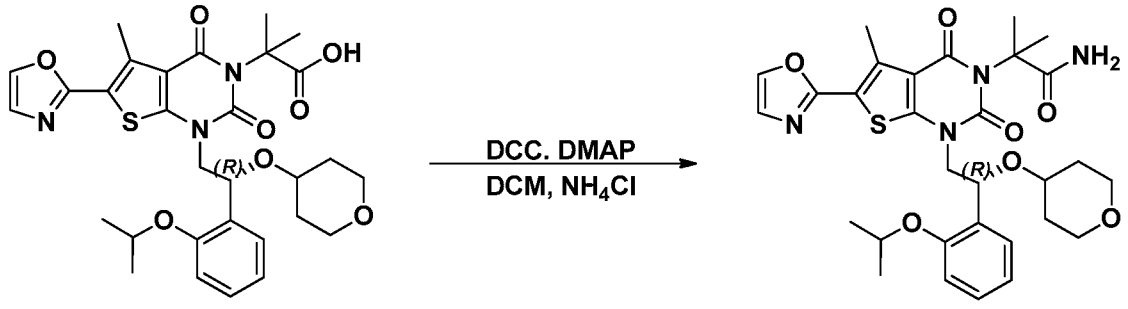
[00747] **Synthesis of compound 147.1.** Into a 100-mL round-bottom flask was placed **105.1** (500 mg, 1.52 mmol, 1.00 equiv) and methanol (10 mL). This was followed by the addition of palladium on carbon (50 mg). Hydrogen was added to the system. The resulting solution was stirred overnight at room temperature. The solids were filtered out. The resulting mixture was concentrated under vacuum to afford 320 mg (88%) of **147.1** as an oil.

[00748] **Synthesis of compound 147.2.** Into a 25-mL round-bottom flask was placed **147.1** (280 mg, 1.18 mmol, 1.00 equiv), potassium carbonate (487 mg, 3.52 mmol, 3.00 equiv), N,N-dimethylformamide (5 mL) and 2-iodopropane (400 mg, 2.35 mmol, 2.00 equiv). The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 10 mL of water. The resulting solution was extracted with 10 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:50). This resulted in 260 mg (79%) of **147.2** as a colorless oil.

[00749] **Synthesis of Compound I-291.** Compound **I-291** was synthesized from **147.2** and intermediate **95.4** in a manner analogous to Example 96. Isolated a white solid in 15% yield from **95.1**. MS (ES): *m/z* 598 $(M+H)^+$, 620 $(M+Na)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 1.19-1.32 (m, 8H), 1.60-1.67 (m, 8H), 2.76 (s, 3H), 3.18-3.35 (m, 2H), 3.45-3.58 (m, 2H), 3.85-4.20 (m,2H), 4.67 (m, 1H), 5.27 (t, 1H), 7.03 (m, 2H), 7.33-7.50 (m, 3H), 8.23 (s, 1H).

[00750]

[00751] **Example 148: Synthesis of 2-methyl-2-[5-methyl-1-[(2R)-2-(oxan-4-yloxy)-2-[2-(propan-2-yloxy)phenyl]ethyl]-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanamide (I-292).**

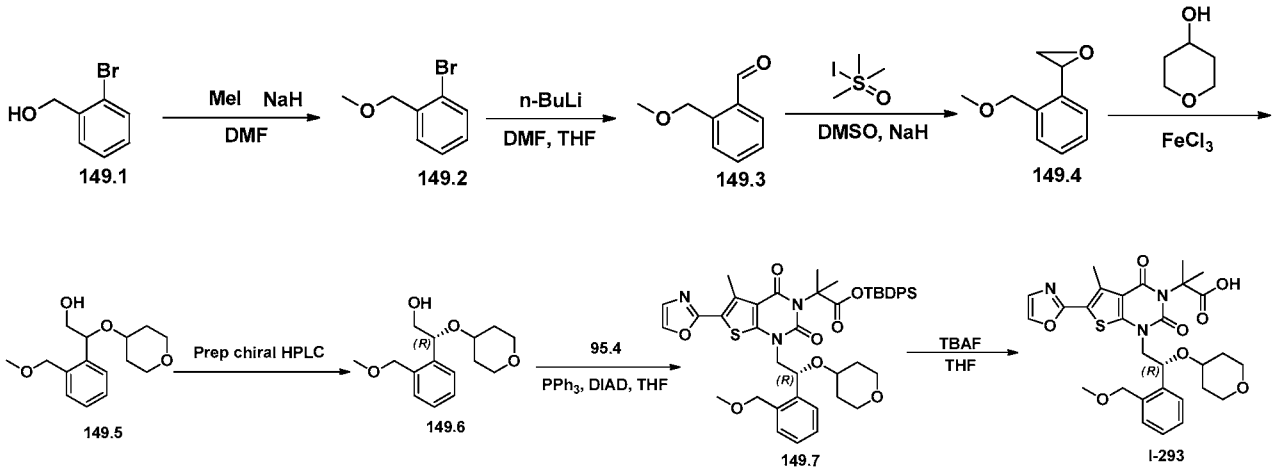


I-291 I-292

[00752] **Synthesis of Compound I-292.** Compound **I-292** was synthesized from **I-291** in a manner analogous to Example 4. Isolated 284.1 mg of a white solid in 81% yield. MS (ES): *m/z*

619 $(M+Na)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 1.18-1.32 (m, 8H), 1.60-1.66 (m, 8H), 2.75 (s, 3H), 3.18-3.33 (m, 2H), 3.47-3.58 (m, 2H), 3.85-4.20 (m, 2H), 4.66 (m, 1H), 5.27 (t, 1H), 6.80 (br s, 1H), 7.01 (m, 3H), 7.30 (m,1H), 7.39 (s,1H) , 7.45 (d,1H), 8.22 (s, 1H).

[00753] Example 149: Synthesis of 2-[1-[(2R)-2-[2-(methoxymethyl)phenyl]-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-293).



[00754] Synthesis of compound 149.2. Into a 250-mL 3-necked round-bottom flask was placed (2-bromophenyl)methanol (20 g, 106.93 mmol, 1.00 equiv), N,N-dimethylformamide (50 mL) and sodium hydride (5.136 g, 128.40 mmol, 1.20 equiv). The resulting solution was stirred for 0.5 h at room temperature. This was followed by the addition of MeI (45.582 g, 323.28 mmol, 3.02 equiv) dropwise with stirring at 0 °C. The resulting solution was allowed to react, with stirring, overnight at room temperature. The reaction was then quenched by the addition of 100 mL of NH_4Cl (aq.). The resulting solution was extracted with 2 x 200 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:200). Purification afforded 6 g (28%) of **149.2** as a brown oil.

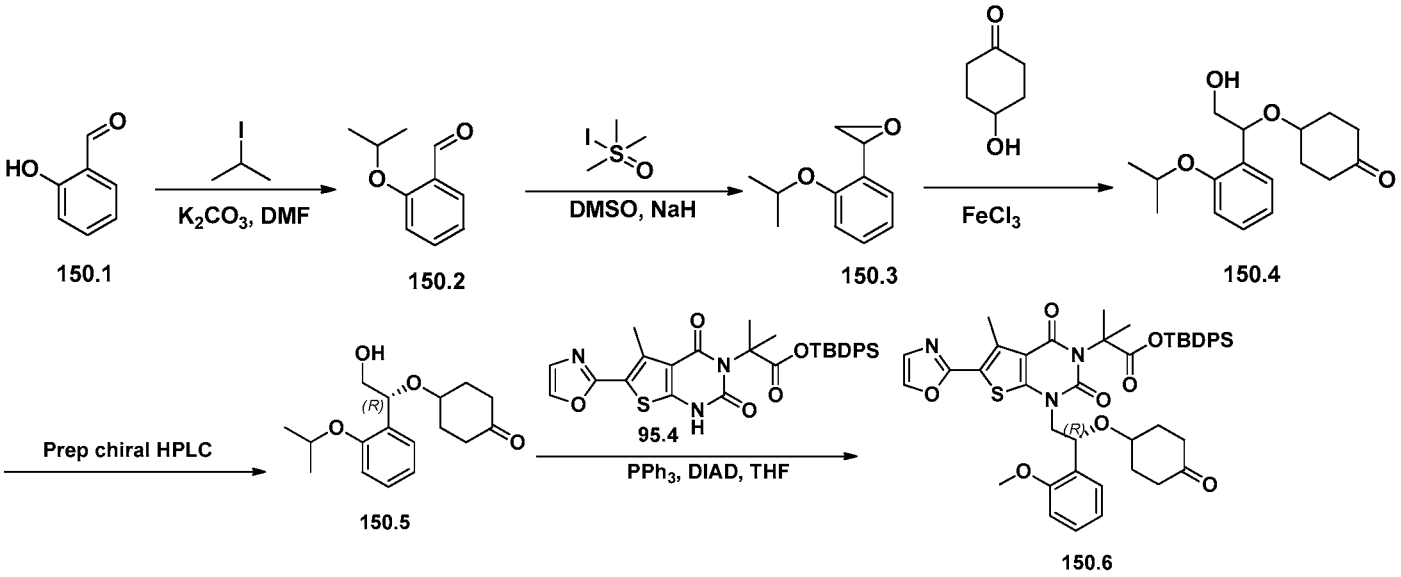
[00755] Synthesis of compound 149.3. Into a 500-mL 3-necked round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed a solution of **149.2** (12 g, 59.68 mmol, 1.00 equiv) in tetrahydrofuran (200 mL). This was followed by the addition of *n*-butyllithium (26.3 mL, 2.5 M) dropwise with stirring at -78 °C. The resulting solution was stirred for 1 h at -78 °C. To this was added N,N-dimethylformamide (8.7 g, 119.03 mmol, 1.99 equiv) dropwise with stirring at -78 °C. The resulting solution was allowed to react, with stirring, for an

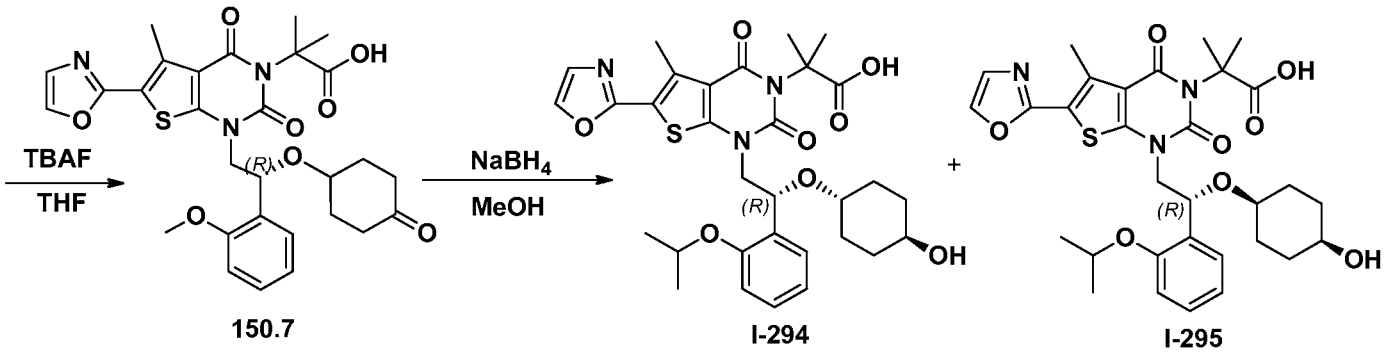
additional 1 h from -78 °C to room temperature. The reaction was then quenched by the addition of 100 mL of NH_4Cl (aq.). The resulting solution was extracted with 3x100 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:50). This resulted in 7.7 g (86%) of **149.3** as a colorless oil.

[00756] Synthesis of compound 149.6. Compound **149.6** was prepared from **149.3** in a manner consistent with the synthesis of compound **57.5**. Isolated 390 mg of a colorless oil in 3% overall yield.

[00757] Synthesis of Compound I-293. Compound **I-293** was prepared from **149.6** and **95.4** in a manner analogous to Example 96. Isolated 68.3 mg (23%) of **I-293** as a white solid. MS (ES): *m/z* 606 $(M+Na)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 1.23 (m, 2H), 1.56-1.70 (m, 8H), 2.77 (s, 3H), 3.18-3.39 (m, 6H), 3.54 (m, 2H), 3.81(m, 1H), 4.22 (d, 1H), 4.44 (d, 1H), 4.70 (d, 1H), 5.22 (dd, 1H), 7.33-7.47 (m, 4H), 7.64 (m, 1H), 8.24 (s, 1H).

[00758] Example 150: Synthesis of 2-(1-((R)-2-(((1r,4R)-4-hydroxycyclohexyl)oxy)-2-(2-isopropoxyphenyl)ethyl)-5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)-2-methylpropanoic acid (I-294) and Example 151: Synthesis of 2-(1-((R)-2-(((1s,4S)-4-hydroxycyclohexyl)oxy)-2-(2-isopropoxyphenyl)ethyl)-5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)-2-methylpropanoic acid (I-295).





[00759] **Synthesis of compound 150.2.** Into a 1000-mL 3-necked round-bottom flask was placed 2-hydroxybenzaldehyde (36 g, 294.79 mmol, 1.00 equiv), 2-iodopropane (100 g, 588.26 mmol, 2.00 equiv), potassium carbonate (122 g, 882.71 mmol, 2.99 equiv) and N,N-dimethylformamide (500 g, 6.84 mol, 23.21 equiv). The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 1000 mL of water. The resulting solution was extracted with 3x500 mL of ethyl acetate and the organic layers combined, dried over anhydrous sodium sulfate and concentrated under vacuum to afford 50 g (crude) of 2-(propan-2-yloxy)benzaldehyde as a yellow oil.

[00760] **Synthesis of compound 150.5.** Compound **150.5** was prepared from **150.2** in a manner analogous to compound **57.5**. Isolated 4.7 g of a colorless oil in 3% overall yield.

[00761] **Synthesis of compound 150.7.** Compound **150.7** was prepared from **150.5** and **95.4** in a manner analogous to Example 96. Isolated 1.2 g of a white solid in 25% overall yield.

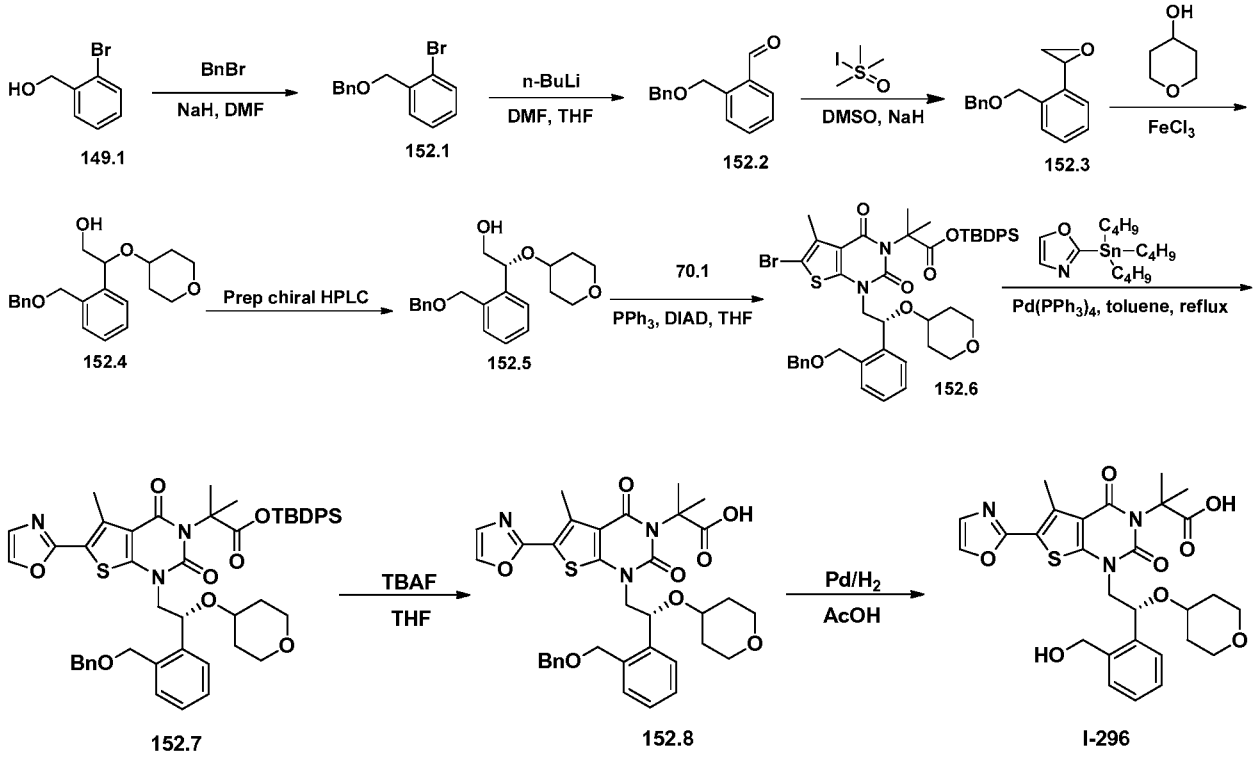
[00762] **Synthesis of Compounds I-294 and I-295.** Into a 50-mL 3-necked round-bottom flask was **150.7** (1.1 g, 1.89 mmol, 1.00 equiv), methanol (20 mL) and $NaBH_4$ (143 mg, 3.78 mmol, 2.00 equiv). The resulting solution was stirred overnight at room temperature and then concentrated under vacuum. The residue was purified by thin layer chromatography developed with dichloromethane/MeOH/HOAc (30:1:0.15) to afford 122.4 mg (9%) of Compound **I-294** and 256.3 mg (22%) of Compound **I-295**.

[00763] Analytical data for Compound **I-294**: MS (ES): *m/z* 612 $(M+H)^+$, 634 $(M+Na)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 0.96-1.32 (m, 10H), 1.50-1.65 (m, 10H), 2.74 (s, 3H), 3.17 (m, 1H), 3.89-4.03 (m,2H), 4.35 (m, 1H), 4.70 (m, 1H), 5.22 (t, 1H), 6.99 (m, 2H), 7.29 (m,1H), 7.38 (s, 1H), 7.45 (m,1H), 8.21 (s, 1H).

[00764] Analytical data for Compound **I-295**: MS (ES): *m/z* 612 $(M+H)^+$, 634 $(M+Na)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ1.29-1.30 (m, 12H), 1.50-1.68 (m, 8H), 2.75 (s, 3H), 3.14 (m,

1H), 3.91-3.99 (m, 1H), 4.11 (m, 1H), 4.24 (m, 1H), 4.68 (m, 1H), 5.25 (t, 1H), 6.97 (m, 2H), 7.29(m, 1H), 7.39 (s, 1H), 7.46 (m, 1H), 8.22 (s, 1H), 12.30 (br s, 1H).

[00765] Example 152: Synthesis of 2-[1-[(2R)-2-[2-(hydroxymethyl)phenyl]-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-296).



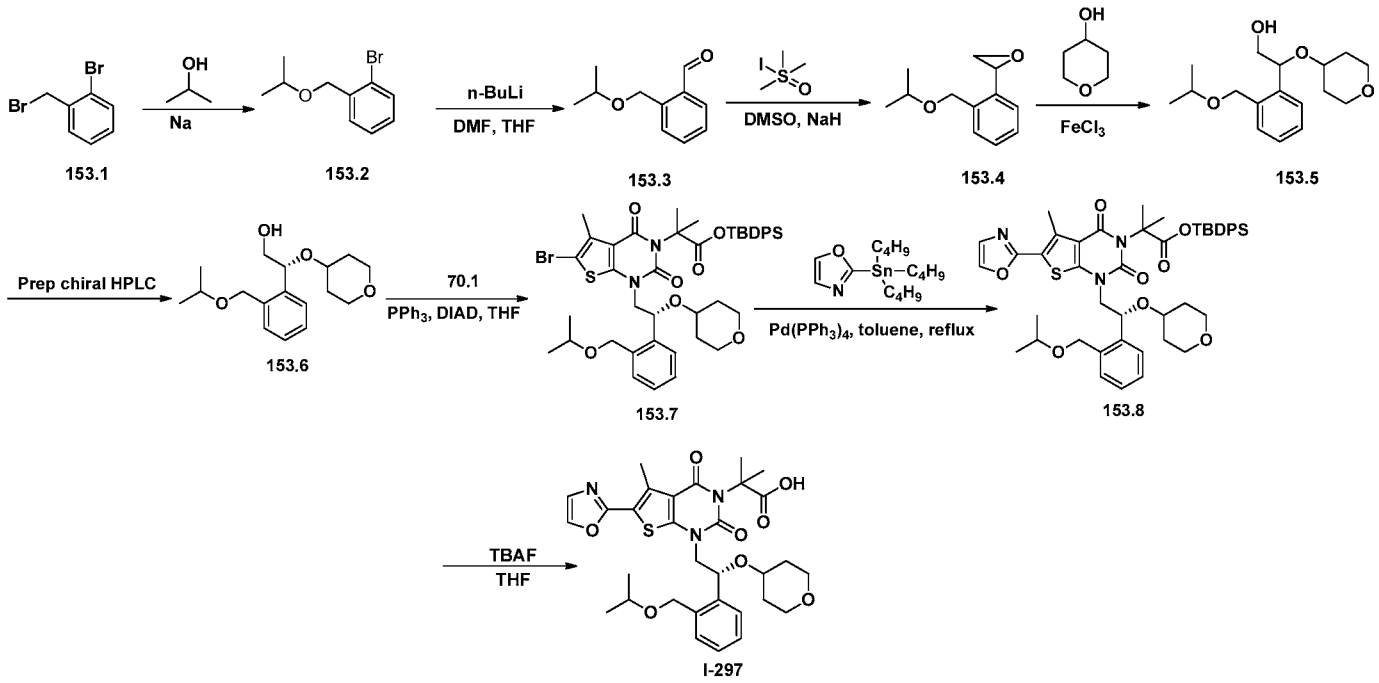
[00766] Synthesis of compound 152.5. Compound **152.5** was prepared from **149.1** in a manner analogous to the preparation of compound **149.6**, substituting benzyl bromide for methyl iodide in the first step. Isolated 0.814 g of a colorless oil in 2% overall yield.

[00767] Synthesis of compound 152.8 (I-299). Compound **152.8** was prepared from **70.1** and **152.5** in a manner analogous to Example 57. Isolated 50 mg of a white solid in 32% overall yield from **70.1**.

[00768] Synthesis of Compound I-296. Into a 50-mL round-bottom flask was placed **152.8** (100 mg, 0.15 mmol, 1.00 equiv), AcOH (5 mL) and 10% palladium on carbon (50 mg). The resulting solution was stirred overnight at room temperature under an atmosphere of hydrogen. The solids were filtered out. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (20:1). Purification afforded 9.9 mg (11%) of Compound **I-296** as a white solid. MS (ES): 570 $(M+H)^+$, 592

$(M+Na)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 8.25 (s, 1 H), 7.59 (d, 1H), 7.46 (d, 1H), 7.41-7.33 (m, 3H), 5.26-5.21 (m, 2H), 4.77 (d, 1H), 4.63 (d, 1H), 4.25-4.17 (m, 1H), 3.72 (s, 1H), 3.49 (m, 1 H), 3.21 (t, 3H), 2.78 (s, 3H), 1.71 (s, 3H), 1.70 (s, 3H), 1.62-1.58 (m, 2H), 1.28-1.24 (m, 2H).

[00769] Example 153: Synthesis of 2-methyl-2-[5-methyl-1-[(2R)-2-(oxan-4-yloxy)-2-[2-[(propan-2-yloxy)methyl]phenyl]ethyl]-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-297).

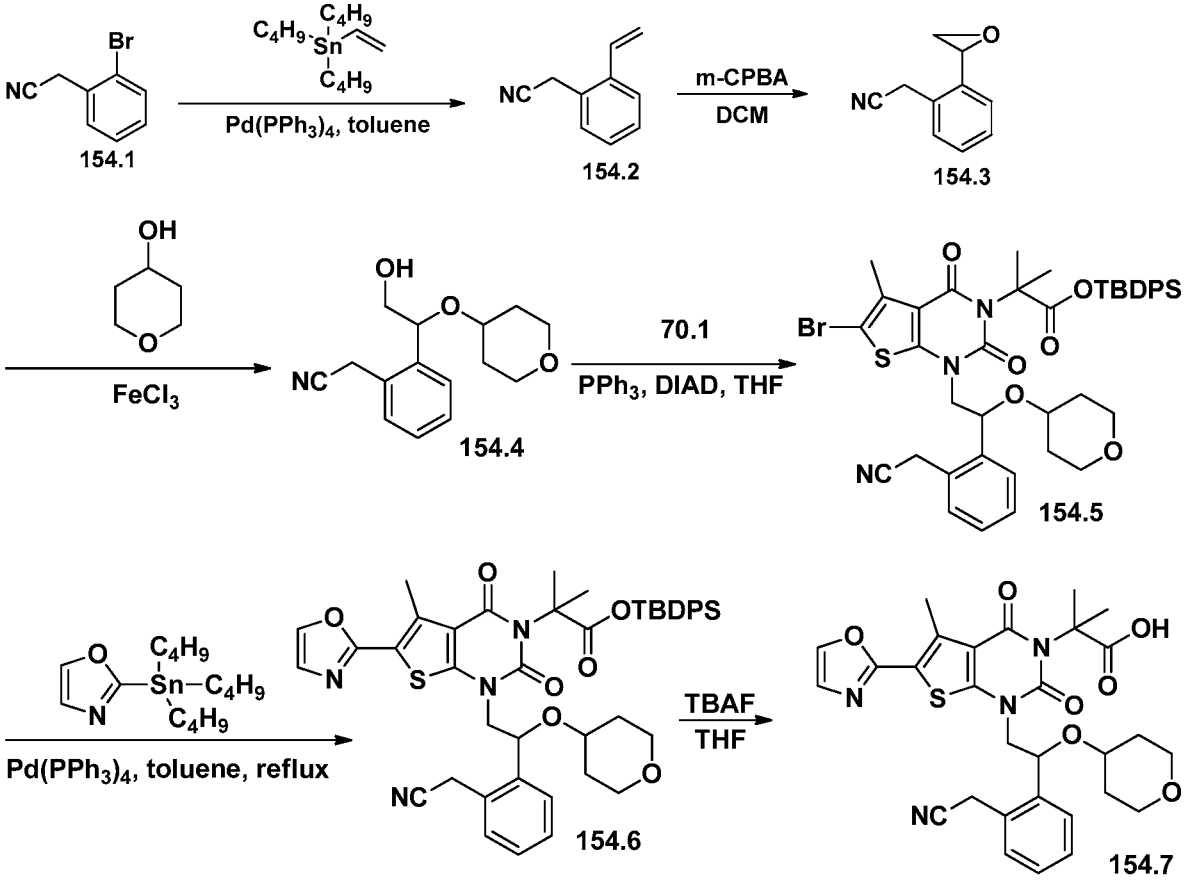


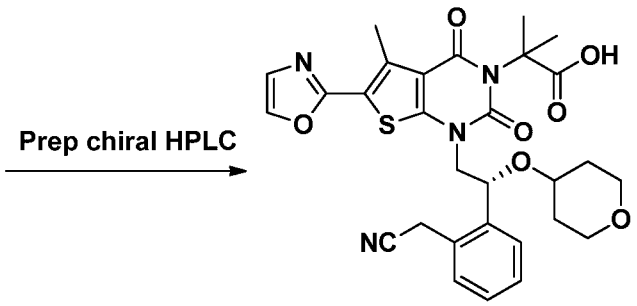
[00770] Synthesis of compound 153.2. Into a 250-mL 3-necked round-bottom flask was placed propan-2-ol (48 g, 798.74 mmol, 9.98 equiv). This was followed by the addition of Na (3.68 g) at 80 °C. When the solids had disappeared 1-bromo-2-(bromomethyl)benzene (20 g, 80.02 mmol, 1.00 equiv) was added dropwise with stirring. The resulting solution was stirred overnight at 80 °C in an oil bath. The reaction was then quenched by the addition of 200 mL of water. The resulting solution was extracted with 200 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:100). This resulted in 16 g (87%) of **153.2** as a light yellow oil.

[00771] Synthesis of compound 153.6. Compound **153.6** was prepared from **153.2** in a manner analogous to the synthesis of compound **149.6** from **149.2**. Isolated 0.8 g of a colorless oil in 13% yield from **153.2**

[00772] Synthesis of Compound I-297. Compound **I-297** was prepared from **70.1** and **153.6** in a manner analogous to Example 57. Isolated 7.4 mg of a white solid in 2% overall yield. MS (ES): *m/z* 634 $(M+Na)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 1.15-1.31 (m, 8H), 1.59-1.71 (m, 8H), 2.73 (s, 3H), 3.20-3.24 (m, 2H), 3.33-3.42 (m, 2H), 3.64-3.81 (m, 2H), 4.24-4.29 (d, 1H), 4.42-4.46 (d, 1H), 4.72-4.76 (d, 1H), 5.27-5.29 (d, 1H), 7.30-7.45 (m, 4H), 7.61-7.64 (d, 1H), 8.24 (s, 1H).

[00773] Example 154: Synthesis of 2-[1-[(2R)-2-[2-(cyanomethyl)phenyl]-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-298).





I-298

[00774] **Synthesis of compound 154.2.** Into a 500-mL 3-necked round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed 2-(2-bromophenyl)acetonitrile (10 g, 51.01 mmol, 1.00 equiv), toluene (200 mL), $Pd(PPh_3)_4$ (5.9 g, 5.11 mmol, 0.10 equiv) and tributyl(ethenyl)stannane (25.6 g, 80.73 mmol, 1.58 equiv). The resulting solution was stirred overnight at 110 °C. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:100). This resulted in 5.5 g (75%) of **154.2** as a colorless oil.

[00775] **Synthesis of compound 154.3.** Into a 250-mL round-bottom flask was placed **154.2** (5.5 g, 38.41 mmol, 1.00 equiv), dichloromethane (100 mL) and *m*-CPBA (20.4 g, 82.75 mmol, 2.15 equiv, 70%). The resulting solution was stirred for 5 h at room temperature. The solids were filtered out. The resulting solution was extracted with 2x100 mL of Na_2SO_3 (aq.) and the organic layers combined. The resulting solution was extracted with 100 mL of sodium bicarbonate(aq.) and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:2). Purification afforded 5.4 g (88%) of **154.3** as a colorless oil.

[00776] **Synthesis of compound 154.4.** Compound **154.4** was prepared from **154.3** in a manner analogous to the synthesis of **57.3**. Isolated 3.0 g (34%) of **154.4** as a colorless oil.

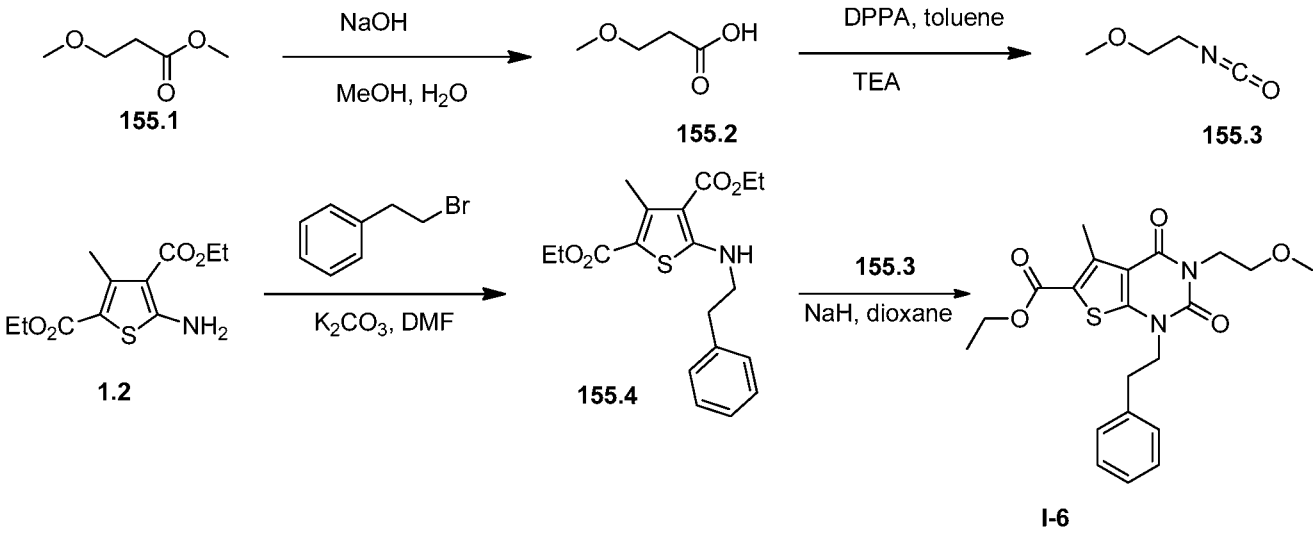
[00777] **Synthesis of compound 154.7.** Compound **154.7** was synthesized from **154.4** and **70.1** in a manner analogous to Example 57. Isolated 120 mg of **154.7** as a white solid in 6% overall yield from **70.1**.

[00778] **Purification of Compound I-298.** The enantiomers of **154.7** (120 mg, 0.21 mmol, 1.00 equiv) were separated by chiral preparative HPLC under the following conditions (Gilson Gx 281): Column: Chiralpak IC, 2*25cm, 5um; mobile phase: hexanes (AcOH 0.1%) and IPA

(hold at 30.0% IPA for 30 min); detector: UV 220/254 nm. This resulted in 11.4 mg of **I-298** (tR = 23.375 min; 10%) as a white solid.

[00779] Analytical data for **I-298**: MS (ES): *m/z* 579 $(M+H)^+$, 601 $(M+Na)^+$. (400 MHz, DMSO-d_6): δ 12.41(br s, 1 H) , 8.26 (s, 1 H) , 7.63 (d, 1 H), 7.49-7.42 (m, 4H), 5.12 (d, 1H), 4.31-4.16 (m, 3H), 3.70 (s, 1H), 3.53 (d, 1H), 3.43-3.32 (m, 2H), 3.25-3.20 (m, 2H), 2.78 (s, 3H), 1.72-1.62 (m, 8H), 1.33-1.21 (m, 2H).

[00780] Example 155: Synthesis of ethyl 3-(2-methoxyethyl)-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-6).



[00781] Synthesis of compound 155.2. A mixture of methyl 3-methoxypropanoate (3 g, 25.40 mmol, 1.00 equiv), methanol (60 mL), water(12 mL) and sodiumol (3.2 g, 80mmol, 3.15 equiv) was stirred for 2 h at 50 °C in an oil bath. The pH value of the solution was adjusted to 2-3 with hydrochloric acid (2 mol/L). The resulting solution was extracted with 3 x 50 mL of dichloromethane and the organic layers combined. The resulting mixture was washed with 50 mL of brine. The resulting solution was dried over anhydrous sodium sulfate and concentrated under vacuum to give 2.0 g (76%) of **155.2** as a colorless oil.

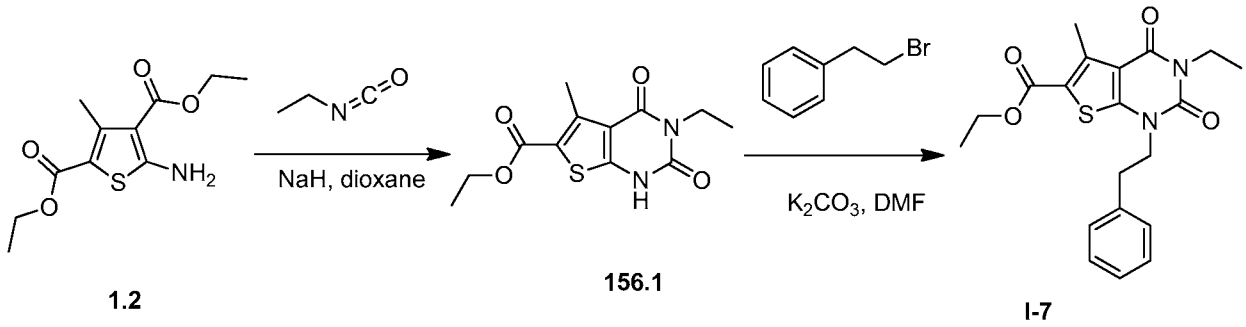
[00782] Synthesis of compound 155.3. A mixture of 3-methoxypropanoic acid (3.0 g, 28.82 mmol, 1.00 equiv), DPPA (8.0 g, 29.07 mmol, 1.01 equiv) and triethylamine (2.92 g, 28.86 mmol, 1.00 equiv) in dry toluene (80 mL) was heated to reflux for 2 hr under nitrogen atmosphere. The reaction mixture was cooled to room temperature and then quenched by the addition of 50 mL of water/ice. The resulting solution was extracted with 100 mL of ethyl

acetate and the organic layer dried over anhydrous sodium sulfate and concentrated under vacuum to yield 1.5 g (51%) of **155.3** as colorless oil.

[00783] Synthesis of compound 155.4. A mixture of 2,4-diethyl 5-amino-3-methylthiophene-2,4-dicarboxylate (5.0 g, 19.43 mmol, 1.00 equiv) and potassium carbonate (5.4 g, 39.07 mmol, 2.01 equiv) in N,N-dimethylformamide (70 mL) was stirred for 15 min at 25 °C. To this was added (2-bromoethyl)benzene (7.2 g, 38.91 mmol, 2.00 equiv). The resulting solution was stirred overnight at 50 °C in an oil bath. The reaction was then quenched by the addition of 100 mL of water and ice mixture. The resulting solution was extracted with 2 x 100 mL of ethyl acetate and the organic layers combined. The resulting solution was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate : petroleum ether (1 : 10) to yield 4.0 g (57%) of **155.4** as a brown solid. The 500mg crude was recrystallized with EtOH to obtain 208.9 mg of the pure compound.

[00784] Synthesis of Compound I-6. Sodium hydride (60%) (100 mg, 2.5 mmol, 1.81 equiv) was added to a solution of **155.4** (500 mg, 1.38 mmol, 1.00 equiv) in dioxane (15 mL) batchwise under a nitrogen atmosphere. 30 minutes later, was added **155.3** (300 mg, 2.97 mmol, 2.15 equiv). The resulting solution was heated to reflux for 8 h in an oil bath. The reaction mixture was cooled to room temperature and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate / petroleum ether (1 / 10) to give 0.25 g (43%) of **I-6** as a white solid. MS (ES): *m/z*: $(M+H)^+$ calcd for $C_{21}H_{25}N_2O_5S$ 417, found 417. ^1H NMR (400 MHz, $CDCl_3$) δ7.28-7.35 (5H, m), 4.36-4.41 (2H, q), 4.26-4.28 (2H, t), 4.14-4.18 (2H, t), 3.64-3.67 (2H, t), 3.39 (3H, s), 3.07-3.11 (2H, t), 2.90 (3H, s), 1.40-1.44 (3H, t).

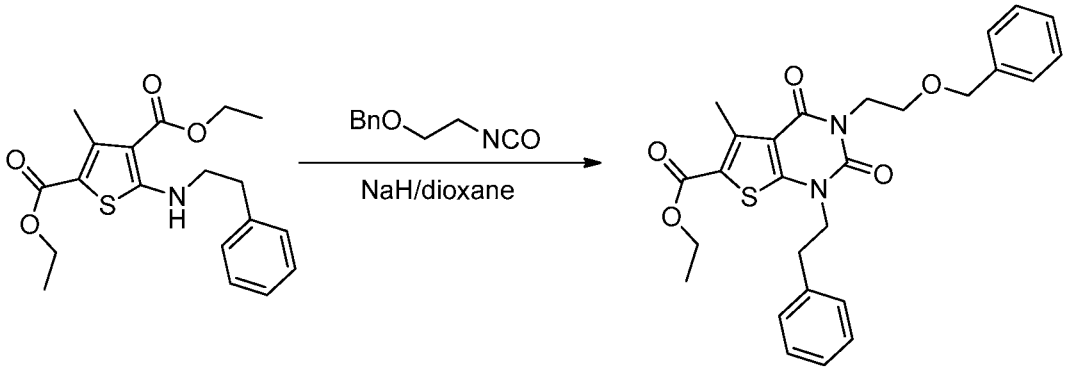
[00785] Example 156: Synthesis of ethyl 3-ethyl-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-7).



1.2 156.1 I-7

[00786] **Synthesis of Compound I-7.** Compound **I-7** was prepared from isocyanatoethane and **1.2** in a manner analogous to the synthesis of compound **136.1**. Isolated a white solid in 45% yield. MS (ES): *m/z*: $(M+H)^+$ calcd for $C_{20}H_{23}N_2O_4S$ 387, found 387. ^1H NMR (300 MHz, $CDCl_3$) δ7.29-7.39 (5H, m) , 4.36-4.43 (2H, q), 4.115-4.20 (2H, t) , 4.05-4.10 (2H, q), 3.08-3.13 (2H, t) , 2.92 (3H, s), 1.41-1.45 (3H, t), 1.25-1.29 (3H, t).

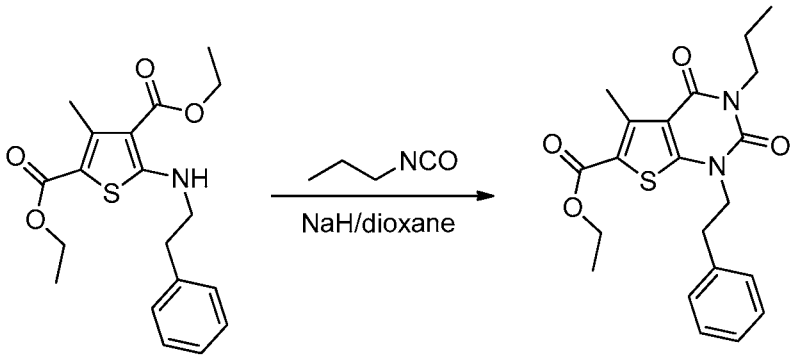
[00787] **Example 157: Synthesis of ethyl 3-[2-(benzyloxy)ethyl]-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-10).**



155.4 I-10

[00788] Compound **I-10** was prepared from **155.4** and [(2-isocyanatoethoxy)methyl]benzene in a manner analogous to Compound **I-6** (Example 155). Isolated a white solid in 51% yield. MS (ES): *m/z*: 493 $(M+H)^+$. ^1H NMR (300 MHz, $CDCl_3$): δ7.21-7.35 (10H, m), 4.55 (2H, s), 4.33-4.40 (2H, q), 4.27-4.31 (2H, t), 4.07-4.13 (2H, t), 3.73-3.77 (2H, t), 3.01-3.06 (2H, t), 2.87 (3H, s) , 1.38-1.42 (3H, t).

[00789] **Example 157: Synthesis of ethyl 5-methyl-2,4-dioxo-1-(2-phenylethyl)-3-propyl-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-9).**

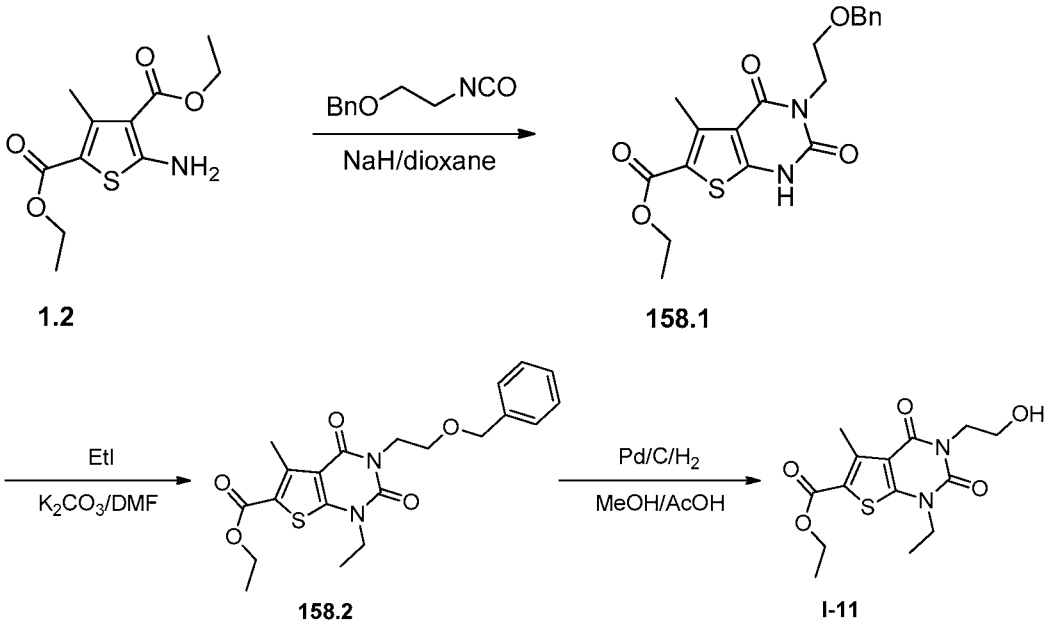


155.4 I-9

Compound **I-9** was prepared from **155.4** and 1-isocyanatopropane in a manner analogous to Compound **I-6** (Example 155). Isolated a white solid in 3% yield. MS (ES): *m/z*: 401 $(M+H)^+$.

^{1}H NMR (400 MHz, $CDCl_3$): δ7.28-7.35 (5H, m), 4.35-4.42 (2H, q), 4.14-4.16 (2H, t), 3.95-4.00 (2H, t), 3.07-3.12 (2H, t), 2.90 (3H, s), 1.67-1.72 (2H, q), 1.40-1.45 (3H, t), 0.96-1.01 (3H, t).

[00790] Example 158: Synthesis of ethyl 1-ethyl-3-(2-hydroxyethyl)-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-11).



[00791] Synthesis of compound 158.1. Compound **158.1** was prepared from **1.2** and [(2-isocyanatoethoxy)methyl]benzene in a manner analogous to the synthesis of compound **135.3**. Isolated 38.9 mg of a white solid in 10% yield. MS (ES): *m/z*: 389 $(M+H)^+$.

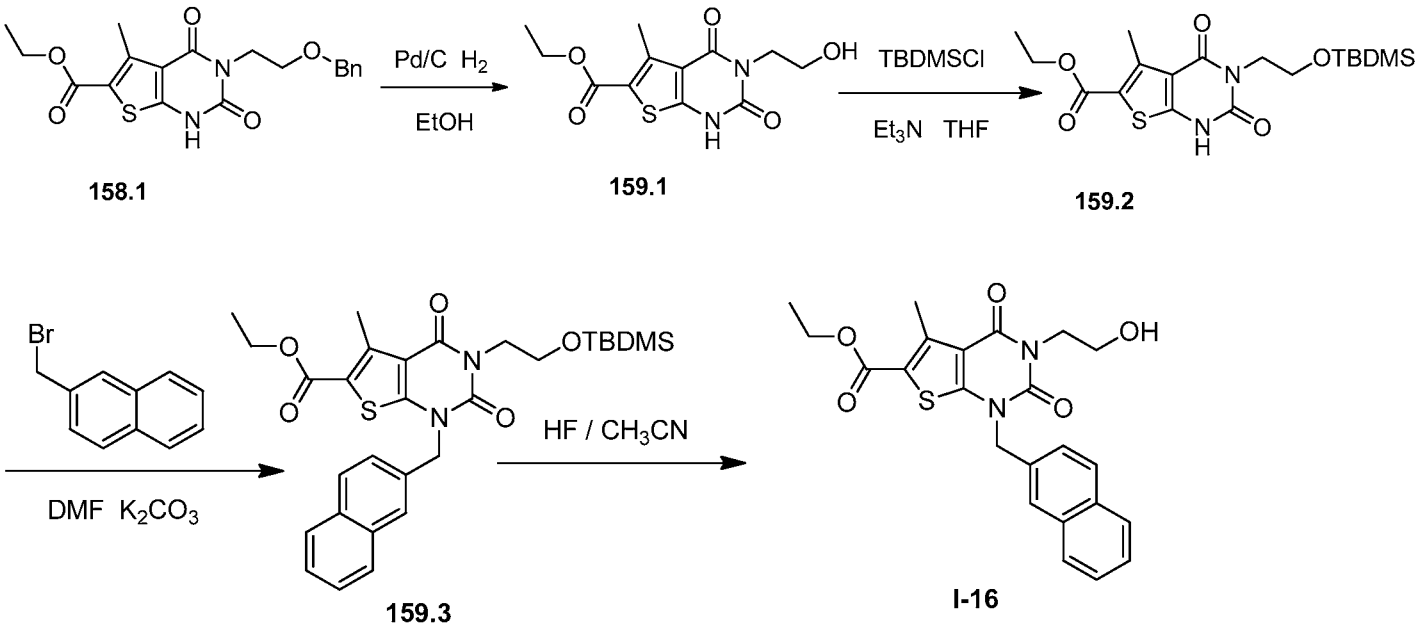
^{1}H NMR (300 MHz, $CDCl_3$):δ9.68 (1H, s), 7.21-7.34 (5H, m), 4.60 (2H, s), 4.28-4.40 (4H, m), 3.81-3.85 (2H, t), 2.86 (3H, s), 1.38-1.42 (3H, t).

[00792] Synthesis of compound 158.2. A mixture of **158.1** (200 mg, 0.51 mmol, 1.00 equiv), potassium carbonate (140 mg, 1.01 mmol, 1.95 equiv) and iodoethane (321 mg, 2.06 mmol, 4.00 equiv) in N,N-dimethylformamide (10 mL) was stirred for 4 h at 35°C. The reaction was then quenched by the addition of 15 mL of water and ice mixture. The resulting solution was extracted with 2 x 15 mL of ethyl acetate and the organic layers combined. The resulting mixture was washed with 2 x 20 mL of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum to give 120 mg (56%) of **158.2** as a yellow solid.

[00793] Synthesis of Compound I-11. Excess hydrogen gas was introduced into a mixture of **158.2** (120 mg, 0.29 mmol, 1.00 equiv), acetic acid (5 mL), 10% palladium on carbon (100 mg) in ethanol (20 mL) and the pressure maintained at 4 atm. The resulting solution was stirred for 12

h at room temperature. The solids were filtered out. The filtrate was concentrated under vacuum. The residue was purified by re-crystallization from ethanol to yield 12.4 mg (13%) of **I-11** as a white solid. MS (ES): *m/z*: 327 $(M+H)^+$. ^1H NMR (300 MHz, $CDCl_3$):δ4.32-4.39 (2H, q), 4.27-4.30 (2H, t), 4.00-4.07 (2H, q), 3.89-3.92 (2H, t), 2.87 (3H, s), 1.36-1.42 (6H, dt).

[00794] Example 159: Synthesis of ethyl 3-(2-hydroxyethyl)-5-methyl-1-(naphthalen-2-ylmethyl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-16).).



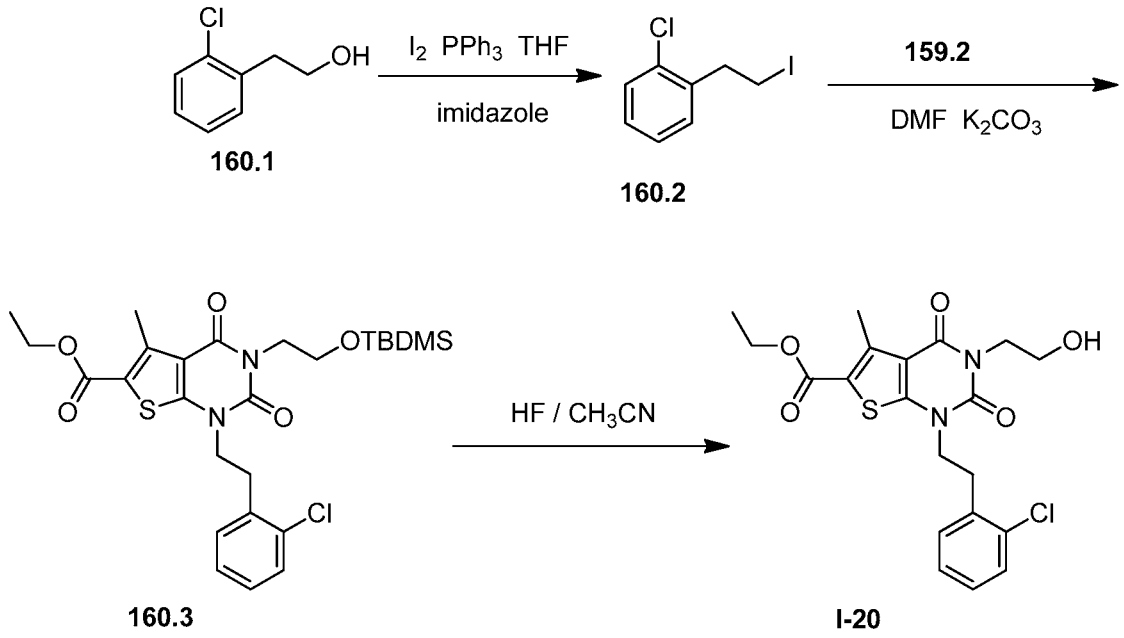
[00795] Synthesis of compound 159.1. Into a 100-mL round-bottom flask was placed **158.1** (650 mg, 1.67 mmol, 1.00 equiv), ethanol (35 mL), acetic acid (7 mL) and 10% palladium on carbon (300 mg). Hydrogen was introduced (4 atm). The resulting solution was stirred for 24 h at room temperature. The solids were filtered out. The filtrate was concentrated under vacuum to yield 400 mg (80%) of **159.1** as a brown solid.

[00796] Synthesis of compound 159.2. A mixture of **159.1** (400 mg, 1.34 mmol, 1.00 equiv), tert-butyl(chloro)dimethylsilane (240 mg, 1.59 mmol, 1.19 equiv) and triethylamine (203 mg, 2.01 mmol, 1.50 equiv) in oxolane (20 mL) was stirred for 12 h at room temperature. The reaction was then quenched by the addition of 20 mL of water. The resulting solution was extracted with 2 x 40 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum to give 360 mg (65%) of **159.2** as a white oil.

[00797] **Synthesis of compound 159.3.** A mixture of **159.2** (120 mg, 0.29 mmol, 1.00 equiv), potassium carbonate (60 mg, 0.43 mmol, 1.48 equiv) and 2-(bromomethyl)naphthalene (77 mg, 0.35 mmol, 1.20 equiv) in N,N-dimethylformamide (10 mL) was stirred for 12 h at 35°C. The reaction was then quenched by the addition of 10 mL of water. The resulting solution was extracted with 2 x 15 mL of ethyl acetate and the organic layers combined. The resulting mixture was washed with 1 x 35 mL of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate / petroleum ether (1 / 15 - 1 / 10) to give 60 mg (37%) of **159.3** as a yellow solid.

[00798] **Synthesis of Compound I-16.** Into a 50-mL round-bottom flask was placed a solution of **159.3** (20 mg, 0.04 mmol, 1.00 equiv, 99%) in CH_3CN (5 mL). This was followed by the addition of HF (0.25 mL) dropwise with stirring. The resulting solution was stirred overnight at room temperature. The resulting solution was diluted with 30 mL of water. The solids were collected by filtration and dried under reduced pressure to yield 15 mg (93%) of **I-16** as a white solid. MS (ES, *m/z*): 439 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, 4H), 7.52-7.45 (m, 3H), 5.35 (s, 2H), 4.37-4.27 (m, 4H), 3.96 (t, 2H), 2.85 (s, 3H), 2.31 (s, 1H), 1.35 (t, 3H).

[00799] **Example 160: Synthesis of ethyl 1-[2-(2-chlorophenyl)ethyl]-3-(2-hydroxyethyl)-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-20).**

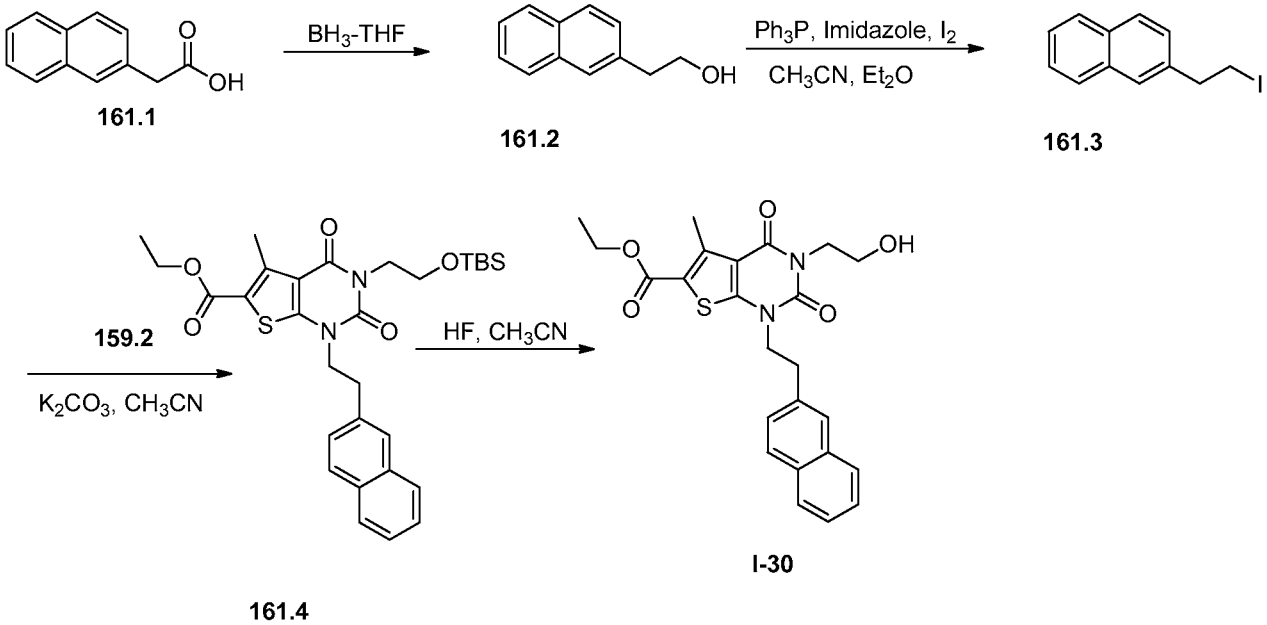


[00800] **Synthesis of compound 160.2.** Into a 50-mL 3-necked round-bottom flask was placed 2-(2-chlorophenyl)ethan-1-ol (1.5 g, 9.58 mmol, 1.00 equiv), PPh_3 (2.5 g, 9.53 mmol,

1.00 equiv), tetrahydrofuran (30 mL) and imidazole (0.9g, 13.2 mmol, 1.4 equiv). This was followed by the addition of I_2 (3.4 g) in several batches. The resulting solution was stirred for 30 min at 0-5°C and then quenched by the addition of 20 mL of water/ice. The resulting solution was extracted with 2 x 50 mL of ether and the organic layers combined. The resulting mixture was washed with 1 x 50 mL of sat. aqueous Na_2SO_3. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate / petroleum ether (1 / 3). This resulted in 2.5 g (98%) of **160.2** as a colorless oil.

[00801] **Synthesis of compound I-20.** Compound **I-20** was prepared from **159.2** and **160.2** in a manner analogous to the synthesis of Compound **I-16** (Example 159). Isolated a white solid in 54% yield. MS (ES): *m/z*: 437 $(M+H)^+$ ^1H NMR (300 MHz, $CDCl_3$): δ 7.39-7.35 (m, 1H), 7.22-7.19 (m, 3H), 4.39-4.32 (m, 2H), 4.28-4.18 (m, 4H), 3.87 (t, 2H), 3.24 (t, 2H), 2.86 (s, 3H), 2.26 (s, 1H), 1.39 (t, 3H).

[00802] **Example 161: Synthesis of ethyl 3-(2-hydroxyethyl)-5-methyl-1-[2-(naphthalen-2-yl)ethyl]-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-30).**

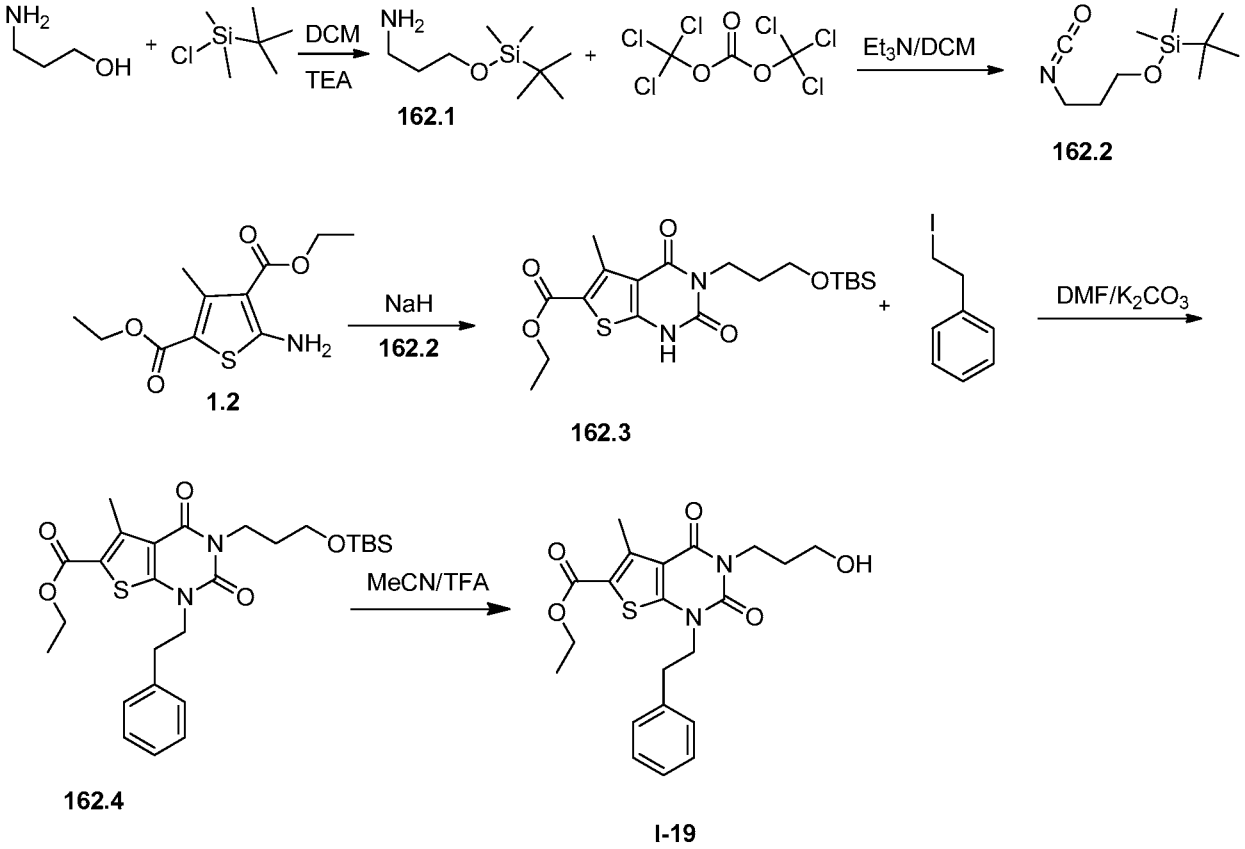


[00803] **Synthesis of compound 161.2.** Into a 250-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed **161.1** (7.44 g, 39.96 mmol, 1.00 equiv) and tetrahydrofuran (80 mL). This was followed by the addition of BH_3/THF (1 M) (80

mL) dropwise with stirring at 0 °C. The resulting solution was stirred for 2 h at room temperature. The reaction was then quenched by the addition of 20 mL of water. The resulting solution was extracted with 2x150 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 7.05 g (crude) of **161.2** as a colorless oil.

[00804] Synthesis of Compound I-30. Compound **I-30** was prepared from **161.2** and **159.2** in a manner analogous to the synthesis of Compound **I-20** (Example 160). Isolated a white solid in 31% yield from **159.2**. MS (ES): *m/z* $(M+H)^+$ 453, $(M+Na)^+$ 475. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.28(t, J = 7.2, 3H), 2.76 (s, 3H), 3.18 (t, J = 7.6, 2H), 3.49 (t, J = 6.4, 2H), 3.95 (t, J = 6.4, 2H), 4.20-4.30 (m, 4H), 7.42-7.51 (m, 3H), 7.78 (s, 3H), 7.85-7.90 (m, 3H).

[00805] Example 162: Synthesis of ethyl 3-(3-hydroxypropyl)-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-19).



162.1 162.2 1.2 162.3 162.4 I-19

[00806] Synthesis of compound 162.1. Into a 500-mL 3-necked round-bottom flask was placed a solution of 3-aminopropan-1-ol (15 g, 195.71 mmol, 1.00 equiv, 98%) in dichloromethane (200 mL), tert-butyl(chloro)dimethylsilane (36 g, 234.07 mmol, 1.20 equiv),

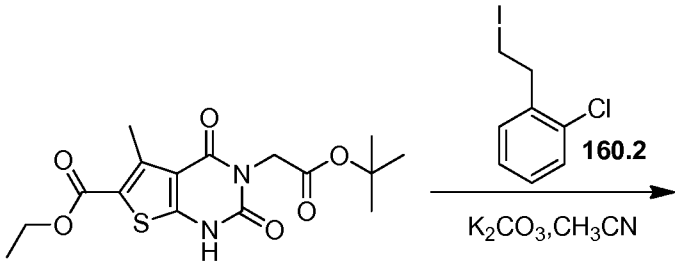
triethylamine (60.6 g, 588.00 mmol, 3.00 equiv, 98%). The resulting solution was stirred for 18 h at 20°C. The reaction was then quenched by the addition of 200 mL of water. The resulting solution was extracted with 1x200 mL of dichloromethane and the organic layers combined. The resulting mixture was washed with 1x200 mL of brine. The mixture was dried over anhydrous magnesium sulfate and concentrated under vacuum. This resulted in 20 g (51%) of **162.1** as a colorless oil.

[00807] Synthesis of compound 162.2. Compound **162.2** was prepared from **162.1** in a manner analogous to **135.2**. Isolated 2 g of a yellow oil in 74% yield.

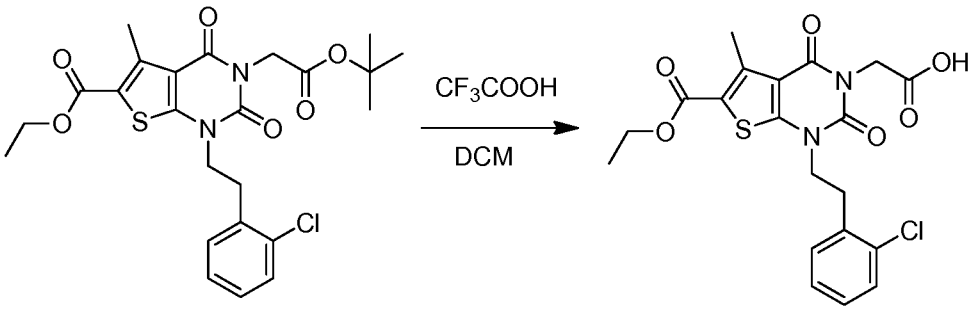
[00808] Synthesis of compound 162.4. Compound **162.4** was prepared from **162.2** and **1.2** in a manner analogous to the synthesis of compound **136.1** (Examples 135 and 136). Isolated 110 mg of a white solid in 15% yield from **1.2**.

[00809] Synthesis of Compound I-19. Into a 50-mL round-bottom flask was placed a solution of **162.4** (110 mg, 0.20 mmol, 1.00 equiv, 98%) in CH_3CN (20 mL) and hydrogen fluoride (1 mL). The resulting solution was stirred for 3 h at 20°C. The reaction was then quenched by the addition of 10 mL of water. The solids were collected by filtration and dried under reduced pressure to give 60 mg (70%) of **I-19** as a white solid. MS (ES): *m/z* 417 $(M+H)^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 7.327 (m, 4H), 7.261 (m, 1H), 4.385 (m, 2H), 4.137 (m, 4H), 3.513 (t, 2H), 3.084 (t, 2H), 2.873 (s, 3H), 1.429 (t, 2H), 0.962 (t, 3H).

[00810] Example 163: Synthesis of 2-[1-[2-(2-chlorophenyl)ethyl]-6-(ethoxycarbonyl)-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-31).



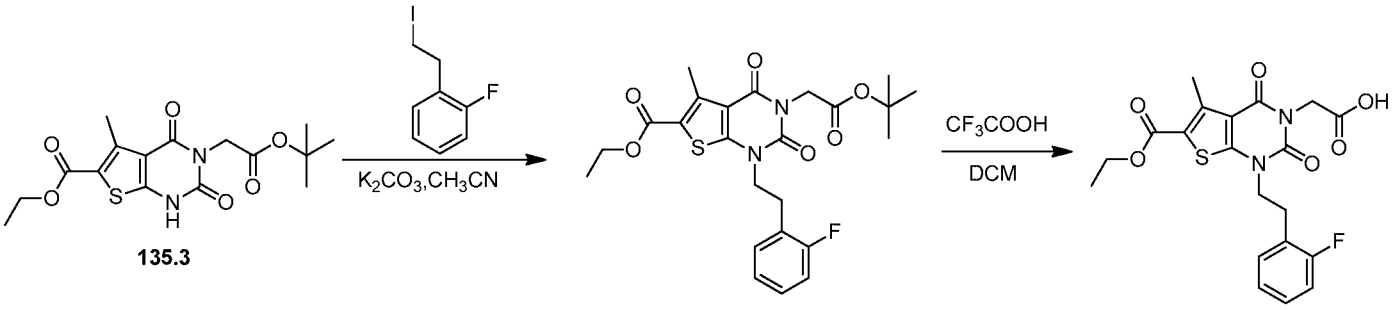
135.3



163.1 I-31

[00811] Compound **I-31** was prepared from **135.3** and **160.2** in a manner analogous to the synthesis of **136.2**. Isolated 73.1 mg of a white solid in 11% overall yield. MS (ES): *m/z* $(M+H)^+$ 451. ^1H NMR (400 MHz, CD_3OD): δ 1.35-1.86 (t, 3H), 2.80 (s, 3H), 3.27-3.37 (m, 2H), 4.23-4.27 (t, 2H), 4.30-4.35 (q, 2H), 4.71 (s, 2H), 7.21-7.23 (t, 2H), 7.30-7.36 (m, 1H), 7.36-7.37 (m, 1H).

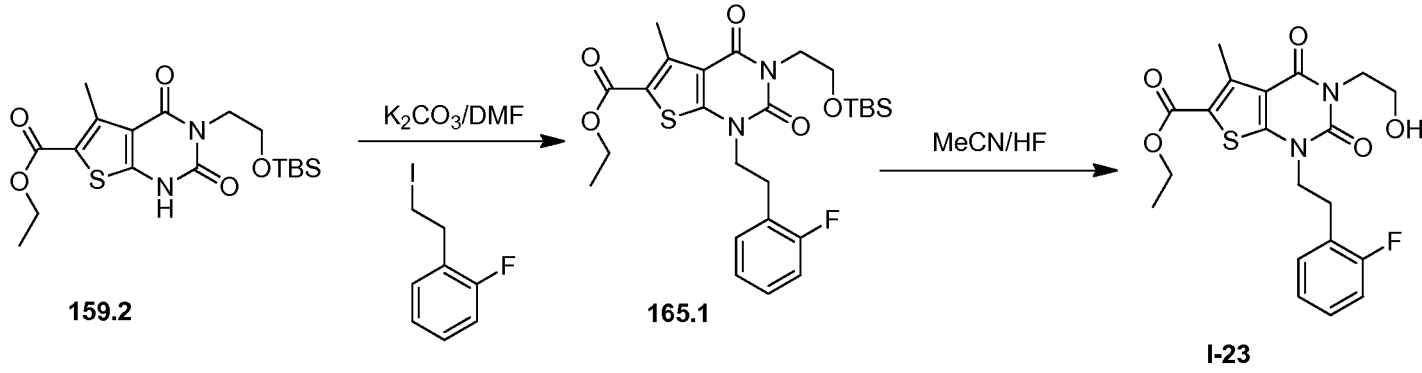
[00812] Example 164: Synthesis of 2-[6-(ethoxycarbonyl)-1-[2-(2-fluorophenyl)ethyl]-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-32).



135.3 164.1 I-32

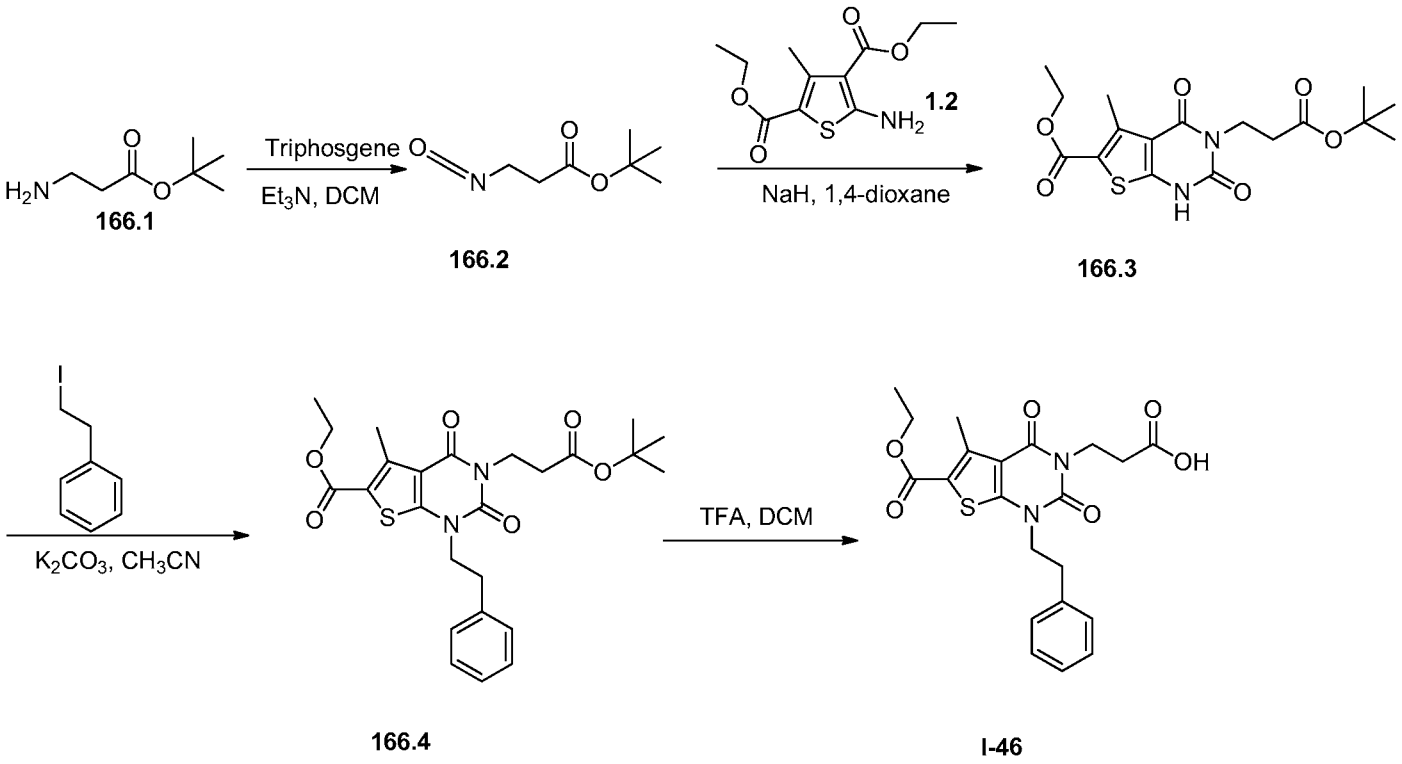
[00813] Compound **I-32** was prepared from **135.3** and 1-fluoro-2-(2-iodoethyl)benzene in a manner analogous to the synthesis of **136.2**. Isolated 42.9 mg of a white solid in 23% overall yield. MS (ES): *m/z* $(M+H)^+$ 435. ^{1}H NMR (400 MHz,CD_3OD): δ 1.36-1.94 (t, 3H), 2.81 (s, 1H), 3.16-3.20 (t, 2H), 4.21-4.24 (t, 2H), 4.31-4.37 (q, 2H), 4.70 (s, 2H), 7.01-7.11 (m, 2H), 7.26-7.28 (q, 2H). ^{19}F-NMR (300 MHz, CD_3OD): δ -120.64(1).

[00814] Example 165: Synthesis of ethyl 1-[2-(2-fluorophenyl)ethyl]-3-(2-hydroxyethyl)-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-23).



[00815] Compound **I-23** was prepared from **159.2** and 1-fluoro-2-(2-iodoethyl)benzene in a manner analogous to the synthesis of Compound **I-16** (Example 159). Isolated 500 mg of a white solid in 59% overall yield. MS (ES): *m/z* 421$(M+H)^+$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.279 (m, 2H), 7.053 (m, 2H), 4.370 (m, 2H), 4.162 (m, 4H), 3.870 (t, 2H), 3.144 (m, 2H), 2.861 (s, 3H), 1.396 (t, 3H).

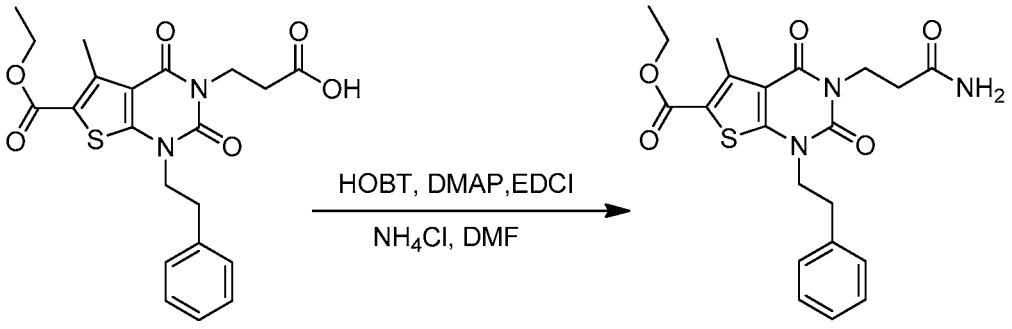
[00816] Example 166: Synthesis of 3-[6-(ethoxycarbonyl)-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-46).



166.1 166.2 166.3 166.4 I-46

[00817] Compound **I-46** was prepared from **166.1** and **1.2** in a manner analogous to the synthesis of compound **136.2** (Examples 135 and 136). Isolated 1.8 g of a white solid in 25% overall yield. MS (ES): *m/z* $(M+H)^+$ 431, $(M+Na)^+$ 453. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.29 (t, J = 7.2, 3H), 2.75 (s, 3H), 3.09 (t, J = 6.3, 2H), 4.04-4.13 (m, 4H), 4.28 (q, J = 6.9, 2H), 7.20-7.32 (m, 5H), 12.37 (s, 1H).

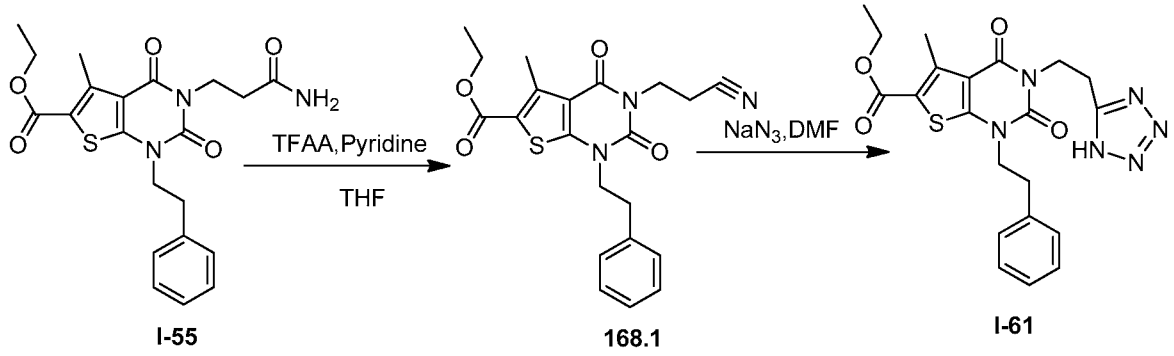
[00818] Example 167: Synthesis of ethyl 3-(2-carbamoylethyl)-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-55).



I-46 I-55

[00819] Compound **I-55** was prepared from **I-46** in a manner analogous to the synthesis of **136.3.** Isolated 0.2 g of a white solid in 56% yield. MS (ES): *m/z* $(M+H)^+$ 430. ^1H NMR (300 MHz, DMSO-d_6): δ 1.29(t, *J* = 7.2, 3H), 2.34 (t, *J* = 7.5, 2H), 2.76 (s, 3H), 3.00 (t, *J* = 7.5, 2H), 4.02-4.13 (m, 4H), 4.28 (q, *J* = 7.2, 2H), 6.86 (s, 1H), 7.24-7.38 (m, 6H).

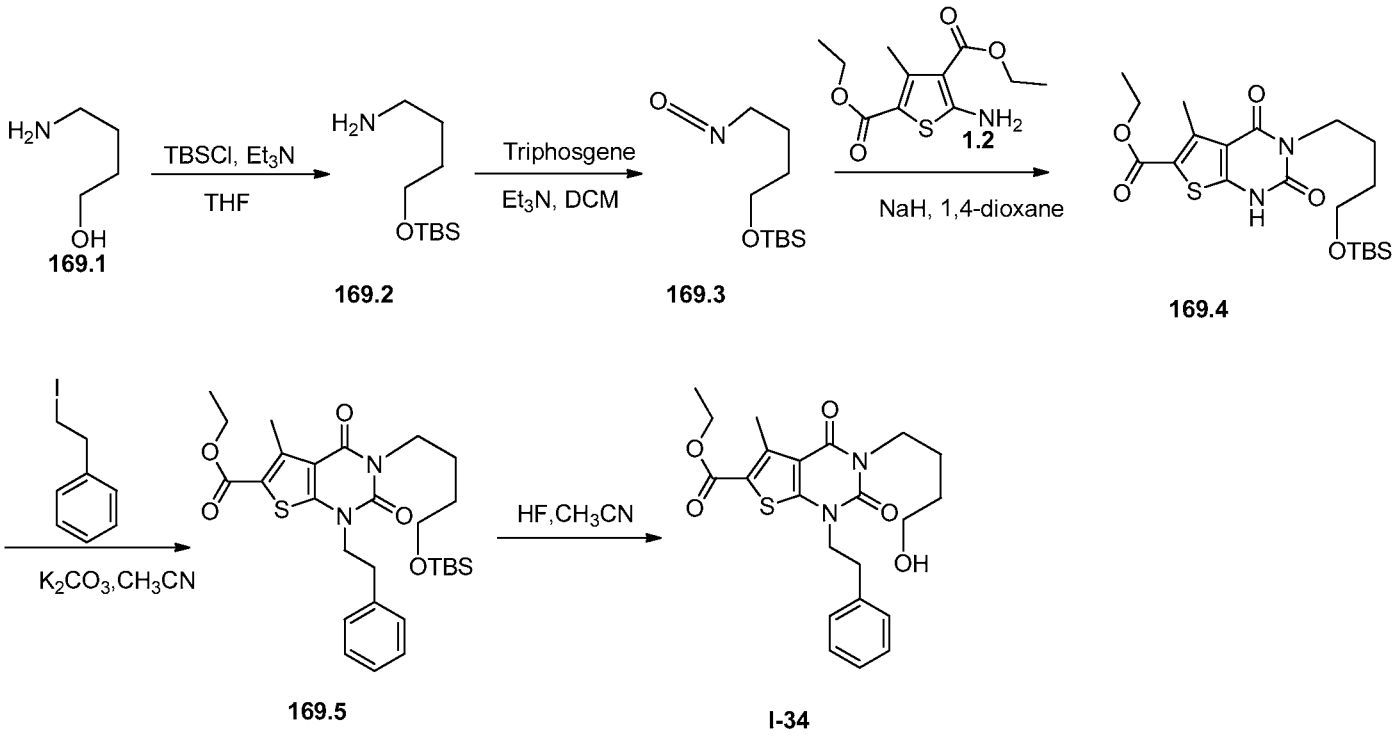
[00820] Example 168: Synthesis of ethyl 5-methyl-2,4-dioxo-1-(2-phenylethyl)-3-[2-(1H-1,2,3,4-tetrazol-5-yl)ethyl]-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-61).



I-55 168.1 I-61

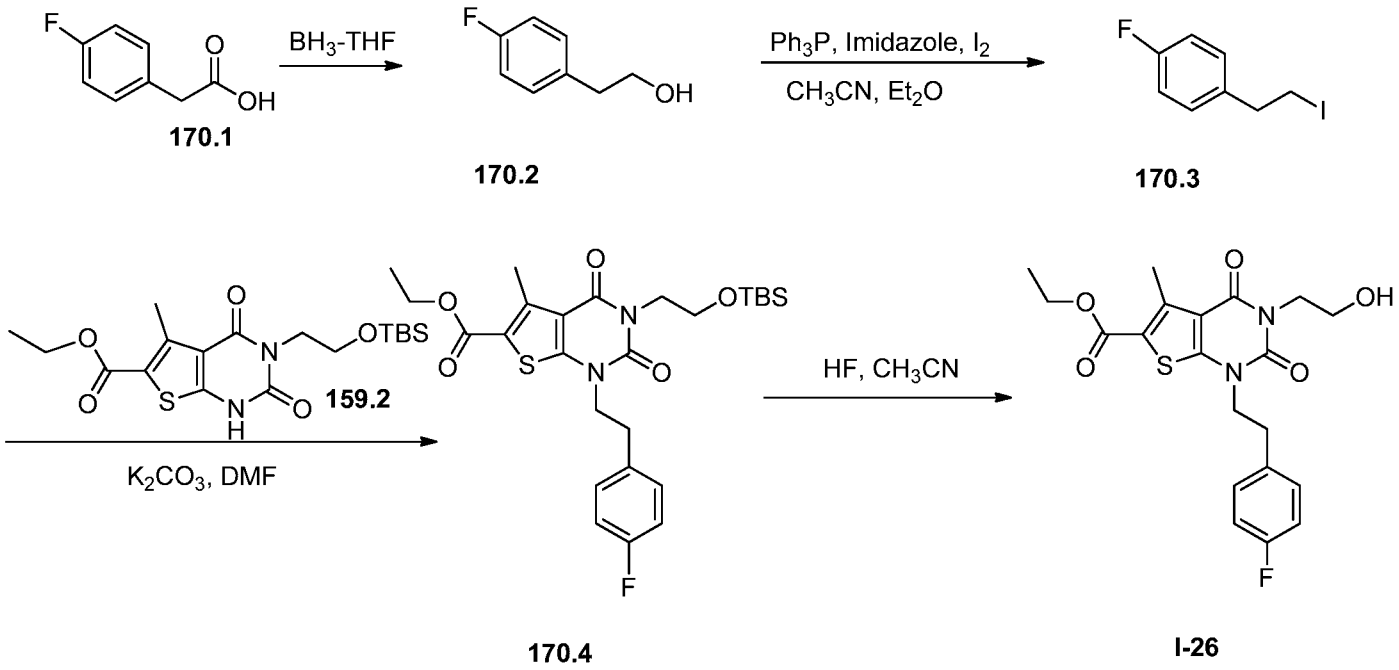
Compound **I-61** was prepared from **I-55** in a manner analogous to the synthesis of Compound **I-45** from **136.3** (Example 136). Isolated 16.7 mg of a white solid in 10% overall yield. MS (ES): *m/z* $(M+H)^+$ 455, $(M+H+CH_3CN)^+$ 496. ^1H NMR (400 MHz, CD_3OD): δ 1.38 (t, *J* = 7.2, 3H), 2.79 (s, 3H), 3.05 (t, *J* = 7.2, 2H), 3.27 (t, *J* = 7.2, 2H), 4.13 (t, *J* = 7.2, 3H), 4.31-4.39 (m, 4H), 7.23-7.32 (m, 5H).

[00821] Example 169: Synthesis of ethyl 3-(4-hydroxybutyl)-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-34).



Compound **I-34** was prepared from **169.1** and **1.2** in a manner analogous to Compound **I-19** (Example 162). Isolated 26 mg of a colorless oil in 1.4% overall yield. MS (ES): *m/z* $(M+H)^+$ 431. ^1H NMR (300 MHz, CD_3OD): δ 1.38 (t, *J*=7.5, 2H), 1.52-1.64 (m, 2H), 1.66-1.78 (m, 2H), 2.82 (s, 3H), 3.10 (t, *J*=7.2, 2H), 3.60 (t, *J*=6.3, 2H), 3.99 (t, *J*=7.2, 2H), 4.19 (t, *J*=7.5, 2H), 4.34 (q, *J*=7.2, 2H), 7.19-7.31 (m, 2H).

[00822] Example 170: Synthesis of ethyl 1-[2-(4-fluorophenyl)ethyl]-3-(2-hydroxyethyl)-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-26).

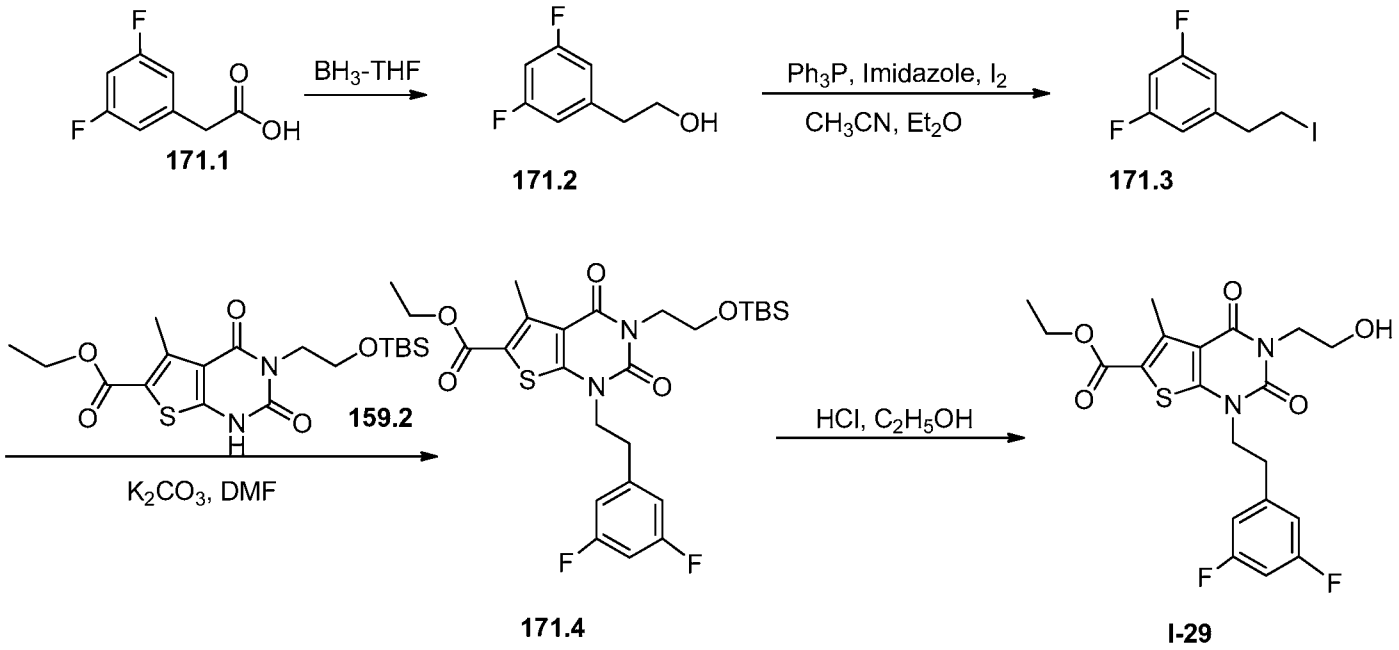


170.1 170.2 170.3

170.4 I-26

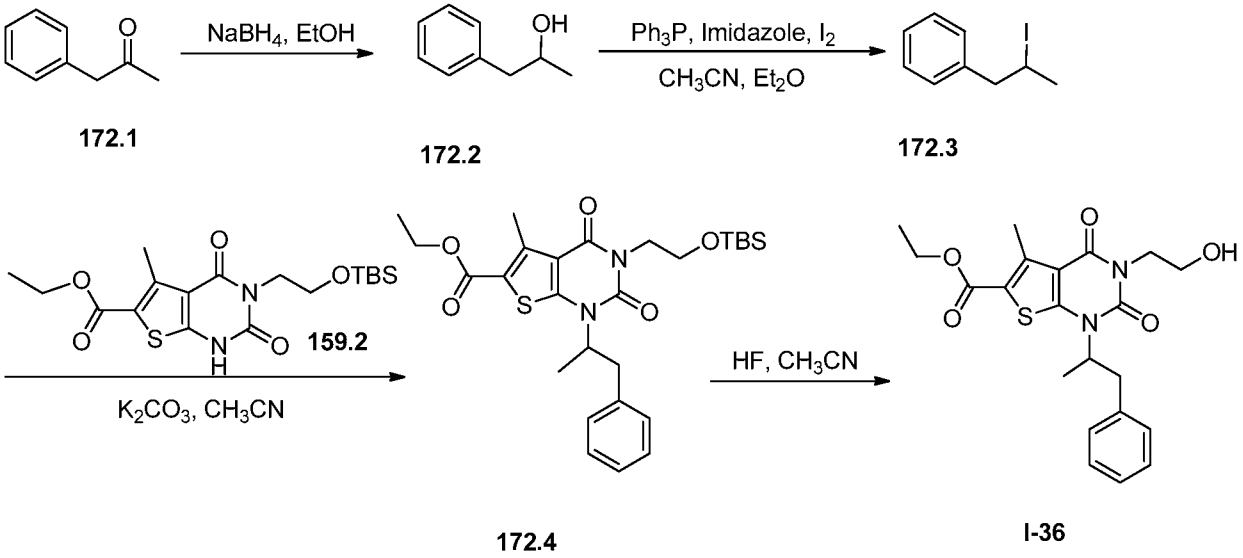
Compound **I-26** was prepared from **170.1** and **159.2** in a manner analogous to the synthesis of Compound **I-30** (Example 161). Isolated 80 mg of a white solid in 60% overall yield. MS (ES): *m/z* $(M+H)^+$ 421. ^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (t, *J*=7.2, 3H), 2.24 (s, 3H), 2.87 (s, 3H), 3.06 (t, *J*=7.5, 2H), 3.89 (s, 2H), 4.12 (t, *J*=7.8, 2H), 4.27 (t, *J*=5.1, 3H), 4.37 (q, *J*=7.2, 3H), 6.91-7.26 (m, 4H).

[00823] Example 171: Synthesis of ethyl 1-[2-(3,5-difluorophenyl)ethyl]-3-(2-hydroxyethyl)-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-29).



[00824] Compound **I-29** was prepared from **171.1** and **159.2** in a manner analogous to Compound **I-30** (Example 161), except that HCl/ethanol was used in the last step rather than HF/acetonitrile. Isolated 60 mg of an off-white solid in 39% overall yield. MS (ES, *m/z*): $(M+H)^+$ 439. ^{1}H NMR(300 MHz, $CDCl_3$): δ 1.41 (t, *J*=7.2, 3H), 2.87 (s, 3H), 3.06 (t, *J*=7.8, 2H), 3.90 (t, *J*=5.4, 2H), 4.14 (t, *J*=8.1, 2H), 4.28 (t, *J*=8.1, 2H), 4.38 (q, *J*=7.2, 2H), 6.69-6.84 (m, 3H).

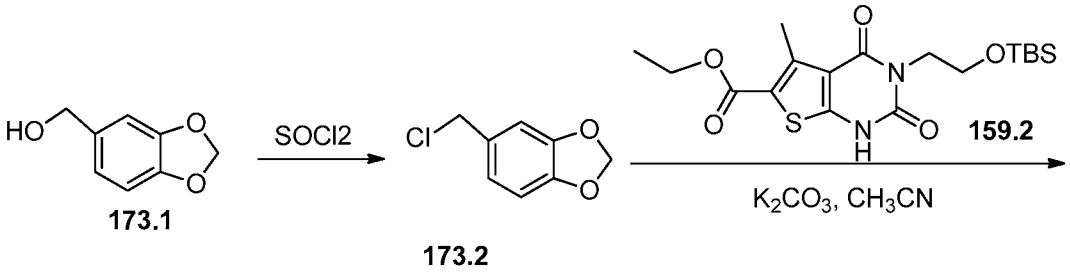
[00825] Example 172: Synthesis of ethyl 3-(2-hydroxyethyl)-5-methyl-2,4-dioxo-1-(1-phenylpropan-2-yl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-36).



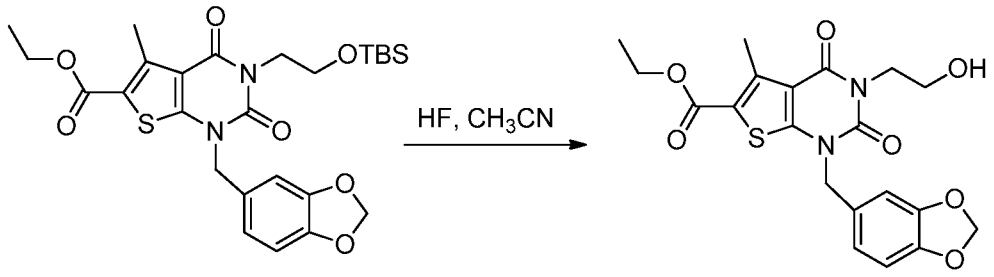
[00826] Synthesis of compound 172.2. Into a 100-mL 3-necked round-bottom flask, maintained with an inert atmosphere of nitrogen, was placed 1-phenylpropan-2-one (3 g, 22.36 mmol, 1.00 equiv) and ethanol (50 mL). This was followed by the addition of $NaBH_4$ (1.7 g, 44.94 mmol, 2.01 equiv) at 5 °C. The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 10 mL of ammonium chloride (sat.). The resulting solution was extracted with 2x50 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:2). This resulted in 2.8 g (92%) of 1-phenylpropan-2-ol as a colorless oil.

[00827] Synthesis of Compound I-36. Compound **I-36** was prepared from **172.2** and **159.2** in a manner analogous to the synthesis of **I-30** (Example 161). Isolated 23.4 mg of a white solid in 45% overall yield. MS (ES): *m/z* 417 $(M+H)^+$, 439 $(M+Na)^+$, 480 $(M+Na+CH_3CN)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.36(t, *J*=7.2, 3H), 1.70 (t, *J*=6.6, 3H), 2.75 (s, 3H), 3.10-3.17 (m, 1H), 3.56-3.63 (m, 4H), 4.13 (s, 2H), 4.32 (q, *J*=6.6, 2H), 7.12-7.21 (m, 5H).

[00828] Example 173: Synthesis of ethyl 1-(2H-1,3-benzodioxol-4-ylmethyl)-3-(2-hydroxyethyl)-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-40).



173.1 173.2

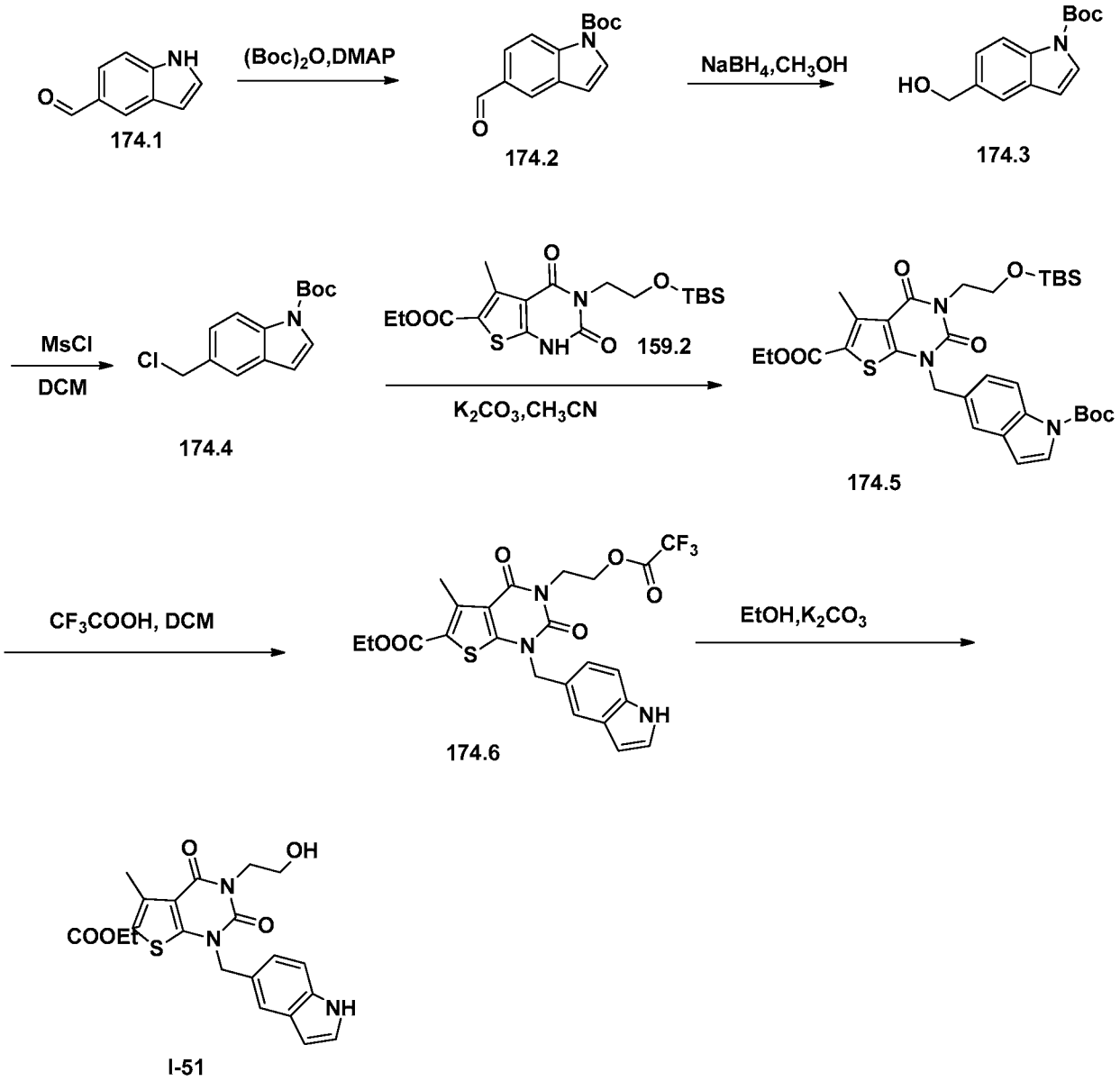


173.3 I-40

[00829] **Synthesis of compound 173.2.** Into a 50-mL round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed **173.1** (400 mg, 2.63 mmol, 1.00 equiv), thionyl chloride (626 mg, 5.26 mmol, 2.00 equiv) and dichloromethane (20 mL). The resulting solution was stirred for 1 h at room temperature. The resulting mixture was concentrated under vacuum. This resulted in 460 mg (97%) of **173.2** as a yellow oil.

[00830] **Synthesis of Compound I-40**. **I-40** was synthesized from **173.2** and **159.2** in a manner consistent with the synthesis of Compound **I-30** (Example 161). Isolated 27.5 mg of a white solid in 39% overall yield. MS (ES): *m/z* 433 $(M+H)^+$, 455 $(M+Na)^+$, 496 $(M+Na+CH_3CN)^+$. ^{1}H NMR(300 MHz, DMSO-d_6): δ 1.26 (t, *J*=7.2, 3H), 2.77 (s, 3H), 3.59 (t, *J*=6.0, 2H), 4.01 (t, *J*=6.6, 2H), 4.25 (q, *J*=7.2, 3H), 4.79 (t, *J*=6.0, 1H), 5.10 (s, 2H), 6.01 (s, 2H), 6.85-6.95 (m, 3H).

[00831] **Example 174: Synthesis of ethyl 3-(2-hydroxyethyl)-1-(1H-indol-5-ylmethyl)-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-51).**



[00832] **Synthesis of compound 174.2.** Into a 50-mL round-bottom flask was placed tetrahydrofuran (20 mL), 4-dimethylaminopyridine (1.32 g, 10.80 mmol, 1.08 equiv), 1H-indole-5-carbaldehyde (1.45 g, 9.99 mmol, 1.00 equiv) and $(Boc)_2O$ (2.18 g, 9.99 mmol, 1.00 equiv). The resulting solution was stirred for 12 h at room temperature. The reaction was then quenched by the addition of 10 mL of water. The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 2.1 g (86%) of **174.2** as a yellow solid.

[00833] **Synthesis of compound 174.3.** Into a 50-mL round-bottom flask was placed a solution of **174.2** (2.1 g, 8.56 mmol, 1.00 equiv) in methanol (20 mL). Then $NaBH_4$ (740 mg,

19.56 mmol, 2.28 equiv) was added at 0 °C. The resulting solution was stirred for 4 h at 0 °C in a water/ice bath. The reaction was then quenched by the addition of 10 mL of water. The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 1.85 g (87%) of **174.3** as a yellow solid.

[00834] **Synthesis of compound 174.4.** Into a 50-mL round-bottom flask was placed a solution of **174.3** (320 mg, 1.29 mmol, 1.00 equiv) in dichloromethane (20 mL). Then Et_3N (0.223 g, 2.21 mmol, 1.70 equiv) and methanesulfonyl chloride (222 mg, 1.94 mmol, 1.50 equiv) were added to the above mixture at 0°C. The resulting solution was stirred for 5 h at 0°C in a water/ice bath. The reaction was then quenched by the addition of 15 mL of water. The resulting solution was extracted with 3x40 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:4). Purification afforded 0.112 g (33%) of **174.4** as a yellow oil.

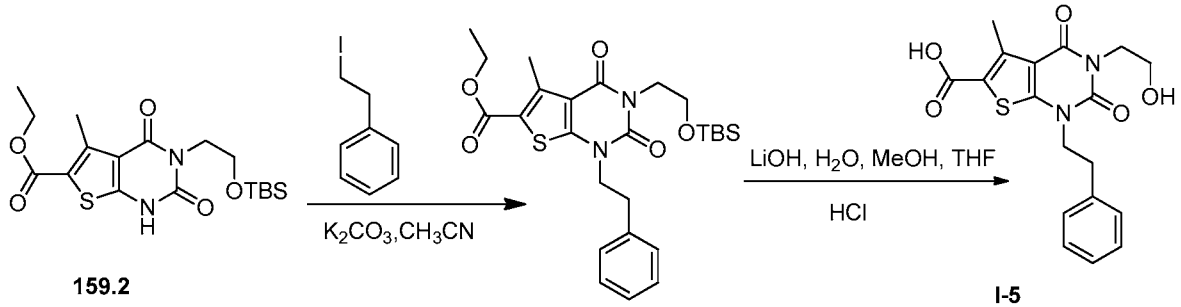
[00835] **Synthesis of compound 174.5.** Into a 25-mL round-bottom flask was placed CH_3CN (5 mL), NaI (0.005 g), potassium carbonate (105 mg, 0.76 mmol, 2.02 equiv), **159.2** (155 mg, 0.38 mmol, 1.00 equiv) and **174.4** (100 mg, 0.38 mmol, 1.00 equiv). The resulting solution was stirred overnight at 50°C in an oil bath. The reaction was then quenched by the addition of 40 mL of water. The resulting solution was extracted with 3x60 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). Purification afforded 0.143 g (59%) of **174.5** as a white solid.

[00836] **Synthesis of compound 174.6.** Into a 25-mL round-bottom flask was placed dichloromethane (10 mL), **174.5** (143 mg, 0.22 mmol, 1.00 equiv) and CF_3COOH (2 mL). The resulting solution was stirred overnight at room temperature and then concentrated under vacuum. This resulted in 0.126 g (crude) of crude **174.6** as a yellow solid.

[00837] **Synthesis of Compound I-51.** Into a 25-mL round-bottom flask was placed ethanol (5 mL), potassium carbonate (276 mg, 2.00 mmol, 8.30 equiv) and **I-51** (126 mg, 0.24 mmol, 1.00 equiv). The resulting solution was stirred overnight at room temperature, concentrated under vacuum and diluted with 50 mL of H_2O. The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined, dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by re-crystallization from ethyl

acetate:hexane(1/10). This resulted in 0.043 g (42%) of **I-51** as a white solid. MS (ES): *m/z* 428 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.27 (t, 3H), 2.85 (s, 3H), 3.96 (m, 2H), 4.34 (m, 4H), 5.29 (s, 2H), 6.56 (s, 1H), 7.25 (m, 2H), 7.38 (m, 1H), 7.70 (s, 1H), 8.23 (s,1H).

[00838] Example 175: Synthesis of 3-[2-[(tert-butyldimethylsilyl)oxy]ethyl]-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylic acid (I-5).

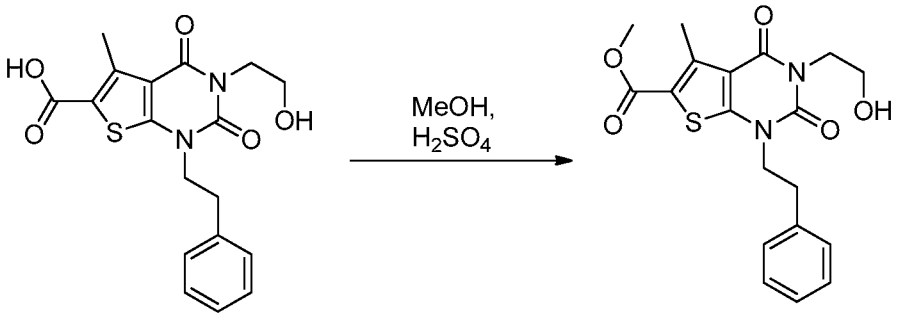


159.2 175.1 I-5

[00839] Synthesis of compound 175.1. Into a 100-mL round-bottom flask was placed a solution of **159.2** (1.2 g, 2.91 mmol, 1.00 equiv) in CH_3CN (50 mL), (2-iodoethyl)benzene (1.35 g, 5.82 mmol, 2.00 equiv) and potassium carbonate (1.2 g). The resulting solution was heated to reflux overnight. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:20). Purification afforded 1.5 g (95%) of **175.1** as a white solid.

[00840] Synthesis of Compound I-5. Into a 100-mL round-bottom flask was placed **175.1** (500 mg, 0.9676 mmol, 1.00 equiv), tetrahydrofuran (5 mL), methanol (5 mL), water (5 mL) and LiOH (0.07 g). The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The pH value of the solution was adjusted to 1 with hydrogen chloride. The mixture was stirred for 1 h at room temperature. The solids were collected by filtration. The filter cake was washed with ethanol. 300 mg (63%) of **I-5** were obtained as a white solid. MS (ES): *m/z* 375 $(M+1)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 2.74 (s, 3H), 3.00 (t, *J*=7.2, 2H), 3.51 (t, *J*=6.3, 2H), 3.96 (t, *J*=6.6, 2H), 4.09 (t, *J*=7.2, 2H), 4.78 (s, 1H), 7.20-7.33 (m, 5H).

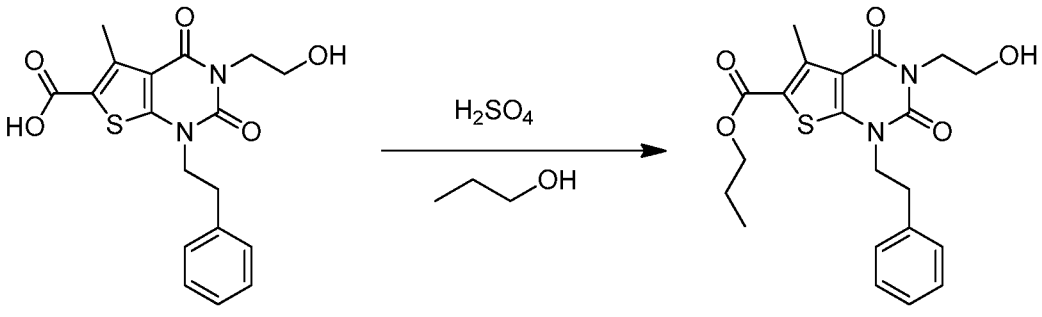
[00841] Example 176: Synthesis of methyl 3-(2-hydroxyethyl)-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-37).



I-5 I-32

Into a 100-mL round-bottom flask was placed **I-5** (200 mg, 0.53 mmol, 1.00 equiv), methanol (20 mL) and sulfuric acid (0.1 mL). The resulting solution was stirred for 4 days at 50 °C. The reaction was then quenched by the addition of 5 mL of water. The pH value of the solution was adjusted to >7 with sodium carbonate (aq.). The resulting solution was extracted with 3x20 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The crude product (200 mg) was purified by preparative HPLC under the following conditions (SHIMADZU): column: SunFire Prep C18, 19*150mm 5um; mobile phase: water with 0.05% NH_4HCO_3 and CH_3CN (8.0% CH_3CN up to 55.0% in 20 min); detector: 254/220 nm. 20.2 mg (10%) of **I-32** were obtained as a white solid. MS (ES): *m/z* 389 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ 2.83(s, 3H), 3.10 (t, *J*=7.5, 2H), 3.74 (t, *J*=6.3, 2H), 3.87 (s, 3H), 4.14-4.20 (m, 4H), 7.22-7.30 (m, 5H).

[00842] Example 177: Synthesis of propyl 3-(2-hydroxyethyl)-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-41).

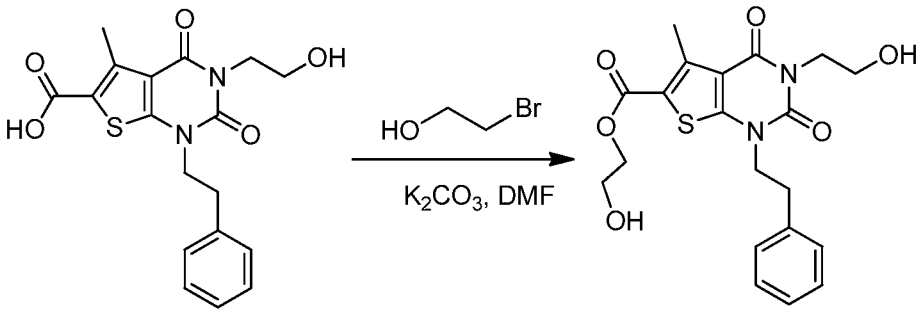


I-5 I-41

Compound **I-41** was prepared from **I-5** and 1-propanol in a manner analogous to the synthesis of Compound **I-32** (Example 176). This resulted in 4.7 mg (2%) of **I-41** as a white solid. MS (ES): *m/z* 417 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.05 (t, *J*=7.6, 3H), 1.78 (m, *J*=7.2, 2H), 2.83

(s, 3H), 3.11 (t, *J*=7.6, 2H), 3.75 (t, *J*=6.8, 2H), 4.15-4.21 (m, 4H), 4.25 (t, *J*=6.4, 2H), 7.23-7.32 (m, 5H).

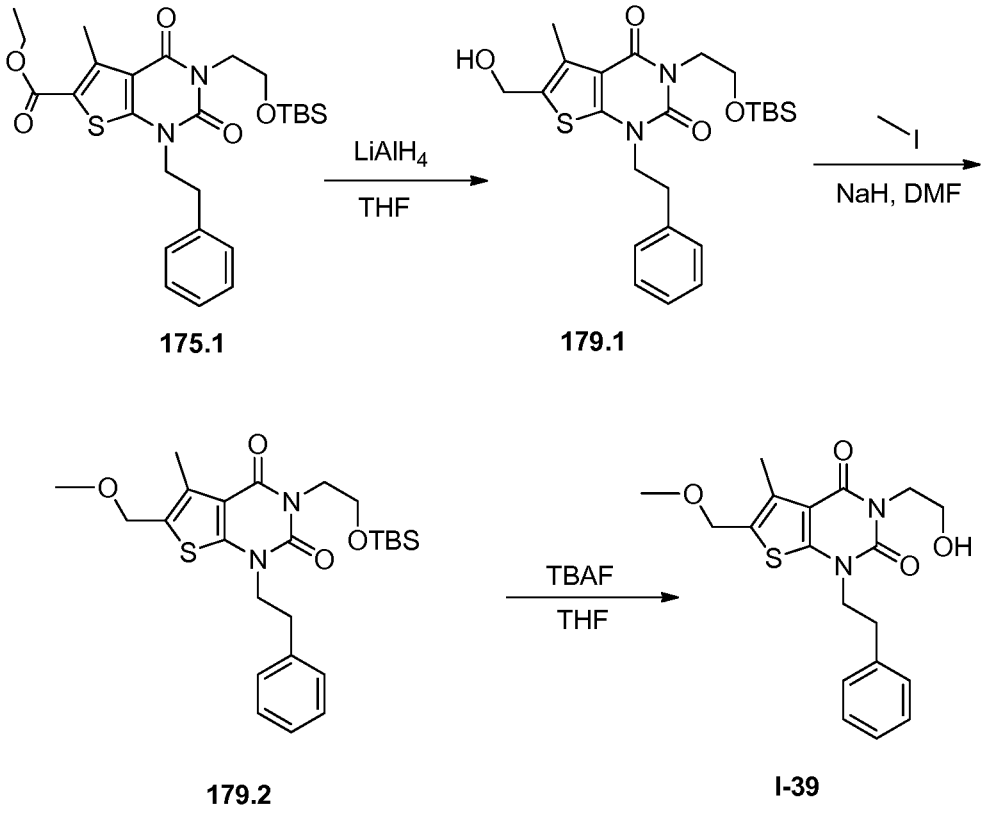
[00843] Example 178: Synthesis of 2-hydroxyethyl 3-(2-hydroxyethyl)-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-42).



I-5 I-42

[00844] Into a 100-mL 3-necked round-bottom flask was placed **I-5** (200 mg, 0.53 mmol, 1.00 equiv), potassium carbonate (221 mg, 1.60 mmol, 2.99 equiv), 2-bromoethan-1-ol (100 mg, 0.80 mmol, 1.50 equiv) and N,N-dimethylformamide (10 mL). The resulting solution was stirred overnight at 80 °C. The reaction mixture was cooled. The resulting mixture was concentrated under vacuum. The crude product (200 mg) was purified by preparative HPLC under the following conditions (SHIMADZU): column: SunFire Prep C18, 19*150 mm 5 μm; mobile phase: water with 0.05% NH_4HCO_3 and CH_3CN (6.0% CH_3CN up to 60.0% in 14 min); detector: 254/220 nm. This resulted in 30.7 mg (14%) of **I-42** as a white solid. MS (ES): *m/z* 419 $(M+H)^+$, 441 $(M+Na)^+$, 482 $(M+Na+ CH_3CN)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 2.77 (s, 3H), 3.01 (t, *J*=7.6, 2H), 3.52 (t, *J*=6.0, 2H), 3.68 (t, *J*=4.8, 2H), 4.11 (t, *J*=7.6, 2H), 3.02 (t, *J*=7.6, 2H), 4.26 (t, *J*=4.8, 2H), 3.02 (t, *J*=7.6, 2H), 4.78 (t, 1H), 4.92 (t, 1H), 7.24-7.33 (m, 5H).

[00845] Example 179: Synthesis of 3-(2-hydroxyethyl)-6-(methoxymethyl)-5-methyl-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-2,4-dione (I-39).



175.1 179.1

179.2 I-39

[00846] **Synthesis of compound 179.1.** Into a 100-mL 3-necked round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed a solution **175.1** (1 g, 1.94 mmol, 1.00 equiv) in tetrahydrofuran (20 mL). This was followed by the addition of $LiAlH_4$ (100 mg, 2.63 mmol, 1.36 equiv) at -78 °C. The resulting solution was stirred for 2 h at room temperature. The reaction was then quenched by the addition of 50 mL of NH_4Cl (aq.). The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:2). This resulted in 0.5 g (54%) of **179.1** as a light yellow solid.

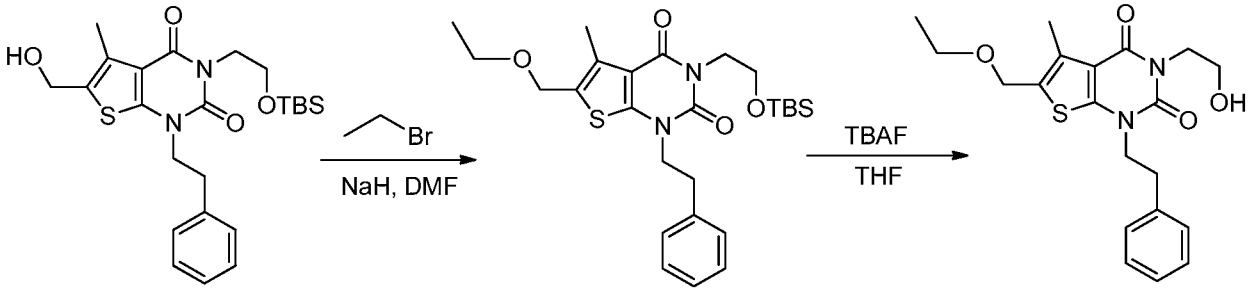
[00847] **Synthesis of compound 179.2.** Into a 10-mL sealed tube was placed a solution of **179.1** (150 mg, 0.31 mmol, 1.00 equiv), N,N-dimethylformamide (5 mL), and sodium hydride (19 mg, 0.55 mmol, 1.76 equiv, 70%). The resulting solution was stirred for 10 min at room temperature. This was followed by the addition of iodomethane (67 mg, 0.47 mmol, 1.50 equiv) dropwise with stirring. The resulting solution was allowed to react, with stirring, for an additional 2 h at room temperature. The reaction was then quenched by the addition of 5 mL of NH_4Cl(aq.). The resulting solution was extracted with 3x10 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel

column with ethyl acetate/petroleum ether (1:10). Purification afforded 90 mg (59%) of **179.2** as a white solid.

[00848] Synthesis of compound I-39. Into a 10-mL sealed tube was placed a solution of **179.2** (90 mg, 0.18 mmol, 1.00 equiv) in tetrahydrofuran (2.5 mL) and TBAF (200 mg). The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:2). Purification afforded 34.7 mg (50%) of **I-39** as a white solid. MS (ES): *m/z* 375 $(M+H)^+$, 397 $(M+Na)^+$.

^{1}H NMR (300 MHz, DMSO-d_6): δ 2.37 (s, 3H), 2.98 (t, *J*=7.5, 2H), 3.26 (s, 3H), 3.50 (q, *J*=6.6, 2H), 3.96 (t, *J*=6.6, 2H), 4.06 (t, *J*=7.5, 2H), 4.51 (s, 2H), 4.76 (t, *J*=6.0, 1H), 7.20-7.33 (m, 5H).

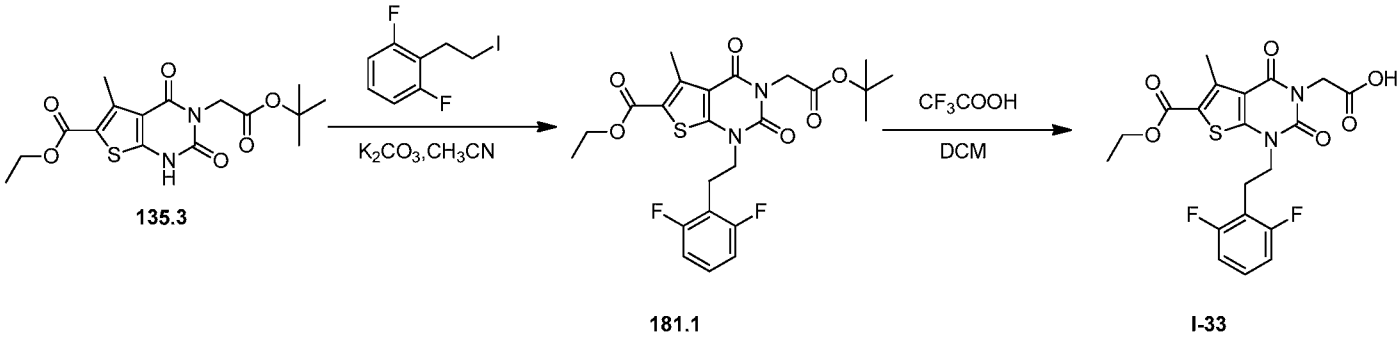
[00849] Example 180: Synthesis of 6-(ethoxymethyl)-3-(2-hydroxyethyl)-5-methyl-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-2,4-dione (I-38).



179.1 180.1 I-38

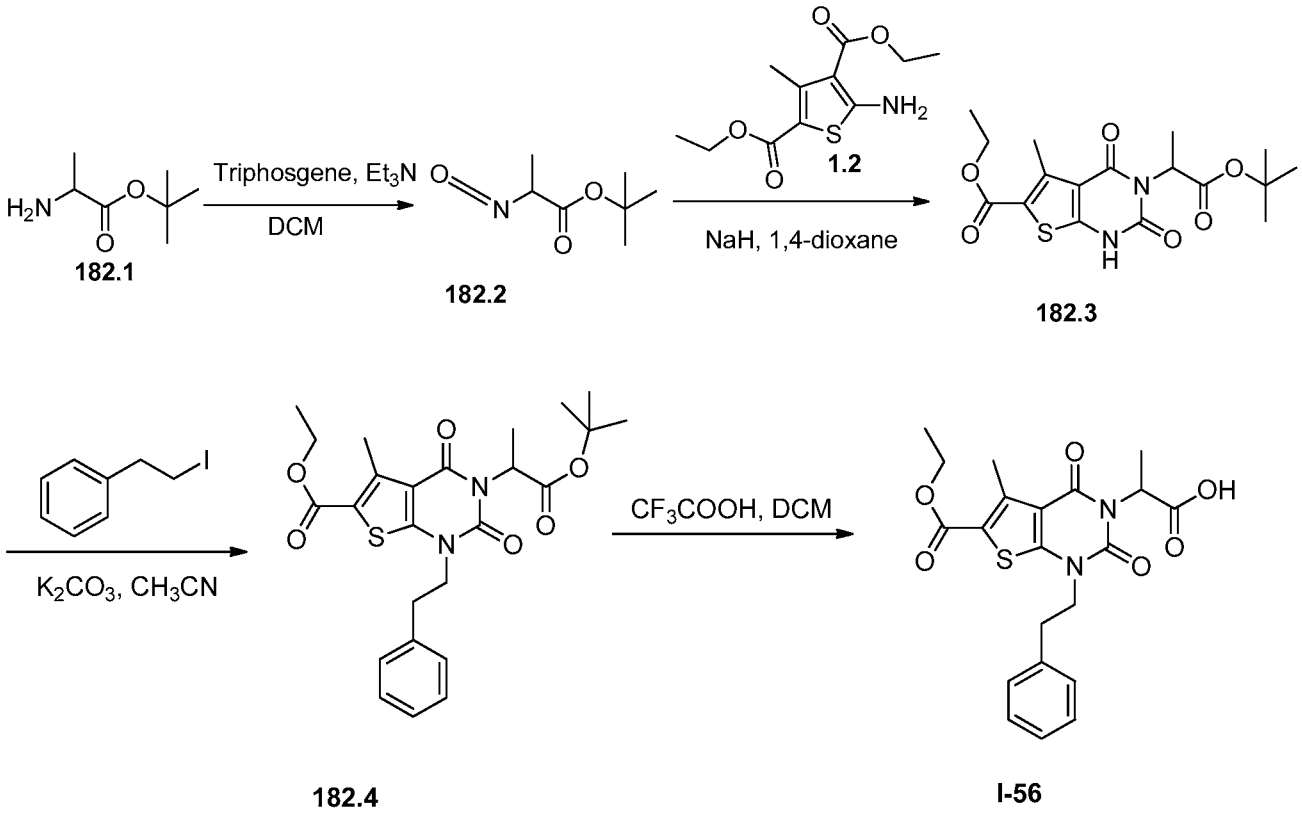
Compound **I-38** was prepared from **179.1** and ethyl bromide in a manner analogous to the synthesis of Compound **I-39** (Example 179). Isolated 50.5 mg of a white solid in 42% overall yield. MS (ES): *m/z* 389 $(M+H)^+$, 411 $(M+Na)^+$, 452 $(M+Na+CH_3CN)^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.13 (t, *J*=7.2, 3H), 2.35 (s, 3H), 2.98 (t, *J*=7.5, 2H), 3.42-3.51 (m, 4H), 4.14-4.20 (m, 4H), 4.54 (s, 2H), 4.74 (s, 1H), 7.20-7.32 (m, 5H).

[00850] Example 181: Synthesis of 2-[1-[2-(2,6-difluorophenyl)ethyl]-6-(ethoxycarbonyl)-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-33).



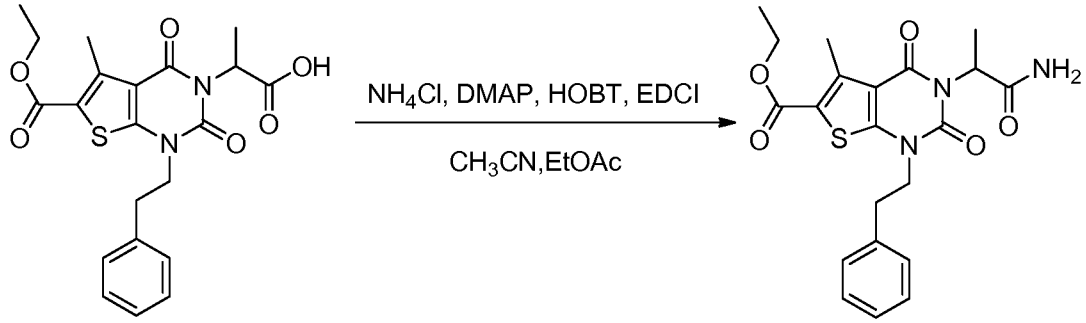
Compound **I-33** was prepared from **135.3** and 1,3-difluoro-2-(2-iodoethyl)benzene in a manner analogous to the synthesis of **136.2**. Isolated 36 mg of a white solid in 30% overall yield. MS (ES): *m/z* 453 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.32-1.40(t, 3H), 2.82 (s, 3H), 3.21-3.26 (t,2H), 4.22-4.27 (t, 2H), 4.31-4.38 (q, 2H), 4.67 (s, 2H), 6.91-6.96 (t, 2H), 7.26-7.31 (m, 1H). ^{19}F-NMR (300 MHz,CD_3OD): δ 117.76.

[00851] Example 182: Synthesis of 2-[6-(ethoxycarbonyl)-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-56).



[00852] Compound **I-56** was prepared from **182.1** and **1.2** in a manner analogous to compound **136.2** (Examples 135 and 136). Isolated 1.4 g of a white solid in 42% overall yield. MS (ES): *m/z* 431 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 1.30 (t, *J*=7.2, 3H), 1.41 (d, *J*=6.8, 3H), 2.75 (s, 3H), 3.01 (t, *J*=7.2, 2H), 4.13 (t, *J*=7.2, 2H), 4.29 (q, *J*=7.2, 2H), 5.39 (q, *J*=6.8, 1H), 7.20-7.30 (m, 5H), 12.70 (s, 1H).

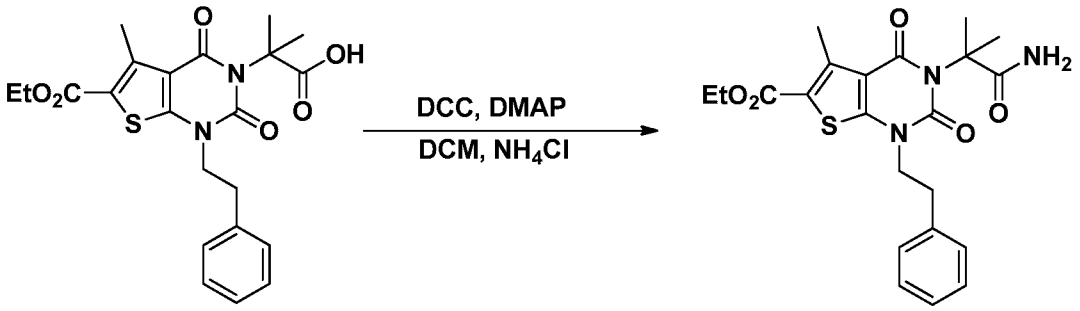
[00853] Example 183: Synthesis of ethyl 3-(1-carbamoylethyl)-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-69).



182.4 **I-69**

[00854] Into a 100-mL round-bottom flask was placed 4-dimethylaminopyridine (82 mg, 0.67 mmol, 1.44 equiv), **182.4** (200 mg, 0.46 mmol, 1.00 equiv), NH_4Cl (1 g, 18.70 mmol, 40.24 equiv), EDCI (130 mg, 0.68 mmol, 1.46 equiv), CH_3CN (10 mL), ethyl acetate (10 mL) and HOBT (100 mg, 0.74 mmol, 1.59 equiv). The resulting solution was stirred for 5 h at room temperature. The reaction was then quenched by the addition of 20 mL of water. The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined and dried over anhydrous magnesium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (20:1). This resulted in 0.12 g (60%) of **I-69** as a white solid. MS (ES): *m/z* 430 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 1.25(t, *J*=7.2 Hz, 3H), 1.36 (d, *J*=6.8 Hz, 3H), 2.68 (s, 3H), 2.97 (t, *J*=7.2 Hz, 2H), 4.07 (t, *J*=7.2 Hz, 2H), 4.23 (q, *J*=7.2 Hz, 2H), 5.30 (q, *J*=7.2 Hz, 1H), 7.15-7.24 (m, 5H).

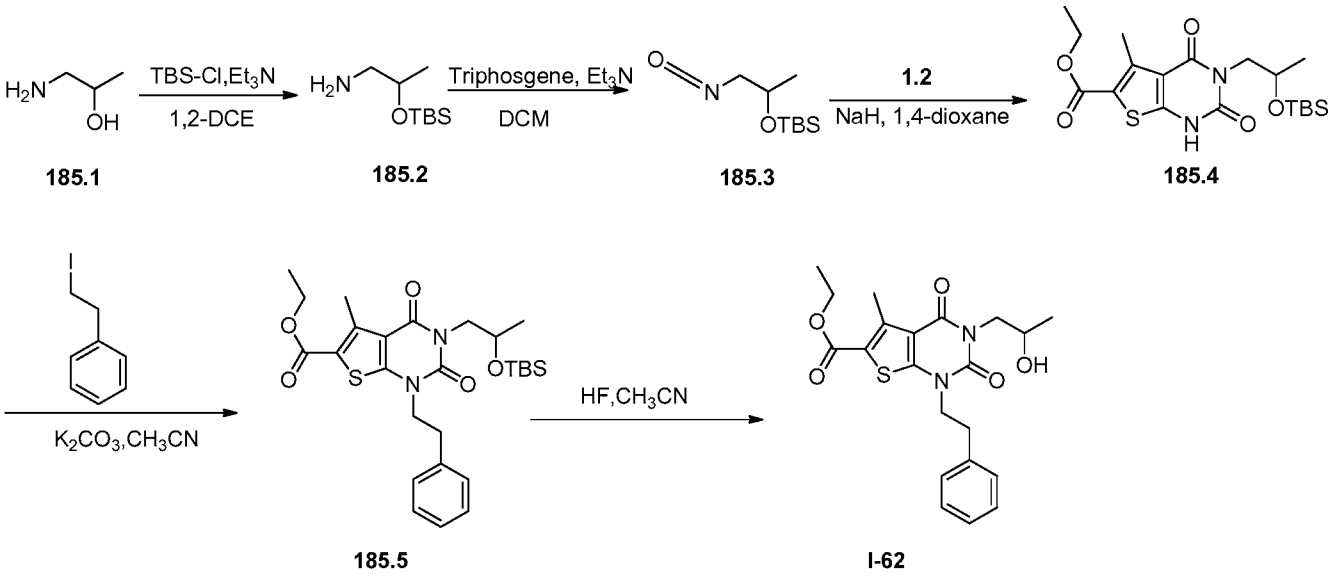
[00855] Example 184: Synthesis of ethyl 3-(1-carbamoyl-1-methylethyl)-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-107).



I-70 I-107

[00856] Compound **I-107** was prepared from **I-70** (Example 120) and ammonium chloride in a manner analogous to the synthesis of Compound **I-121** (Example 4). Isolated 70 mg of a white solid in 70% yield. MS (ES): *m/z* 466 $(M+Na)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.37 (t, *J*=7.2, 3H), 1.80 (s, 6H), 2.76 (s, 3H), 3.07 (t, *J*=7.2, 2H), 4.12 (t, *J*=7.2, 2H), 4.33 (q, *J*=7.2, 2H), 7.22-7.34 (m, 5H).

[00857] Example 185: Synthesis of ethyl 3-(2-hydroxypropyl)-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-62).

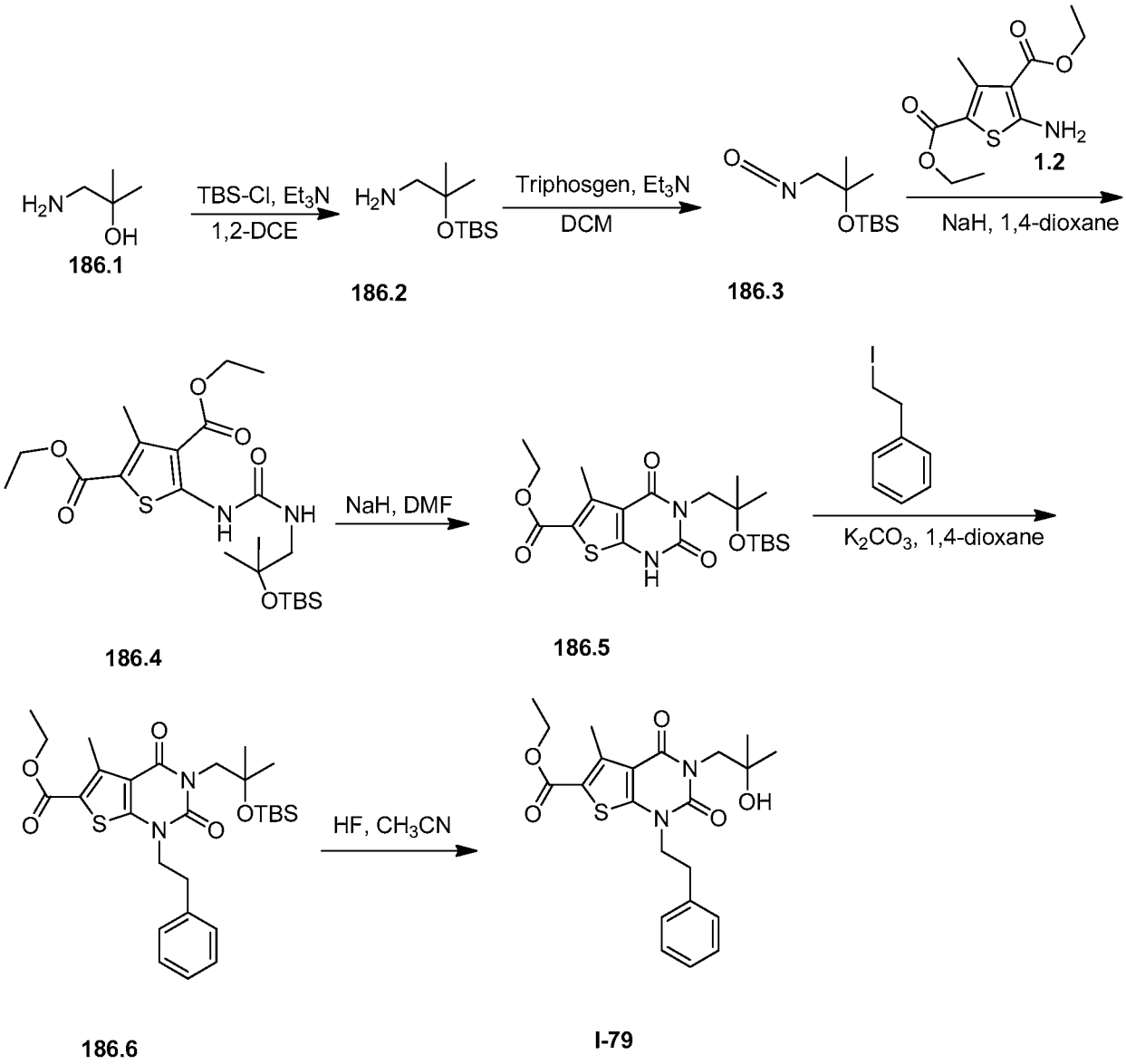


185.1 185.2 185.3 185.4

185.5 I-62

[00858] Compound **I-62** was prepared from **185.1** and **1.2** in a manner analogous to the synthesis of Compound **I-34** (Example 169). Isolated 0.34 g of a white solid in 8% overall yield. MS (ES): *m/z* 417 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 1.02 (d, *J*=7.6Hz, 3H), 1.29 (t, *J*=9.6Hz, 3H), 2.75 (s, 3H), 2.99 (t, *J*=9.6 Hz, 2H), 3.69 (q, *J*=10.8 Hz, 1H), 3.94 (m, J=7.2 Hz, 2H), 4.27 (q, *J*=9.2 Hz, 2H), 4.15 (t, *J*=10.0 Hz, 2H), 4.77 (s, 1H), 7.19-7.32 (m, 5H).

[00859] Example 186: Synthesis of ethyl 3-(2-hydroxy-2-methylpropyl)-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-79).



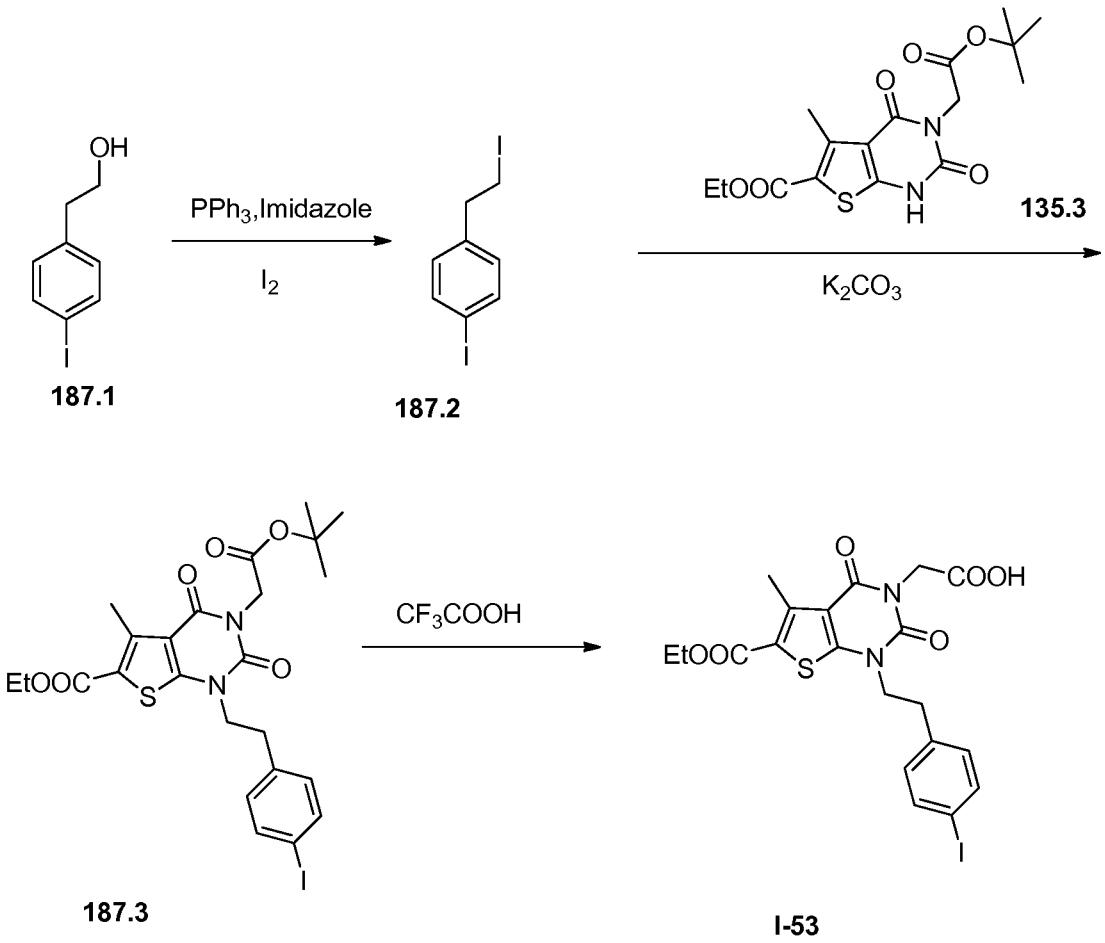
186.1 186.2 186.3 1.2

186.4 186.5

186.6 I-79

Compound **I-79** was prepared from **186.1** and **1.2** in a manner analogous to the synthesis of Compound **I-34** (Example 169). Isolated 80 mg of a white solid in 10% overall yield. MS (ES): *m/z* 431 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 1.07(s, 6H), 1.30 (t, *J*=7.2 Hz, 3H), 2.76 (s, 3H), 3.01 (t, *J*=7.2 Hz, 2H), 3.96 (s, 2H), 4.13 (t, *J*=7.2 Hz, 2H), 4.29 (q, 2H), 4.41 (s, 1H), 7.20-7.32 (m, 5H).

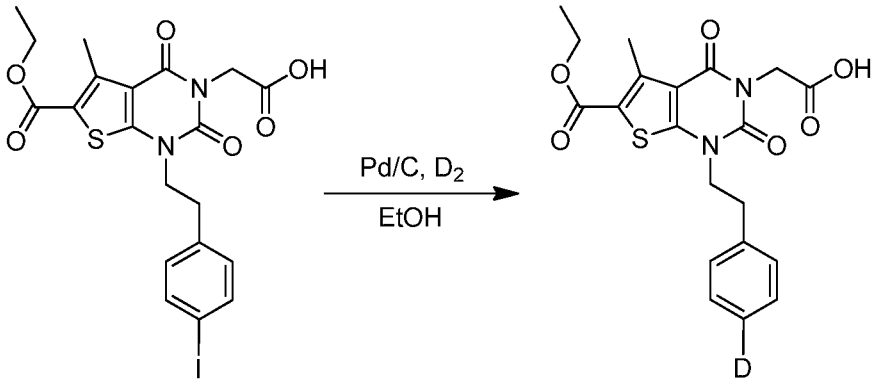
[00860] Example 187: Synthesis of 2-[6-(ethoxycarbonyl)-1-[2-(4-iodophenyl)ethyl]-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-53).



[00861] **Synthesis of compound 187.2. 187.2** was prepared from **187.1** in a manner analogous to the synthesis of **160.2**. Isolated 2.23 g of a white solid in 78% yield.

[00862] **Synthesis of Compound I-53. I-53** was prepared from **187.2** and **135.3** in a manner analogous to the synthesis of **136.2**. Isolated 0.134 g of an off-white solid in 57% overall yield from **135.3**. MS (ES): *m/z* 543 $(M+H)^+$. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.43 (t, 3H), 2.88 (s, 3H), 3.04 (m, 2H), 4.14 (m, 2H), 4.38 (m, 2H), 4.85 (s, 2H), 7.03 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H).

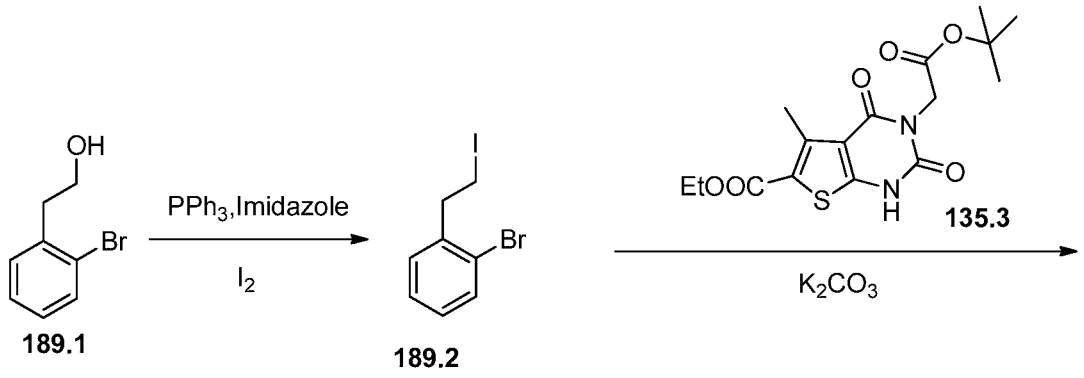
[00863] **Example 188: Synthesis of 2-(1-(4-deuterophenethyl)-6-(ethoxycarbonyl)-5-methyl-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)acetic acid (I-66).**



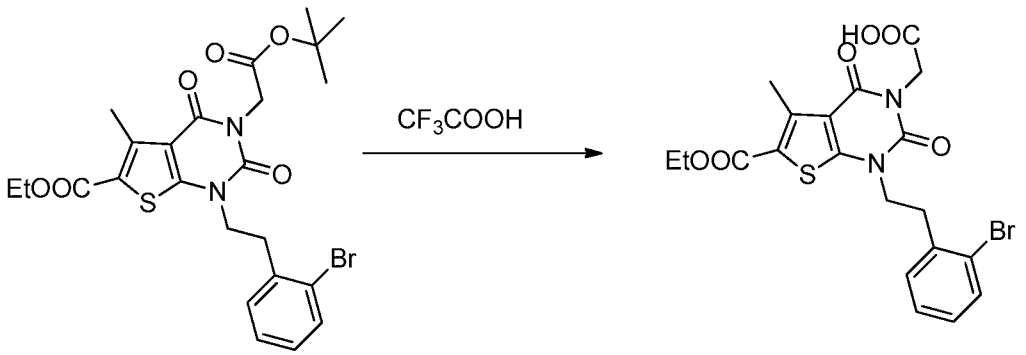
I-53 I-66

[00864] Into a 50-mL round-bottom flask was placed ethanol (20 mL), **I-53** (Example 187; 73 mg, 0.13 mmol, 1.00 equiv). This was followed by the addition of 10% palladium on carbon (100 mg) under nitrogen. The flask was evacuated and flushed three times with nitrogen, followed by flushing with deuterium gas. The mixture was stirred overnight at room temperature under an atmosphere of deuterium gas. The solids were filtered out. The resulting mixture was concentrated under vacuum. The crude product (80 mg) was purified by preparative HPLC under the following conditions (SHIMADZU): column: SunFire Prep C18, 19*150 mm 5 μm; mobile phase: water with 0.05% NH_4HCO_3 and CH_3CN (5.0% CH_3CN up to 53.0% in 16 min); detector: 254/220 nm. This resulted in 0.04 g (71%) of **I-66** as a white solid. MS (ES): *m/z* $(M+H)^+$ 418. ^1H NMR (300 MHz, $CDCl_3$): δ 1.41 (t, *J*=7.2, 3H), 2.87 (s, 3H), 3.09 (t, *J*=8.1, 2H), 4.16 (t, 2H), 4.38 (q, *J*=7.2, 2H), 4.82 (s, 2H), 7.26-7.35 (m, 4H).

[00865] Example 189: Synthesis of 2-[1-[2-(2-bromophenyl)ethyl]-6-(ethoxycarbonyl)-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-54).



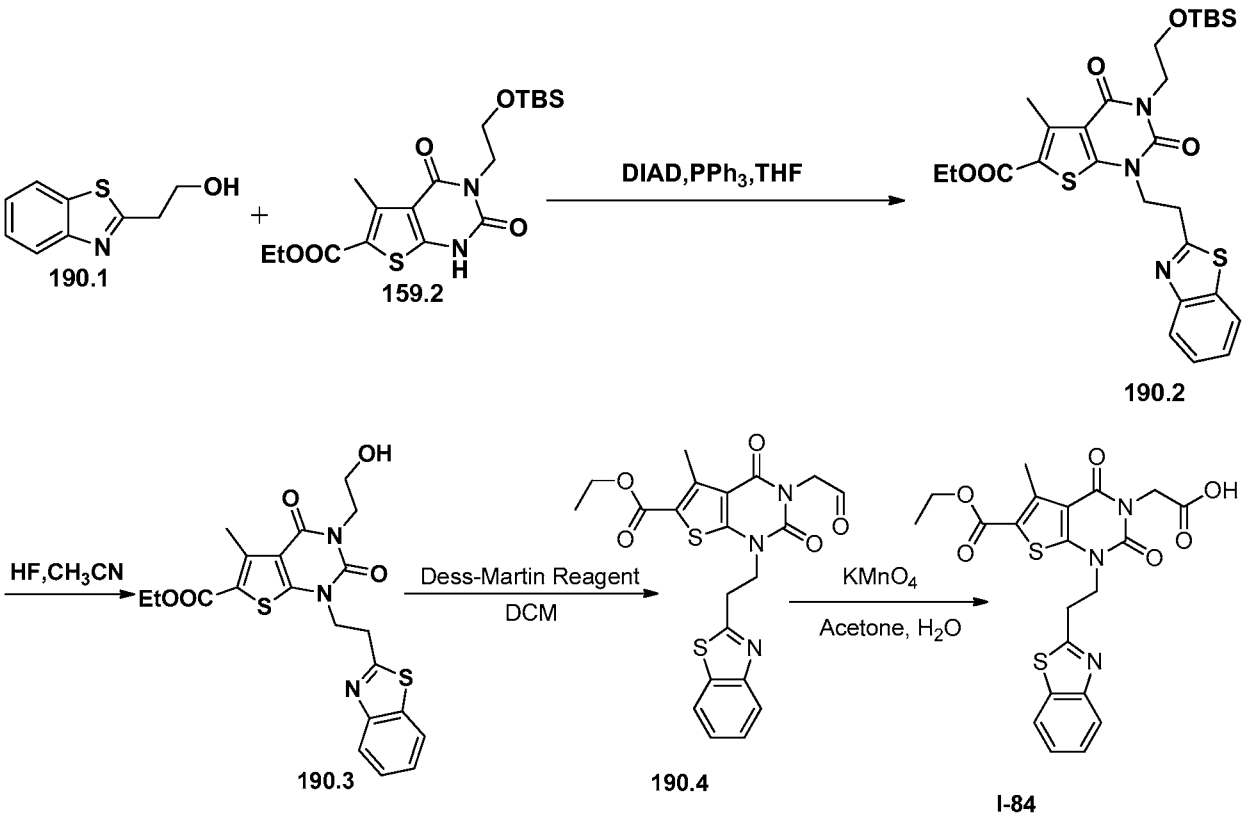
189.1 189.2 135.3



189.3 I-54

Compound **I-54** was prepared from **189.1** and **135.3** in a manner analogous to the synthesis of **I-53** (Example 187). Isolated 0.2 g of a white solid in 38% overall yield from **135.3**. MS (ES): *m/z* 495 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.38 (t, 3H), 2.85 (s, 3H), 3.24 (t, 2H), 4.24 (t, 2H), 4.37 (t, 2H), 4.81 (s, 2H), 7.11 (m, 1H), 7.20 (m, 2H), 7.54 (m, 1H).

[00866] Example 190: Synthesis of 2-[1-[2-(1,3-benzothiazol-2-yl)ethyl]-6-(ethoxycarbonyl)-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-84).



190.1 159.2 190.2 190.3 190.4 I-84

[00867] **Synthesis of compound 190.2.** Into a 25-mL round-bottom flask flushed with N_2 was placed tetrahydrofuran (5 mL), 2-(1,3-benzothiazol-2-yl)ethan-1-ol (358 mg, 2.00 mmol, 2.00 equiv), PPh_3 (524 mg, 2.00 mmol, 2.00 equiv), DIAD (292 mg, 1.44 mmol, 1.45 equiv) and **159.2** (412 mg, 1.00 mmol, 1.00 equiv). The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 50 mL of water. The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). This resulted in 0.350 g (61%) of **190.2** as a white solid.

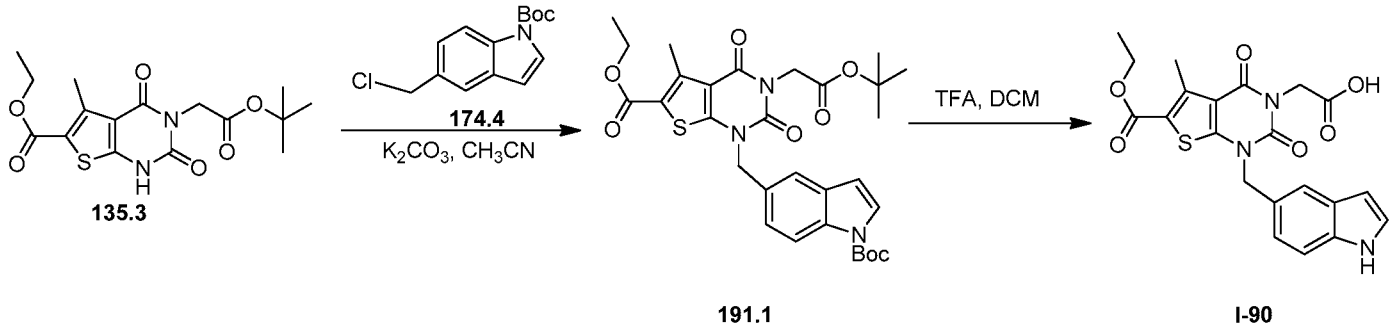
[00868] **Synthesis of compound 190.3.** Into a 50-mL round-bottom flask was placed CH_3CN (15 mL), **190.2** (352 mg, 0.61 mmol, 1.00 equiv) and HF (5 mL). The resulting solution was stirred for 2 h at room temperature. The reaction was then quenched by the addition of 20 mL of sodium bicarbonate (sat.). The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product (50 mg) was purified by preparative HPLC under the following conditions (SHIMADZU): column: SunFire Prep C18, 19*150 mm 5 μm; mobile phase: water with 0.05% TFA and CH_3CN (12.0% CH_3CN up to 58.0% in 10 min); detector: 254/220 nm. 142 mg product was obtained. This resulted in 14.7 mg (5%) of **190.3** as a white solid. MS (ES): *m/z* 460 $(M+H)^+$. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.39 (m, 3H), 2.89 (s, 3H), 3.62 (m, 2H), 3.90 (m, 2H), 4.28 (m, 2H), 4.36 (m, 2H), 4.53 (m, 2H), 7.42 (m, 1H), 7.49 (m, 1H), 7.88 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 8.0 Hz,1H).

[00869] **Synthesis of compound 190.4.** Into a 50-mL round-bottom flask was placed **190.3** (74 mg, 0.16 mmol, 1.00 equiv), dichloromethane (10 mL) and Dess-Martin reagent (740 mg, 1.75 mmol, 10.84 equiv). The resulting solution was stirred overnight at 40 °C in an oil bath. The solids were filtered out. The filtrate was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:2). This resulted in 87 mg (crude) of **190.4** as a white solid.

[00870] **Synthesis of Compound I-84.** Into a 10-mL round-bottom flask was placed **190.4** (87 mg, 0.19 mmol, 1.00 equiv), acetone (3 mL), H_2O (2 mL) and tetraoxo(potassio)manganese (25.4 mg, 0.16 mmol, 0.85 equiv). The resulting solution was stirred for 4 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel

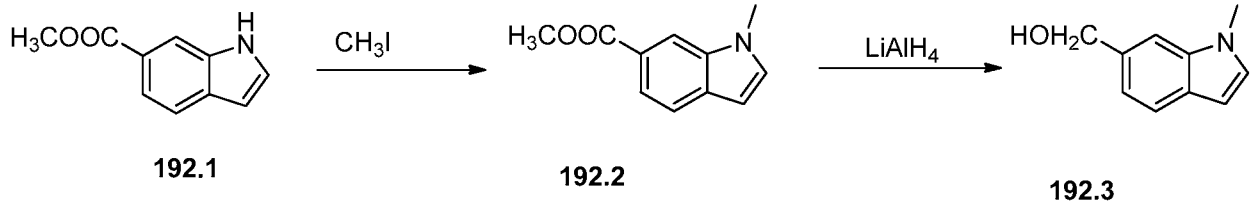
column with ethyl acetate/petroleum ether (1:2). This resulted in 16 mg (18%) of **I-84** as a white solid. MS (ES): *m/z* 474 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 1.27 (t, *J*=7.2, 3H), 2.76 (s, 3H), 3.57 (t, *J*=7.2, 2H), 4.27 (q, *J*=7.2, 2H), 4.44 (t, *J*=7.2, 2H), 4.53 (s, 3H), 7.43 (t, *J*=7.6, 1H), 7.51 (t, *J*=7.2, 1H), 7.95 (d, *J*=8.0, 1H), 8.08 (d, *J*=7.6, 1H).

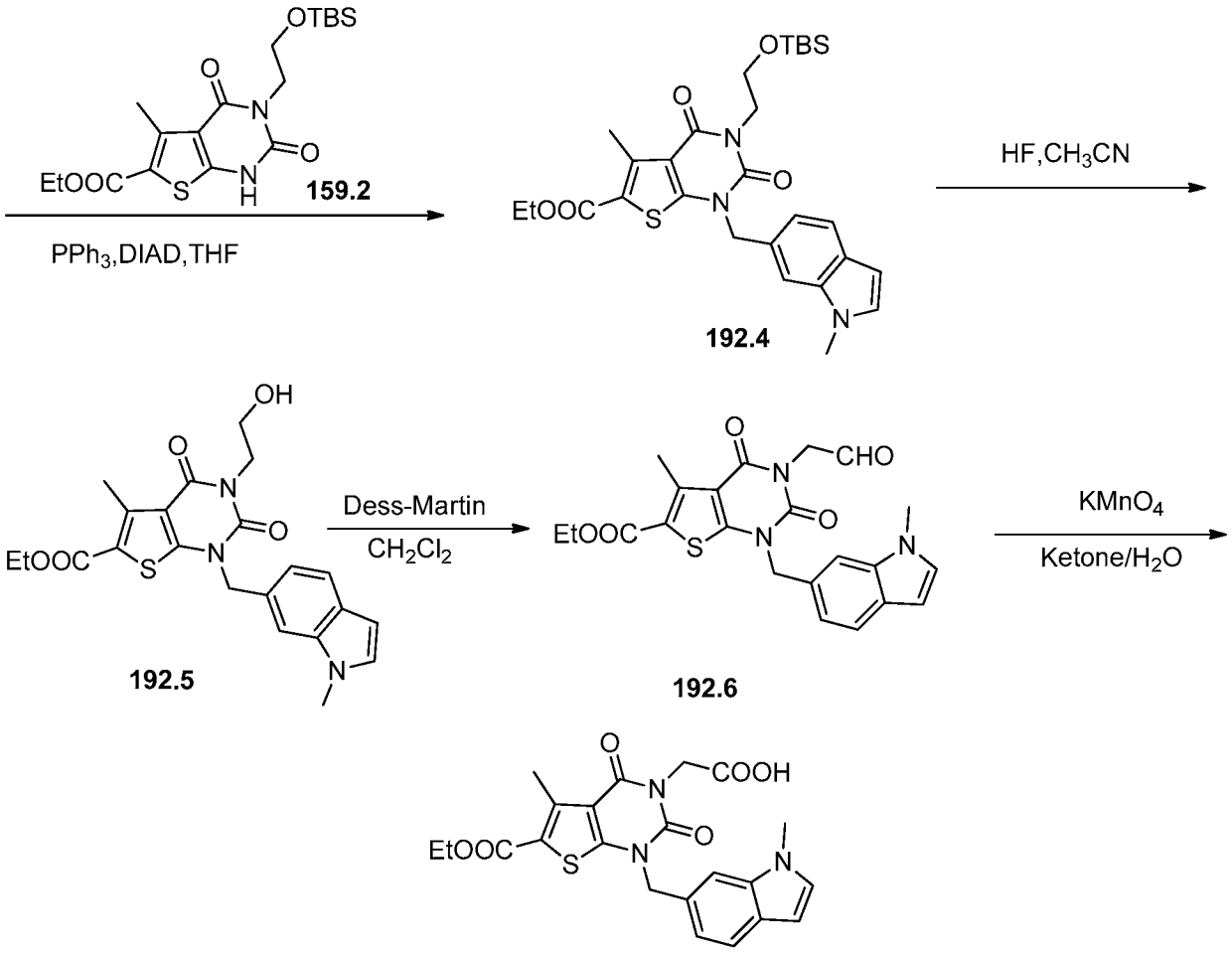
[00871] Example 191: Synthesis of 2-[6-(ethoxycarbonyl)-1-(1H-indol-5-ylmethyl)-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-90).



[00872] Compound **I-90** was prepared from **135.3** and **174.4** in a manner analogous to the synthesis of **136.2**. Isolated 11 mg of an off-white solid in 12% yield from **135.3**. MS (ES): *m/z* 442 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 1.25 (t, *J*=7.2, 3H), 2.75 (s, 3H), 4.23 (q, *J*=7.2, 2H), 4.46 (s, 2H), 5.28 (s, 2H), 6.40 (s, 1H), 7.08 (d, *J*=6.6, 1H), 7.34-7.39 (m, 2H), 7.52 (s, 1H), 11.14 (s, 3H).

[00873] Example 192: Synthesis of 2-[6-(ethoxycarbonyl)-5-methyl-1-[(1-methyl-1H-indol-6-yl)methyl]-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-74).





I-74

[00874] **Synthesis of compound 192.2.** Into a 500-mL round-bottom flask was placed N,N-dimethylformamide (200 mL) and methyl 1H-indole-6-carboxylate (7 g, 39.96 mmol, 1.00 equiv). Sodium hydride (1.9 g, 47.50 mmol, 1.19 equiv, 60%) was added at 0°C and stirring continued for 30 min at this temperature, whereupon CH_3I (6.8 g, 47.91 mmol, 1.20 equiv) was added. The resulting solution was stirred for 2 h at 0°C in a water/ice bath. The reaction was then quenched by the addition of 120 mL of water. The resulting solution was extracted with 3x150 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). Purification afforded 7.2 g (95%) of **192.2** as a yellow solid.

[00875] **Synthesis of compound 192.3.** Into a 500-mL round-bottom flask was placed tetrahydrofuran (300 mL) and **192.2** (5.67 g, 29.97 mmol, 1.00 equiv). To this solution $LiAlH_4$ (2.28 g, 60.08 mmol, 2.00 equiv) was added at -5°C. The resulting solution was stirred for 2 h at

-5°C in an ice/salt bath. The reaction was then quenched by the addition of 10 mL of ethyl acetate and 150 mL of NH_4Cl (aq). The resulting solution was extracted with 3x150 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:2). Purification afforded 5.0 g (98%) of **192.3** as a light yellow oil.

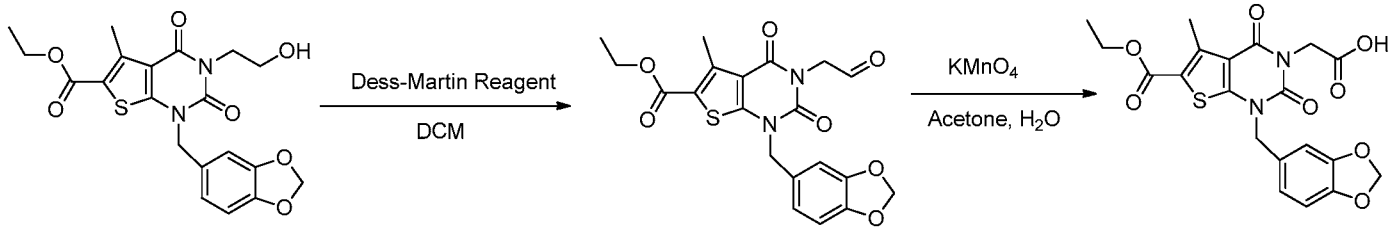
[00876] **Synthesis of compound 192.4.** Into a 25-mL round-bottom flask was placed a solution of **192.3** (322 mg, 2.00 mmol, 2.00 equiv) in tetrahydrofuran (5 mL), PPh_3 (524 mg, 2.00 mmol, 2.00 equiv), DIAD (292 mg, 1.44 mmol, 1.45 equiv) and **159.2** (412 mg, 1.00 mmol, 1.00 equiv). The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 50 mL of water. The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). This resulted in 0.12 g (22%) of **192.4** as a white solid.

[00877] **Synthesis of compound 192.5.** Into a 50-mL round-bottom flask was placed CH_3CN (15 mL), **192.4** (120 mg, 0.22 mmol, 1.00 equiv) and HF (3 mL). The resulting solution was stirred for 4 h at room temperature. The reaction was then quenched by the addition of 10 mL of $NaHCO_3$ (sat.). The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined, washed with sodium carbonate (aq.) and brine, dried and concentrated under vacuum. The crude product (80 mg) was purified by preparative HPLC under the following conditions (SHIMADZU): column: SunFire Prep C18, 19*150 mm 5 μm; mobile phase: water with 0.05% NH_4HCO_3 and CH_3CN (7.0% CH_3CN up to 63.0% in 18 min); detector: 254/220nm. This resulted in 0.075 g (79%) of **192.5** as a white solid. MS (ES): *m/z* 442 $(M+H)^+$. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.38 (t, 3H), 2.86 (s, 3H), 3.81 (s, 3H), 3.97 (m, 2H), 4.36 (m, 4H), 5.34 (s, 2H), 6.48 (d, *J* = 2.8Hz, 1H), 7.09 (d, *J* = 3.2 Hz, 1H), 7.16 (m,1H), 7.39 (s,1H), 7.61 (d, *J* = 8.0Hz, 1H).

[00878] **Synthesis of compound 192.6.** Into a 50-mL round-bottom flask was placed dichloromethane (20 mL), **192.5** (61 mg, 0.14 mmol, 1.00 equiv) and Dess-Martin reagent (157 mg, 0.37 mmol, 2.68 equiv). The resulting solution was heated to reflux overnight in an oil bath. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:2). This resulted in 0.035 g (58%) of **192.6** as a white solid.

[00879] Synthesis of Compound I-74. Into a 50-mL round-bottom flask was placed water (4 mL), acetone (20 mL) and **192.6** (35 mg, 0.08 mmol, 1.00 equiv). This was followed by the addition of $KMnO_4$ (13 mg, 0.08 mmol, 1.03 equiv). The resulting solution was stirred for 1 h at room temperature. The reaction was then quenched by the addition of 2 mL of ethyl acetate. The resulting mixture was concentrated under vacuum. The crude product (50 mg) was purified by preparative HPLC under the following conditions (SHIMADZU): column: SunFire Prep C18, 19*150 mm 5 μm; mobile phase: water with 0.05% TFA and CH_3CN (8.0% CH_3CN up to 57.0% in 16 min); detector: 254/220 nm. This resulted in 0.011 g (30%) of **I-74** as a white solid. MS (ES): *m/z* 456 $(M+H)^+$. ^1H NMR (DMSO-d_6, 400 MHz): δ 1.25 (t, 3H), 2.76 (s, 3H), 3.76 (s, 3H), 4.23 (m, 2H), 4.65 (s, 2H), 5.36 (s, 2H), 6.41 (d, J = 2.8 Hz, 1H), 7.00 (d, J = 7.2 Hz, 1H), 7.34 (d, J = 3.2 Hz, 1H), 7.42 (s, 1H), 7.52 (d, J = 8.0 Hz, 1H).

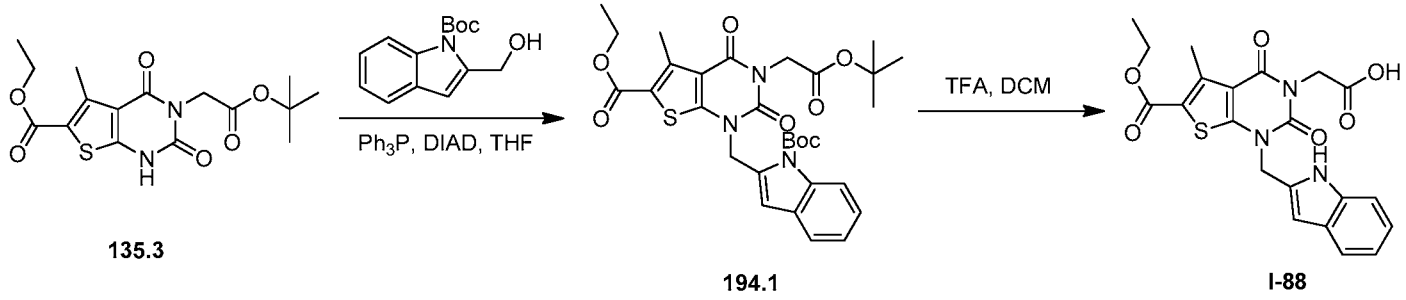
[00880] Example 193: Synthesis of 2-[1-(2H-1,3-benzodioxol-5-ylmethyl)-6-(ethoxycarbonyl)-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-50).



I-40 193.1 I-50

[00881] Compound **I-50** was prepared from Compound **I-40** (Example 173) in a manner analogous to the synthesis of Compound **I-74** (Example 192). Isolated 7.6 mg of a white solid in 6% yield from **I-40.** MS (ES): *m/z* 447 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.35 (t, J=7.2, 3H), 2.81 (s, 3H), 4.32 (q, J=7.2, 3H), 4.76 (s, 2H), 5.15 (s, 2H), 5.94 (s, 3H), 6.79-6.91 (m, 3H).

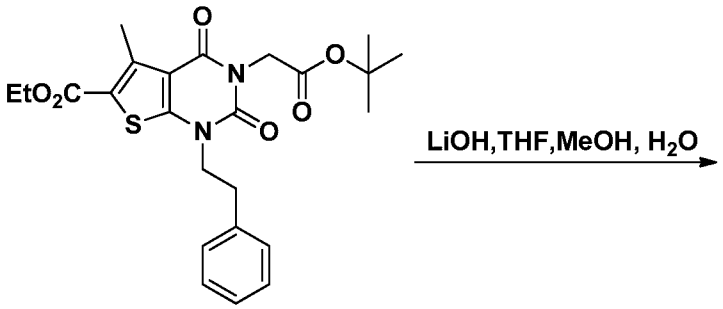
[00882] Example 194: Synthesis of 2-[6-(ethoxycarbonyl)-1-(1H-indol-2-ylmethyl)-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-88).



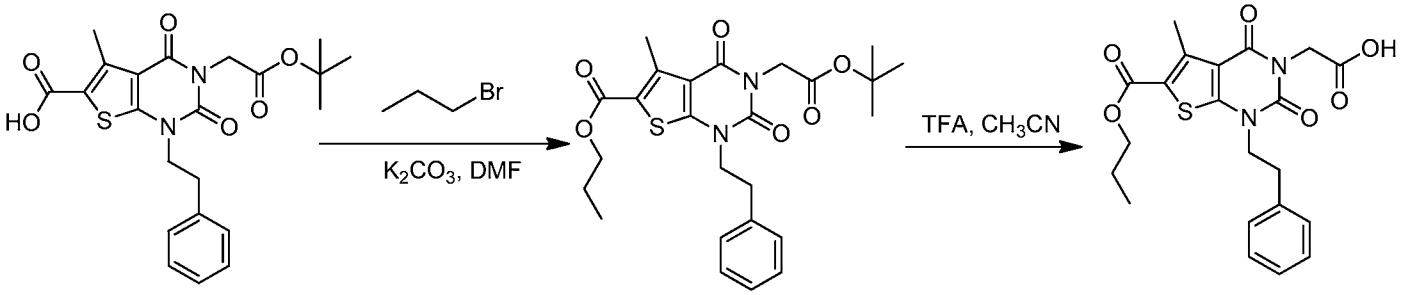
[00883] Synthesis of compound 194.1. Into a 25-mL round-bottom flask was placed a solution of **174.4** (322 mg, 1.30 mmol, 1.30 equiv) in tetrahydrofuran (5 mL), PPh_3 (524 mg, 2.00 mmol, 2.00 equiv), DIAD (292 mg, 1.44 mmol, 1.45 equiv) and **135.3** (368 mg, 1.00 mmol, 1.00 equiv). The resulting solution was stirred for 48 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:15). Purification afforded 0.244 g (41%) of **194.1** as a white solid.

[00884] Synthesis of Compound I-88. Into a 25-mL round-bottom flask was placed dichloromethane (10 mL), **194.1** (20 mg, 0.03 mmol, 1.00 equiv) and CF_3COOH (4 mL). The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The crude product (30 mg) was purified by preparative HPLC under the following conditions (SHIMADZU): column: SunFire Prep C18, 19*150 mm 5 μm; mobile phase: water with 0.05% NH_4HCO_3 and CH_3CN (6.0% CH_3CN up to 55.0% in 13 min); detector: 254/220 nm. This resulted in 0.0065 g (44%) of **I-88** as a white solid. MS (ES): *m/z* 442 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 1.44 (t, *J*=7.2, 3H), 2.85 (s, 3H), 4.40 (q, *J*=7.2, 2H), 4.89 (s, 2H), 5.25 (s, 2H), 6.71 (s, 1H), 7.11 (t, *J*=7.2, 1H), 7.20 (t, *J*=7.6, 1H), 7.36 (d, *J*=8.4, 1H), 7.60 (d, *J*=8.0, 1H), 8.79 (s, 1H).

[00885] Example 195: Synthesis of 2-[5-methyl-2,4-dioxo-1-(2-phenylethyl)-6-(propoxycarbonyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-68).



136.1



195.1 195.2 I-68

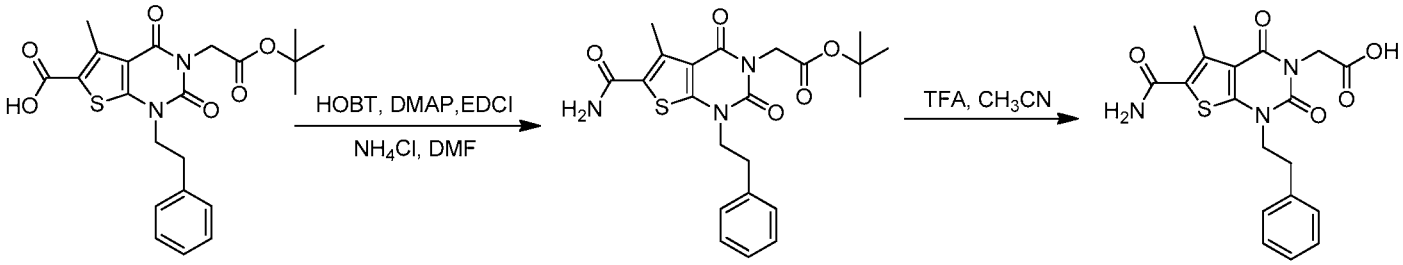
[00886] **Synthesis of compound 195.1.** Into a 100-mL round-bottom flask was placed **136.1** (5.1 g, 10.79 mmol, 1.00 equiv), tetrahydrofuran (5 mL), methanol (10 mL), water (10 mL) and LiOH (770 mg, 32.15 mmol, 2.98 equiv). The resulting solution was stirred overnight at room temperature. The resulting mixture was diluted with 100 mL of H_2O. The pH value of the solution was adjusted to 3 with hydrogen chloride (10%). The resulting solution was extracted with 3x100 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with dichloromethane/methanol (100:1). This resulted in 2.3 g (48%) of **195.1** as a white solid.

[00887] **Synthesis of compound 195.2.** Into a 50-mL round-bottom flask was placed **195.1** (150 mg, 0.34 mmol, 1.00 equiv), N,N-dimethylformamide (10 mL), potassium carbonate (140 mg, 1.01 mmol, 3.00 equiv) and 1-bromopropane (83 mg, 0.67 mmol, 2.00 equiv). The resulting solution was stirred overnight at 50 °C. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:50). This resulted in 130 mg (79%) of **195.2** as a white solid.

[00888] **Synthesis of Compound I-68.** Into a 25-mL round-bottom flask was placed **195.2** (130 mg, 0.27 mmol, 1.00 equiv), CF_3COOH (2 mL) and CH_3CN (5 mL). The resulting solution was stirred for 5 h at room temperature and then concentrated under vacuum. The crude product

was re-crystallized from EA:*n*-hexane in the ratio of 1:5. This resulted in 40.9 mg (36%) of **I-68** as a white solid. MS (ES): *m/z* 431 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 0.87 (t, *J*=6.4, 3H), 1.65-1.74 (m, 2H), 2.75 (s, 3H), 3.01 (t, *J*=7.2, 2H), 4.14 (t, *J*=7.2, 2H), 4.21 (t, *J*=6.8, 3H), 2.75 (s, 2H), 7.20-7.31 (m, 5H).

[00889] Example 196: Synthesis of 2-[6-carbamoyl-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-71).

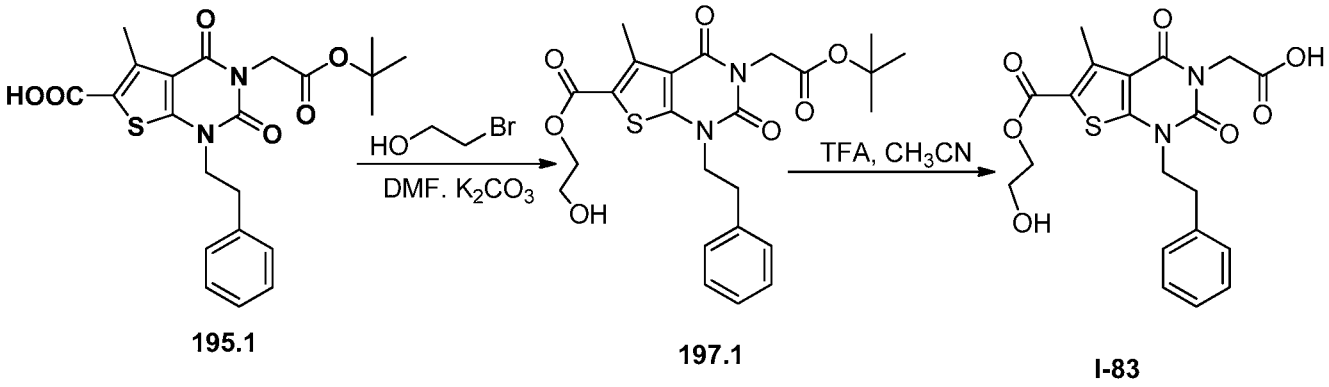


195.1 196.1 I-71

[00890] Synthesis of compound 196.1. Into a 50-mL round-bottom flask was placed HOBT (50 mg, 0.37 mmol, 1.10 equiv), **195.1** (150 mg, 0.34 mmol, 1.00 equiv), 4-dimethylaminopyridine (45 mg, 0.37 mmol, 1.09 equiv), NH_4Cl (72 mg, 1.35 mmol, 3.99 equiv), N,N-dimethylformamide (10 mL) and EDC (71 mg, 0.46 mmol, 1.36 equiv). The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 20 mL of water. The resulting solution was extracted with 3x20 mL of ethyl acetate and the organic layers combined, dried and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). This resulted in 500 mg (crude) of **196.1** as a white solid.

[00891] Synthesis of Compound I-71. Compound **I-71** was prepared from **196.1** in a manner analogous to the synthesis of Compound **I-68** (Example 195). Isolated 27 mg of a white solid in 6% yield. MS (ES): *m/z* 388 $(M+H)^+$, 410 $(M+Na)^+$, 429 $(M+H+CH_3CN)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 2.66 (s, 3H), 2.99 (t, *J*=8.0, 2H), 4.07 (t, *J*=7.6, 2H), 4.37 (s, 2H), 7.22-7.34 (m, 5H), 7.55 (s, 2H).

[00892] Example 197: Synthesis of 2-[6-[(2-hydroxyethoxy)carbonyl]-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-83).

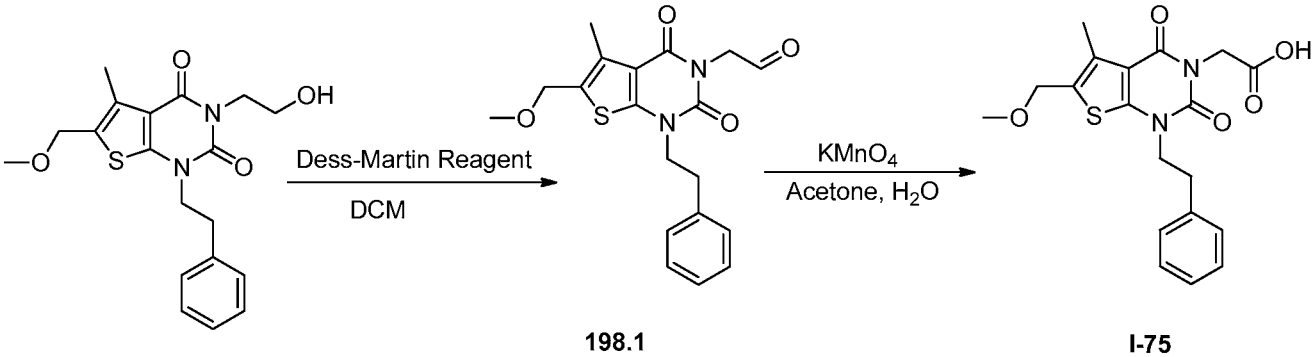


195.1 197.1 I-83

[00893] Synthesis of compound 197.1. 197.1 was prepared from **195.1** in a manner analogous to the synthesis of **I-42** (Example 178). Isolated 140 mg (85%) of a white solid.

[00894] Synthesis of Compound I-83. Compound **I-83** was prepared from **197.1** in a manner analogous to Compound **I-68** (Example 195). Isolated 35.2 mg of a white solid in 28% yield. MS (ES): *m/z* 433 $(M+H)^+$, 455 $(M+Na)^+$, 496 $(M+H+CH_3CN)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 2.76 (s, 3H), 3.02 (t, *J*=7.6, 2H), 3.68 (t, *J*=4.8, 2H), 4.14 (t, *J*=7.6, 2H), 4.27 (t, *J*=4.8, 2H), 4.56 (s, 2H), 7.21-7.32 (m, 5H).

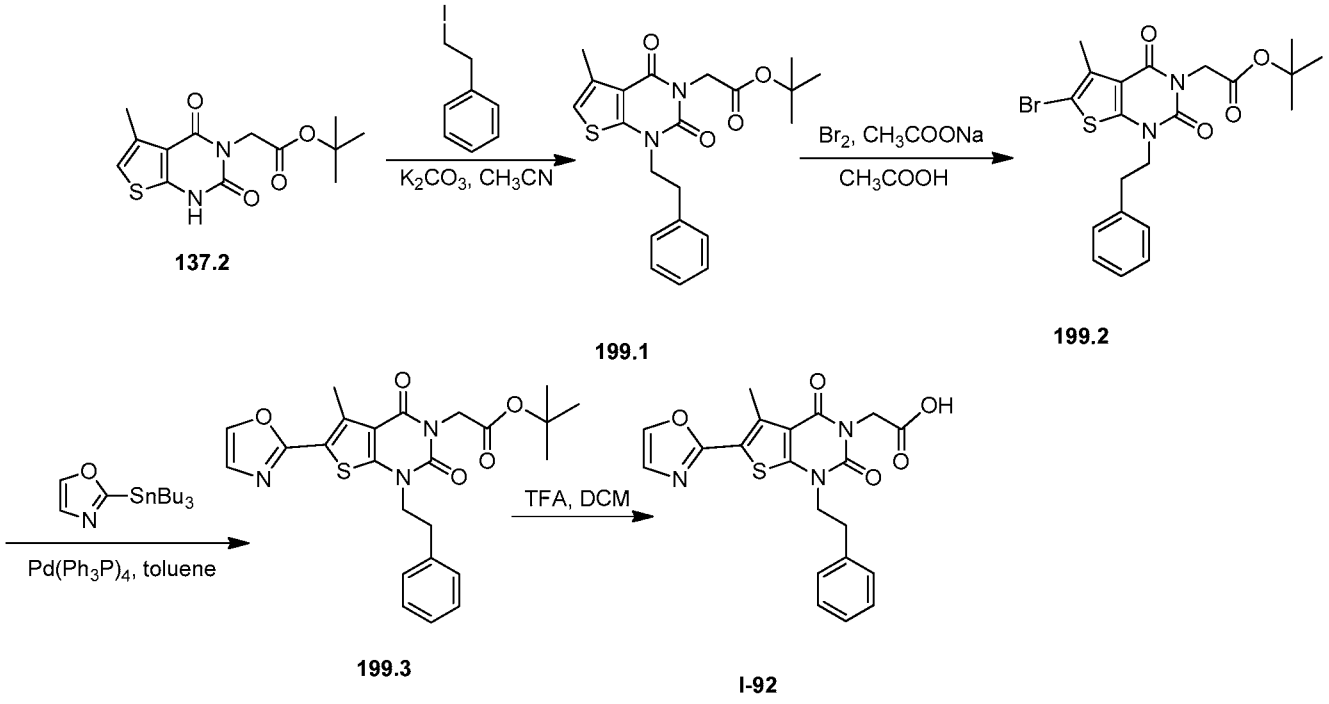
[00895] Example 198: Synthesis of 2-[6-(methoxymethyl)-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-75).



I-39 198.1 I-75

[00896] Compound **I-75** was prepared from **I-39** (Example 179) in a manner analogous to the synthesis of Compound **I-84** (Example 190). Isolated a 49.5 mg of a white solid in 40% yield from **I-39**. MS (ES): *m/z* 389 $(M+H)^+$, 411 $(M+Na)^+$, 452 $(M+Na+CH_3CN)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 2.35 (s, 3H), 2.99 (t, *J*=7.5, 2H), 3.32 (s, 3H), 4.08 (t, *J*=7.2, 2H), 4.51 (s, 2H), 7.19-7.32 (m, 5H), 12.94 (s, 1H).

[00897] Example 199: Synthesis of 2-[5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-92).



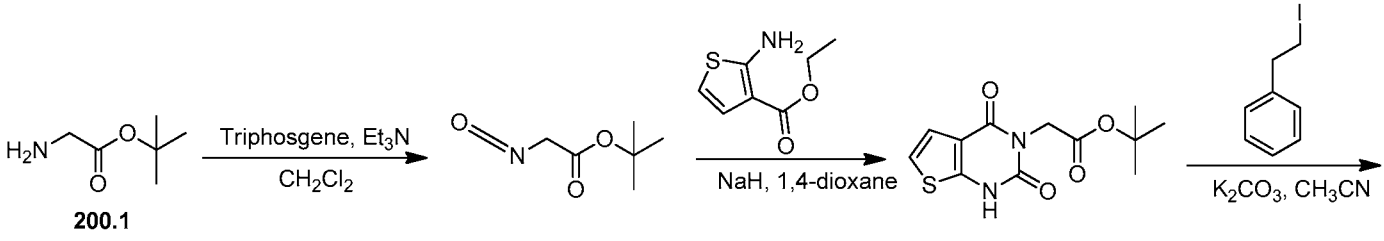
137.2 199.1 199.2 199.3 I-92

[00898] Synthesis of compound 199.1. Compound **199.1** was prepared from **137.2** in a manner analogous to the synthesis of **136.1.** Isolated 0.87 g of a yellow solid in 64% yield.

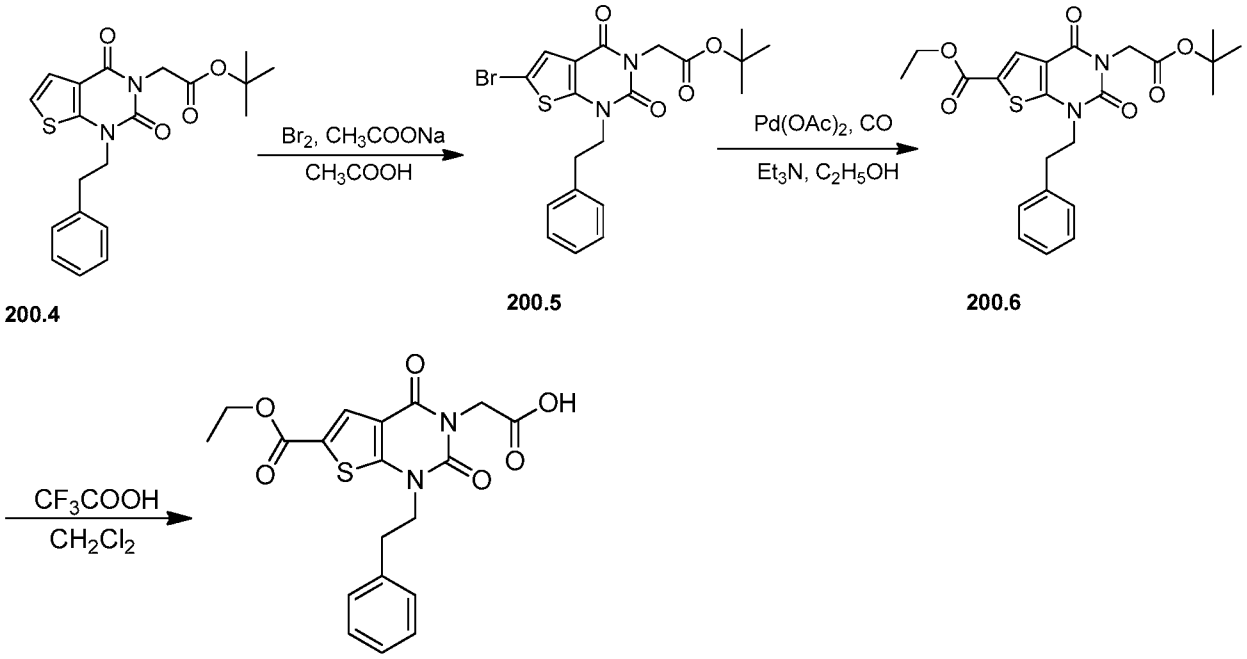
[00899] Synthesis of compound 199.2. Compound **199.2** was prepared from **199.1** in a manner analogous to the synthesis of compound **137.3**. Isolated 0.56 g of a white solid in 94% yield.

[00900] Synthesis of Compound I-92. Compound **I-92** was prepared from **199.2** in a manner analogous to Compound **I-141** (Example 7). Isolated 24 mg (52%) of a white solid.

[00901] Example 200: Synthesis of 2-[6-(ethoxycarbonyl)-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-91).



200.1 200.2 200.3



200.4 200.5 200.6

I-91

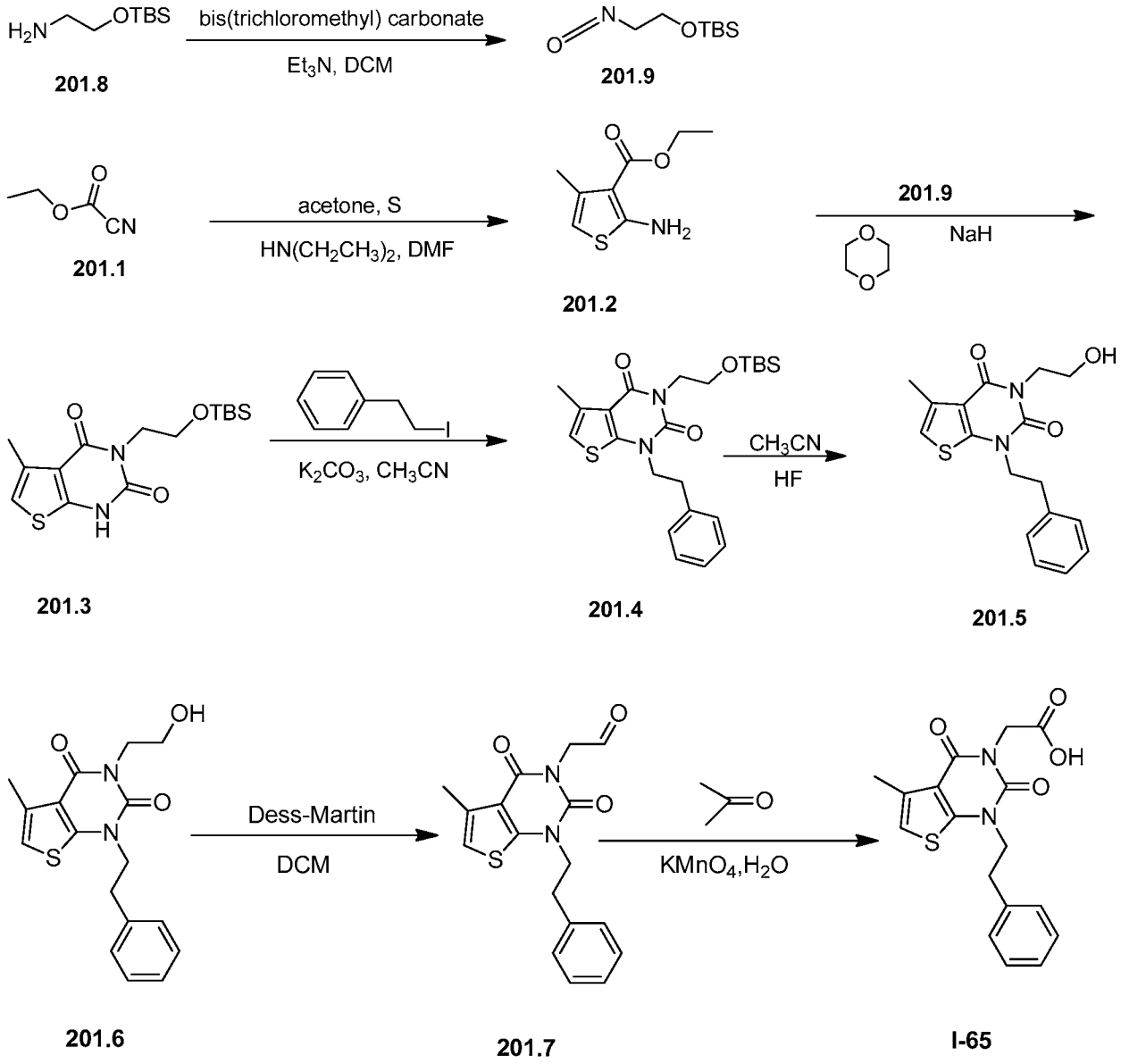
[00902] **Synthesis of compound 200.4.** Compound **200.4** was prepared from **200.1** and ethyl 2-aminothiophene-3-carboxylate in a manner analogous to the synthesis of **136.1** (Examples 135 and 136). Isolated 1.1 g of a yellow solid in 12% overall yield.

[00903] **Synthesis of compound 200.5.** Compound **200.5** was prepared from **200.4** in a manner consistent with the synthesis of **137.3**. Isolated 1.1 g of a white solid in 83% yield.

[00904] **Synthesis of compound 200.6.** Into a 100-mL pressure tank reactor (7 atm) was placed $Pd(OAc)_2$ (100 mg, 0.45 mmol, 0.41 equiv), **200.5** (500 mg, 1.07 mmol, 1.00 equiv), ethanol (50 mL) and triethylamine (220 mg, 2.17 mmol, 2.02 equiv). Then CO (gas) was introduced to keep the pressure at 7 atm. The resulting solution was stirred overnight at 100°C. After cooling, the resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:20). Purification afforded 130 mg (26%) of **200.6** as a white solid.

[00905] **Synthesis of Compound I-91.** Compound **I-91** was prepared from **200.6** in a manner analogous to the synthesis of compound **2.5**. MS (ES): *m/z* 403 $(M+H)^+$, 425 $(M+Na)^+$, 444 $(M+H+CH_3CN)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 1.29 (t, *J*=6.9, 3H), 3.02 (t, *J*=7.2, 2H), 4.15 (t, *J*=7.2, 2H), 4.30 (q, *J*=6.9, 2H), 4.56 (s, 2H), 7.18-7.30 (m, 5H), 7.81 (s, 1H), 13.09 (s, 1H).

[00906] Example 201: Synthesis of 2-[2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-65).



[00907] Synthesis of compound 201.9. Compound **201.9** was prepared from (2-aminoethoxy)(tert-butyl)dimethylsilane in a manner analogous to compound **169.3**. Isolated 13 g (crude) of a yellow liquid.

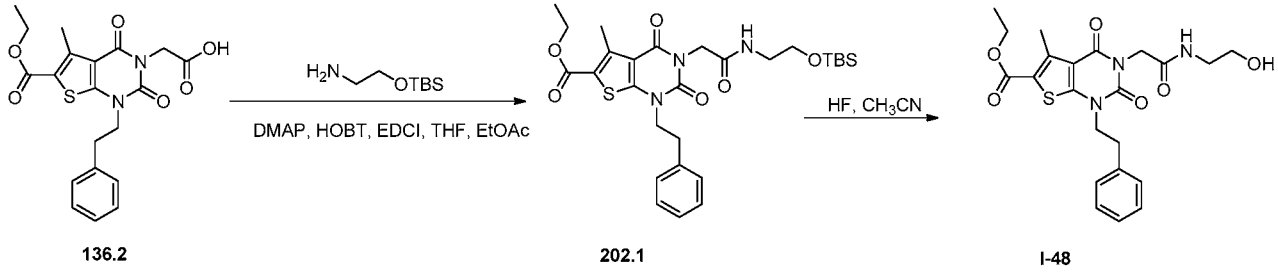
[00908] Synthesis of compound 201.2. Into a 500-mL 3-necked round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed ethyl 2-cyanoacetate (22.6 g, 199.80 mmol, 1.00 equiv), ethanol (200 mL), propan-2-one (11.6 g, 199.73 mmol, 1.00 equiv), diethylamine (14.6 g) and S (6.4 g). The resulting solution was stirred overnight at 50 °C. The

solids were filtered out. The filtrate was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/PE (1:100-1:20). This resulted in 6.47 g (17%) of **201.2** as a white solid.

[00909] **Synthesis of compound 201.5.** Compound **201.5** was prepared from **201.2** in a manner analogous to Compound **I-34** (Example 169). Isolated 12.6 mg of a white solid in 0.003% overall yield. MS (ES): *m/z* 331.1 $(M+H)^+$. ^1H NMR ($CDCl_3$, 400 MHz): δ 2.37 (s,3H), 2.96-3.01 (t, 2H), 3.58-3.62 (t, 2H), 3.92-3.96 (t, 2H), 4.04-4.09 (t, 2H), 6.81 (s, 1H), 7.21-7.32 (m, 5H).

[00910] **Synthesis of Compound I-65.** Compound **I-65** was prepared from **201.5** in a manner analogous to Compound **I-84** (Example 190). Isolated 30.8 mg of a white solid in 29% yield from **201.5**. MS (ES): *m/z* 367.1 $(M+Na)^+$. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.36 (s, 3H), 2.97-3.02 (t, 2H), 4.06-4.11 (t, 2H), 4.55 (s, 2H), 6.90 (s, 1H), 7.19-7.32 (m, 5H).

[00911] **Example 202: Synthesis of ethyl 3-[[(2-hydroxyethyl)carbamoyl]methyl]-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-48).**



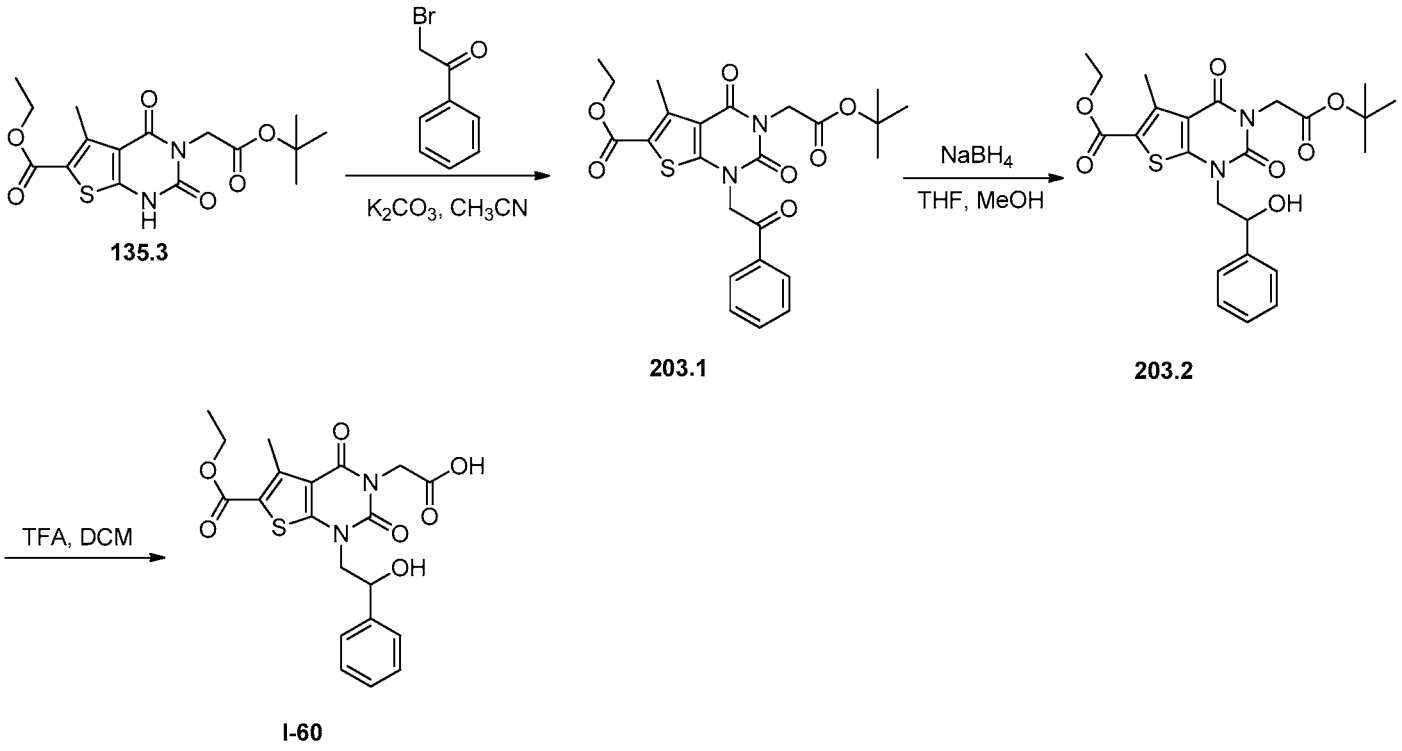
136.2 202.1 I-48

[00912] **Synthesis of compound 202.1.** Compound **202.1** was prepared from **136.2** and (2-aminoethoxy)(tert-butyl)dimethylsilane in a manner analogous to **136.3.** Isolated 0.7 g of a white solid in 98% yield.

[00913] **Synthesis of Compound I-48.** Compound **I-48** was prepared from **202.1** in a manner analogous to Compound **I-20** (Example 160). Isolated 0.46 g of a white solid in 80% yield. MS (ES): *m/z* 460 $(M+H)^+$.

^1H NMR (CD_3OD, 400 MHz): δ 1.38 (t, *J*=7.2 Hz, 3H), 2.82 (s, 3H), 3.10 (t, *J*=7.2 Hz, 2H), 3.37 (t, *J*=5.6 Hz, 2H), 3.64 (t, *J*=5.6 Hz, 2H), 4.18 (t, *J*=7.2 Hz, 2H), 4.34 (q, 2H), 4.69 (s, 2H), 7.23-7.33 (m, 5H).

[00914] Example 203: Synthesis of 2-[6-(ethoxycarbonyl)-1-(2-hydroxy-2-phenylethyl)-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-60).



135.3 203.1 203.2 I-60

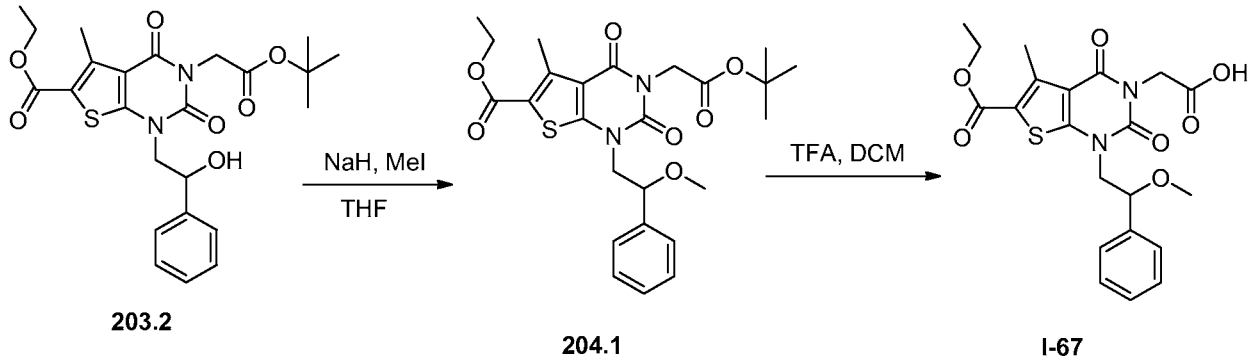
[00915] Synthesis of 203.1. Compound **203.1** was prepared from **135.3** and 2-bromo-1-phenylethan-1-one in a manner analogous to **136.1**. Isolated 0.34 g of a light yellow solid in 51% yield.

[00916] Synthesis of 203.2. Into a 50-mL round-bottom flask was placed **203.1** (300 mg, 0.62 mmol, 1.00 equiv), methanol (5 mL), tetrahydrofuran (5 mL) and $NaBH_4$ (25 mg, 0.66 mmol, 1.07 equiv). The resulting solution was stirred for 2 h at room temperature. The reaction was then quenched by the addition of 5 mL of NH_4Cl (aq.). The resulting solution was extracted with 2x5 mL of ethyl acetate and the organic layers combined, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). This resulted in 160 mg (53%) of **203.2** as a white solid.

[00917] Synthesis of Compound I-60. Compound **I-60** was prepared from **203.2** in a manner consistent with the synthesis of compound **2.5**. Isolated 20.4 mg of a white solid in 38% yield. MS (ES): *m/z* 433 $(M+H)^+$, 455 $(M+Na)^+$, 496 $(M+Na+CH_3CN)^+$.

^1H NMR (300 MHz, DMSO-d_6): δ 1.31 (t, *J*=7.2, 3H), 2.76 (s, 3H), 3.77-3.85 (m, 1H), 4.12-4.15 (m, 1H), 4.29 (q, *J*=6.9, 2H), 4.44 (s, 2H), 4.99 (d, *J*=7.2, 1H), 5.89(s, 1H), 7.30-7.43 (m, 5H).

[00918] Example 204: Synthesis of 2-[6-(ethoxycarbonyl)-1-(2-methoxy-2-phenylethyl)-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-67).

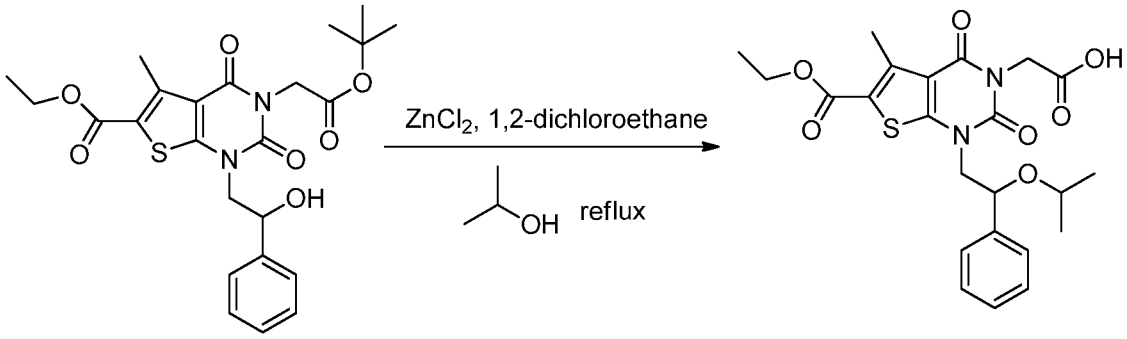


203.2 204.1 I-67

[00919] Synthesis of compound 204.1. Into a 50-mL round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed **203.2** (100 mg, 0.20 mmol, 1.00 equiv), tetrahydrofuran (10 mL). This was followed by the addition of sodium hydride (8.2 mg, 0.20 mmol, 1.00 equiv). The mixture was stired for 15 min at 0°C. To this was added CH_3I (43.6 mg, 0.31 mmol, 1.50 equiv). The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 5 ml of NH_4Cl (aq.). The resulting solution was extracted with 2x5 mL of ethyl acetate. The organic layers were combined, dried over sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/PE (1:10). This resulted in 70 mg (68%) of **204.1** as a white solid.

[00920] Synthesis of Compound I-67. Compound **I-67** was prepared from **204.1** in a manner consistent with the synthesis of compound **2.5**. Isolated 30.5 mg of a white solid in 49% yield. MS (ES): *m/z* 447 $(M+H)^+$, 469 $(M+Na)^+$, 469 $(M+Na+CH_3CN)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 1.31 (t, *J*=7.2, 3H), 2.76 (s, 3H), 3.09 (s, 3H), 3.94-4.15 (m, 2H), 4.30 (q, *J*=6.6, 2H), 4.56-4.65 (m, 3H), 7.34-7.46 (m, 5H), 12.98 (s, 1H).

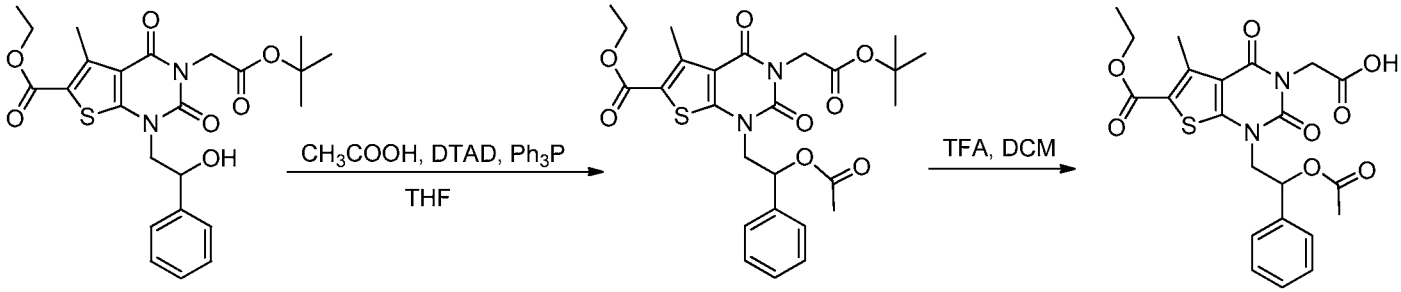
[00921] Example 205: Synthesis of 2-[6-(ethoxycarbonyl)-5-methyl-2,4-dioxo-1-[2-phenyl-2-(propan-2-yloxy)ethyl]-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-89). .



203.2 I-89

[00922] Into a 50-mL round-bottom flask was placed **203.2** (100 mg, 0.20 mmol, 1.00 equiv), 1,2-dichloroethane (20 mL), $ZnCl_2$ (33 mg, 0.24 mmol, 1.18 equiv) and propan-2-ol (25 mg, 0.42 mmol, 2.03 equiv). The resulting solution was stirred overnight at 50°C. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). The crude product (110 mg) was purified by preparative HPLC under the following conditions (SHIMADZU): column: SunFire Prep C18, 19*150 mm 5 μm; mobile phase: water with 0.05% NH_4HCO_3 and CH_3CN (6.0% CH_3CN up to 49.0% in 19 min); detector: 254/220 nm. Purification afforded 23.8 mg (25%) of **I-89** as a white solid. MS (ES): *m/z* 475 $(M+H)^+$, 497 $(M+Na)^+$, 538 $(M+Na+CH_3CN)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 0.85 (d, 3H), 0.95 (d, 3H), 1.33 (t, 3H), 2.77 (s, 3H), 3.46 (m, 1H), 3.78 (m, 1H), 3.91 (m, 1H), 4.14 (m, 1H), 4.34 (m, 2H), 4.61 (m, 2H), 4.81 (m, 1H), 7.34-7.42 (m, 5H).

[00923] Example 206: Synthesis of 2-[1-[2-(acetyloxy)-2-phenylethyl]-6-(ethoxycarbonyl)-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-85).

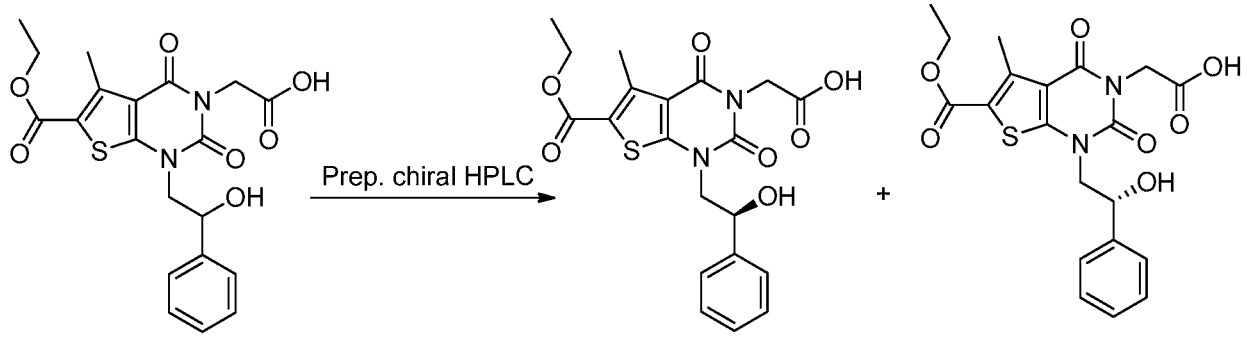


203.2 206.1 I-85

[00924] **Synthesis of compound 206.1.** Into a 10-mL seal-tube, purged and maintained with an inert atmosphere of nitrogen, was placed **203.2** (200 mg, 0.41 mmol, 1.00 equiv), DTAD (188 mg, 0.82 mmol, 2.00 equiv), tetrahydrofuran (5 mL), PPh_3 (214 mg, 0.82 mmol, 2.00 equiv) and acetic acid (49 mg, 0.82 mmol, 2.00 equiv). The resulting solution was stirred overnight at room temperature and then concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/PE (1:15). This resulted in 76 mg (35%) of **206.1** as a white solid.

[00925] **Synthesis of Compound I-85.** Compound **I-85** was prepared from **206.1** in a manner analogous to **2.5**. Isolated 23.1 mg (34%) of a white solid. MS (ES): *m/z* 475 $(M+H)^+$, 415 $(M+H\text{-}CH_3COOH]^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.40 (t, *J*=7.2, 3H), 2.00 (s, 3H), 2.84 (s, 3H), 4.33-4.40 (m, 4H), 4.72 (t, *J*=5.1, 2H), 6.25 (t, *J*=7.2, 1H), 7.37-7.50 (m, 5H).

[00926] **Example 207: Synthesis of 2-[6-(ethoxycarbonyl)-1-[(2S)-2-hydroxy-2-phenylethyl]-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-77) and Example 208: 2-[6-(ethoxycarbonyl)-1-[(2R)-2-hydroxy-2-phenylethyl]-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-78).**



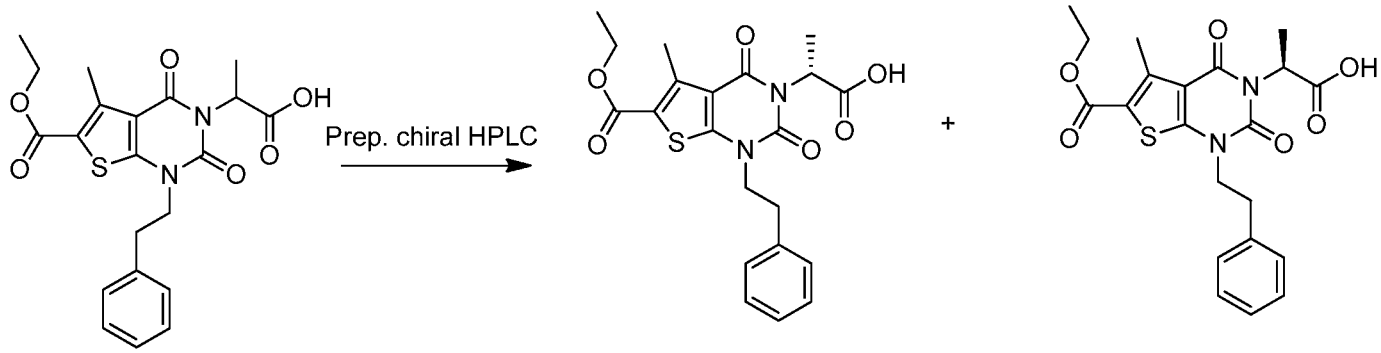
I-60 **I-77** **I-78**

[00927] **I-60** (120 mg, 0.28 mmol, 1.00 equiv) was purified by chiral preparative HPLC under the following conditions (Gilson Gx 281): column: Chiralpak IC(SFC), 2*25 cm, 5 μm; mobile phase: hexanes and ethanol (0.1% TFA) (hold at 20.0% ethanol (0.1%TFA) in 18 min); detector: UV 220/254 nm. This resulted in 24.6 mg (tR = 10.1 min, 21%) of **I-77** as a white solid and 15.2 mg (12.5 min, 13%) of **I-78** as a white solid.

[00928] Analytical data for **I-77**: MS (ES): *m/z* 433 $(M+H)^+$, 496 $(M+Na+CH3CN)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 1.32(t, *J*=7.2, 3H), 2.77 (s, 3H), 3.80-3.86 (m, 1H), 4.13-4.18 (m, 1H), 4.29 (q, *J*=6.9, 2H), 4.57 (d, *J*=6.0, 2H), 4.99 (t, *J*=4.8, 1H), 5.90 (d, *J*=4.4, 1H), 7.29-7.44 (m, 5H).

[00929] Analytical data for **I-78**: MS (ES): *m/z* 433 $(M+H)^+$, 496 $(M+Na+CH_3CN)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 1.32 (t, *J*=7.2, 3H), 2.77 (s, 3H), 3.80-3.86 (m, 1H), 4.13-4.18 (m, 1H), 4.29 (q, *J*=6.9, 2H), 4.57 (d, *J*=6.0, 2H), 4.99 (t, *J*=4.8, 1H), 5.90 (d, *J*=4.4, 1H), 7.29-7.44 (m, 5H).

[00930] Example 209: Synthesis of (2R)-2-[6-(ethoxycarbonyl)-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-76) and Example 210: Synthesis of (2S)-2-[6-(ethoxycarbonyl)-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-80).



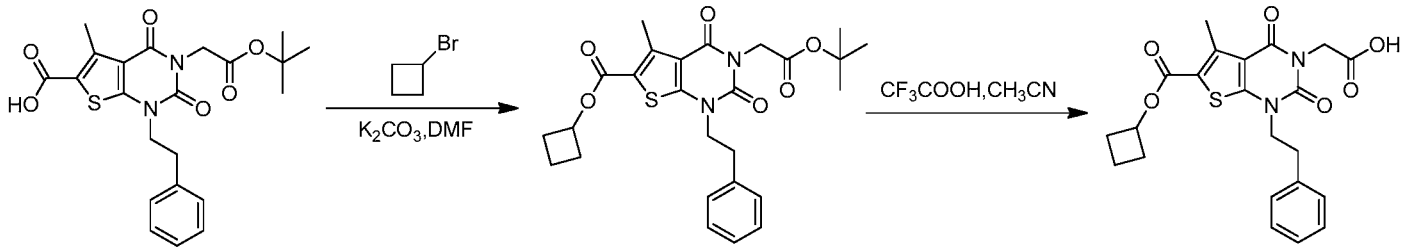
I-56 **I-76** **I-80**

[00931] The enantiomers of **I-56** were separated by chiral HPLC under the following conditions (Gilson Gx 281): column: Chiralpak IA, 2*25 cm, 5 μm; mobile phase: hexanes and ethanol (0.1% DEA) (hold at 40.0% ethanol (0.1% DEA) in 20 min); detector: UV 220/254 nm. This resulted in 20 mg (tR = 5.27 min, 31%) of **I-76** as a white solid and 20 mg (tR = 10.4 min, 27%) of **I-80** as a white solid.

[00932] Analytical data for **I-76**: MS (ES): *m/z* 431 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.29 (t, *J*=9.6 Hz, 3H), 1.48 (d, *J*=10.0 Hz, 3H), 2.74 (s, 3H), 3.00 (t, *J*=9.6 Hz, 2H), 4.12 (t, *J*=10.0 Hz, 2H), 4.28 (q, *J*=9.6 Hz, 2H), 5.37(q, 1H), 7.18-7.30 (m, 5H), 12.72 (s, 1H).

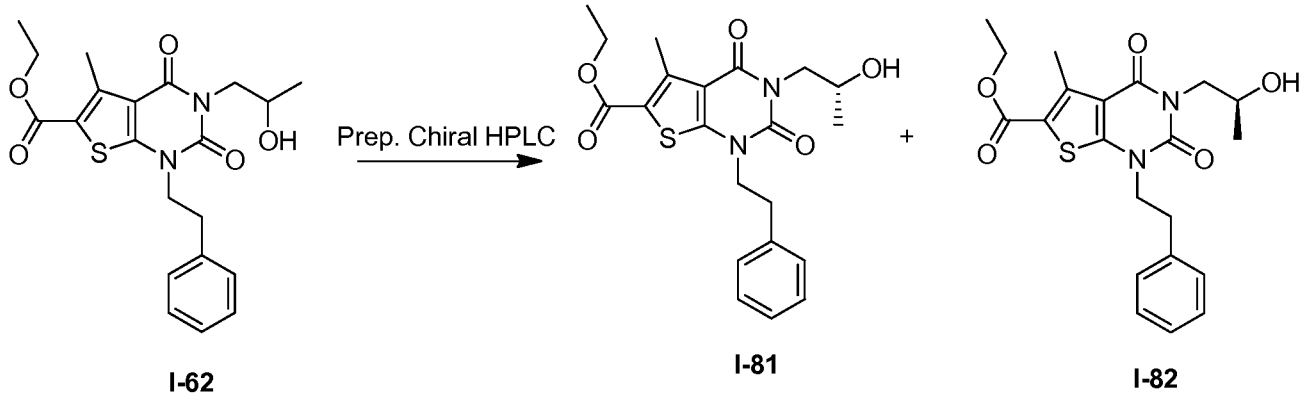
[00933] Analytical data for **I-80:** MS (ES): *m/z* 431 $(M+H)^+$. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.29 (t, *J*=9.6 Hz, 3H), 1.42 (d, *J*=9.6 Hz, 3H), 2.73 (s, 3H), 2.98 (t, *J*=9.6 Hz, 2H), 4.12 (t, *J*=6.8 Hz, 2H), 4.27 (q, 2H), 4.96 (q, 1H), 7.19-7.32 (m, 5H).

[00934] Example 211: Synthesis of 2-[6-(cyclobutoxycarbonyl)-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-86).



[00935] Compound **I-86** was prepared from **195.1** and bromocyclobutane in a manner analogous to the synthesis of Compound **I-68** (Example 195). Isolated 93 mg (55%) of a dark yellow solid. MS (ES): *m/z* 443 $(M+H)^+$. ^1H NMR (CD_3OD, 300 MHz): δ 1.69-1.95 (m, 2H), 2.14-2.28 (m, 2H), 2.39-2.48 (m, 2H), 2.80 (s, 3H), 3.08-3.13 (t, 2H), 4.17-4.22 (t, 2H), 4.71 (s, 2H), 5.12-5.22 (m, 1H), 7.22-7.32 (m, 5H).

[00936] Example 212: Synthesis of ethyl 3-[(2R)-2-hydroxypropyl]-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-81) and Example 213: Synthesis of ethyl 3-[(2S)-2-hydroxypropyl]-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-82).

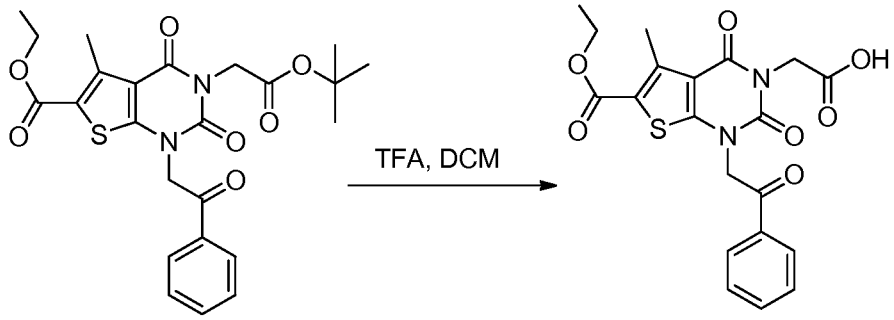


[00937] The enantiomers of **I-62** (250 mg) were separated by chiral preparative HPLC under the following conditions (Gilson Gx 281): column: Chiralpak IB, 2*25 cm, 5 μm; mobile phase: hexanes and ethanol (hold 5.0% ethanol in 12 min); detector: UV 220/254 nm. This resulted in 100 mg (tR = 15.2 min, 80%) of **I-81** as a white solid and 100 mg (tR = 17.6 min, 80%) of **I-82** as a white solid.

[00938] Analytical data for **I-81:** MS (ES): *m/z* 417 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 1.03(d, *J*=5.2 Hz, 3H), 1.30 (t, *J*=6.8 Hz, 3H), 2.76 (s, 3H), 3.00 (m, *J*=7.2 Hz, 2H), 3.70 (q, 1H), 3.95 (t, *J*=8.0 Hz, 2H), 4.12 (t, *J*=8.0 Hz, 2H), 4.28 (m, *J*=7.2 Hz, 2H), 4.77 (s, 1H), 7.19-7.32 (m, 5H).

[00939] Analytical data for **I-82**: MS (ES): *m/z* 417 $(M+H)^+$. ^1H NMR (DMSO-d_6, 400 MHz): δ 1.03 (d, *J*=5.2 Hz, 3H), 1.30 (t, *J*=6.8 Hz, 3H), 2.76 (s, 3H), 3.00 (t, *J*=7.2 Hz, 2H), 3.70 (q, 1H), 3.95 (t, *J*=8.0 Hz, 2H), 4.12 (t, *J*=8.0 Hz, 2H), 4.28 (q, *J*=7.2 Hz, 2H), 4.77 (s, 1H), 7.19-7.32 (m, 5H).

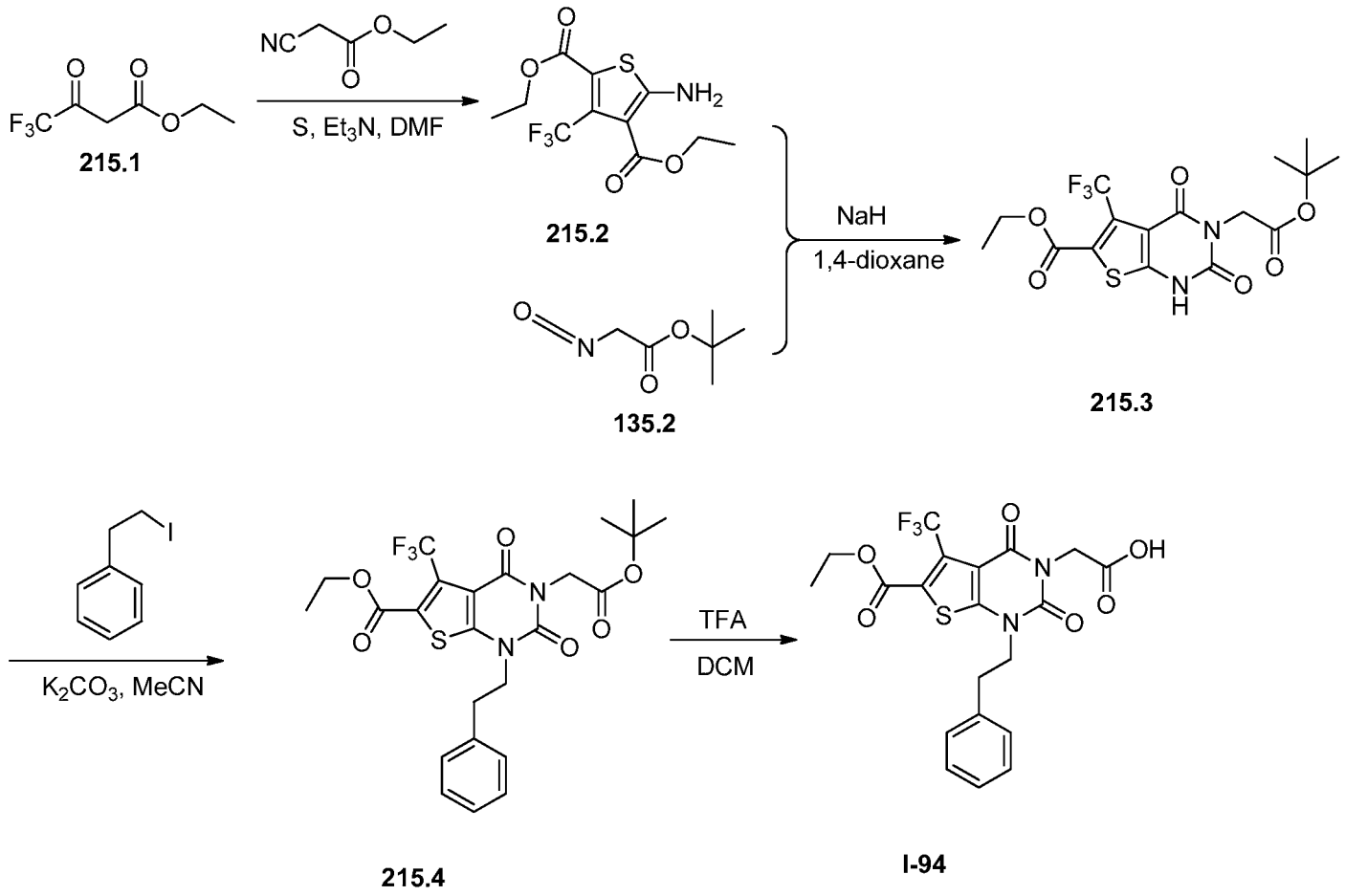
[00940] Example 214: Synthesis of 2-[6-(ethoxycarbonyl)-5-methyl-2,4-dioxo-1-(2-oxo-2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-73).



203.1 **I-73**

[00941] Compound **I-73** was prepared from **203.1** in a manner analogous to the synthesis of **2.5**. Isolated 69.2 mg (78%) of a white solid. MS (ES): *m/z* 431 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 1.26 (t, *J*=7.2, 3H), 2.80 (s, 3H), 4.26 (q, *J*=7.2, 2H), 4.57 (s, 2H), 5.73 (s, 2H), 7.63 (t, *J*=7.6, 2H), 7.78 (t, *J*=7.6, 1H), 8.12 (d, *J*=7.6, 2H).

[00942] Example 215: Synthesis of 2-[6-(ethoxycarbonyl)-2,4-dioxo-1-(2-phenylethyl)-5-(trifluoromethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-94).

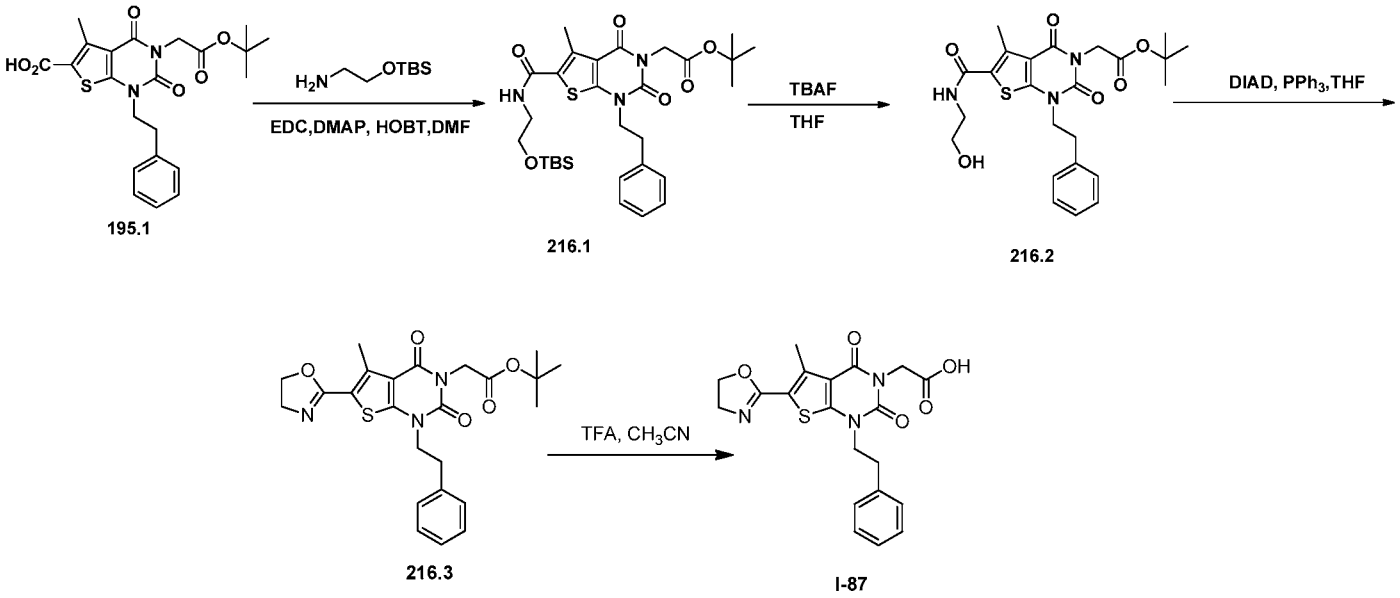


[00943] **Synthesis of compound 215.2.** Into a 1-L 3-necked round-bottom flask was placed S (8.84 g, 276.25 mmol, 1.00 equiv), ethyl 4,4,4-trifluoro-3-oxobutanoate (50.8 g, 275.92 mmol, 1.00 equiv), N,N-dimethylformamide (300 mL) and ethyl 2-cyanoacetate (31.2 g, 275.83 mmol, 1.00 equiv). This was followed by the addition of triethylamine (28 g, 276.71 mmol, 1.00 equiv) dropwise with stirring at 0°C. The resulting solution was stirred overnight at room temperature. The resulting solution was allowed to react, with stirring, for an additional 1 day while the temperature was maintained at 40°C in an oil bath. The reaction was then quenched by the addition of 500 mL of water. The resulting solution was extracted with 3x500 mL of ether and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:12). This resulted in 5.8 g (7%) of **215.2** as a yellow solid.

[00944] **Synthesis of Compound I-94.** Compound **I-94** was prepared from **215.2** and **135.2** in a manner analogous to the synthesis of compound **136.2**. Isolated 0.4 g of a white solid in 53% yield. MS (ES): *m/z* 471 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 1.30 (t, *J*=6.8, 3H), 3.02(t,

J=7.2, 2H), 4.17 (t, *J*=7.2, 2H), 4.34 (t, *J*=7.2, 2H), 4.58 (s, 2H), 7.21-7.32 (m, 5H), 13.11 (s, 1H).

[00945] Example 216: Synthesis of 2-[6-(4,5-dihydro-1,3-oxazol-2-yl)-5-methyl-2,4-dioxo-1-(2-phenylethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-87).



[00946] Synthesis of compound 216.1. Compound **216.1** was prepared from **195.1** in a manner analogous to compound **136.3**. Isolated 600 mg (89%) of a white solid.

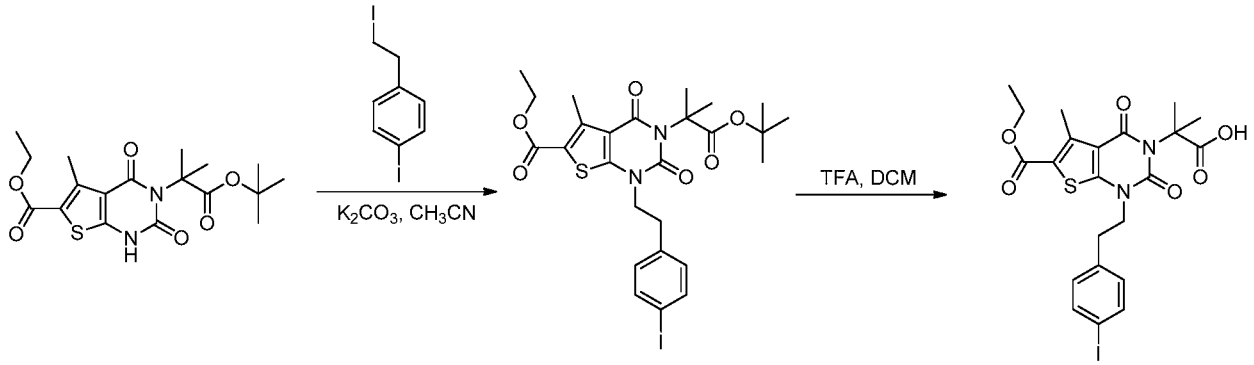
[00947] Synthesis of compound 216.2. Into a 50-mL round-bottom flask was placed **216.1** (600 mg, 1.00 mmol, 1.00 equiv), oxolane (10 mL) and TBAF (300 mg, 1.15 mmol, 1.15 equiv). The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/PE (1:5). Purification afforded 205 mg (42%) of **216.2** as a white solid.

[00948] Synthesis of compound 216.3. Into a 10-mL round-bottom flask was placed **216.2** (100 mg, 0.21 mmol, 1.00 equiv), DIAD (94 mg, 0.46 mmol, 1.99 equiv), PPh_3 (107 mg, 0.41 mmol, 2.00 equiv) and tetrahydrofuran (5 mL). The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:20). Purification afforded 70 mg (73%) of **216.3** as a white solid.

[00949] Synthesis of Compound I-87. Compound **I-87** was prepared from **216.3** in a manner analogous to the synthesis of **2.5.** Isolated 2.8 mg (9%) of **I-87** as a white solid. MS (ES): *m/z*

414 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD): δ 2.76 (s, 1H), 3.11 (t, *J*=8.0, 2H), 3.99 (t, *J*=9.6, 2H), 4.17 (t, *J*=7.6, 2H), 4.49 (t, *J*=9.6, 2H), 4.62 (s, 2H), 7.22-7.30 (m, 5H).

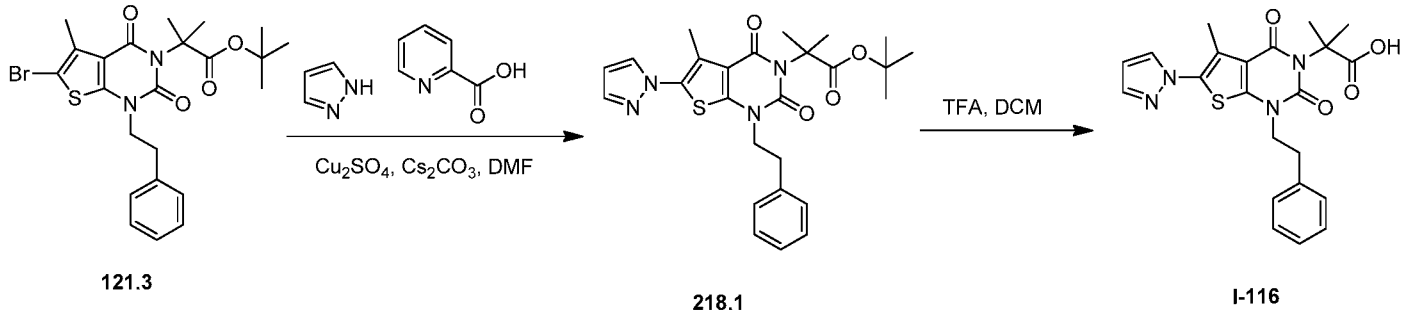
[00950] Example 217: Synthesis of 2-[6-(ethoxycarbonyl)-1-[2-(4-iodophenyl)ethyl]-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-95).



1.4 217.1 I-95

[00951] Synthesis of Compound I-95. Compound **I-95** was prepared from **1.4** and 1-iodo-4-(2-iodoethyl)benzene in a manner analogous to the synthesis of **136.2.** MS (ES): *m/z* 571 $(M+H)^+$, 612 $(M+H+CH_3CN)^+$. ^1H NMR (400 MHz, CD_3CN): δ 1.32 (t, *J*=7.2, 3H), 1.67 (s, 6H), 2.71 (s, 3H), 2.98 (t, *J*=7.2, 2H), 4.05 (t, *J*=7.2, 2H), 4.28 (q, *J*=7.2, 2H), 7.01 (d, *J*=8.4, 2H), 7.62 (d, *J*=8.0, 2H).

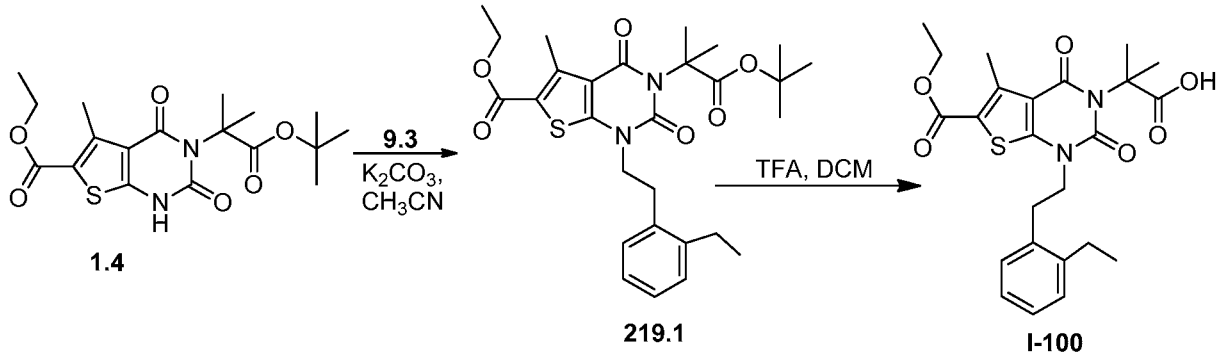
[00952] Example 218: Synthesis of 2-methyl-2-[5-methyl-2,4-dioxo-1-(2-phenylethyl)-6-(1H-pyrazol-1-yl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]propanoic acid (I-116).



121.3 218.1 I-116

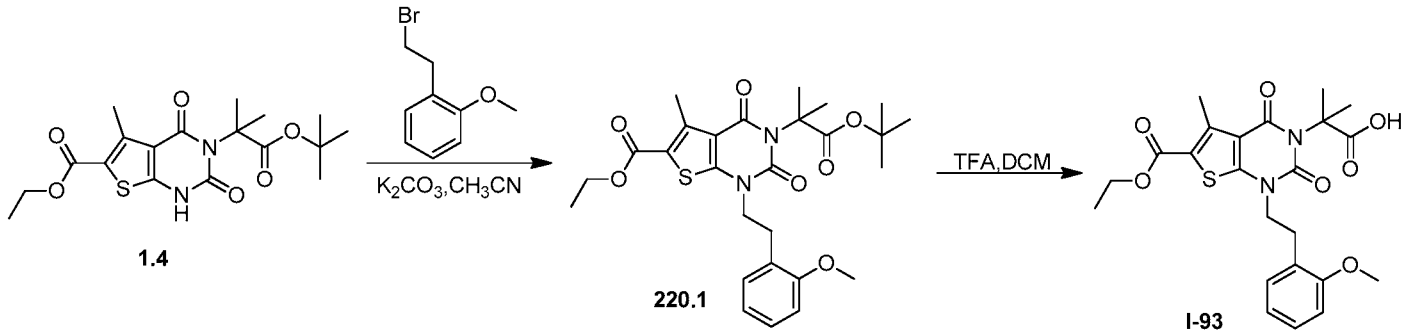
[00953] Compound **I-116** was prepared from **121.3** and pyrazole in a manner analogous to Compound **I-157**. Isolated 150 mg of a white solid in 30% overall yield. MS (ES): *m/z* 439 $(M+H)^+$, 480 $(M+H+CH_3CN)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 1.62 (s, 6H), 2.27 (s, 3H), 2.95 (t, *J*=7.2, 2H), 4.00 (t, *J*=7.2, 2H), 6.52 (t, *J*=2.1, 1H), 7.15-7.28 (m, 5H), 7.73 (d, *J*=2.1, 1H), 8.10 (d, *J*=2.4, 1H), 12.40 (s, 1H).

[00954] Example 219: Synthesis of 2-[6-(ethoxycarbonyl)-1-[2-(2-ethylphenyl)ethyl]-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-100).



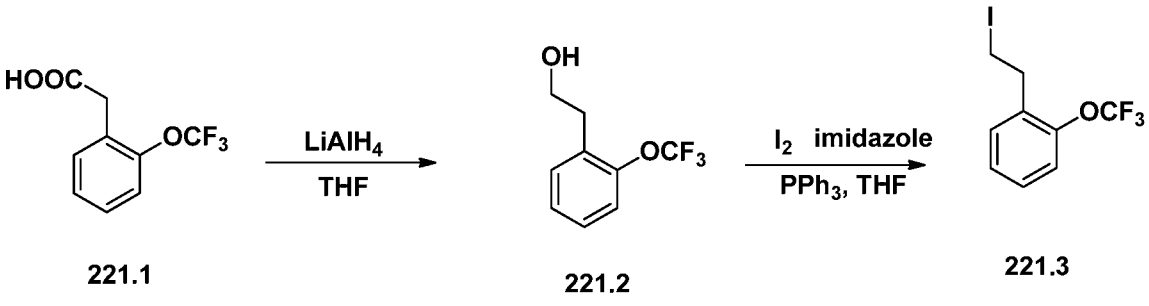
[00955] Compound **I-100** was prepared from **1.4** and **9.3** in a manner analogous to the synthesis of **136.2**. Isolated 0.041 g of a white solid in 59% overall yield from **1.4**. MS (ES): *m/z* 473 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.25 (t, *J*=7.5, 3H), 1.36 (t, *J*=7.5, 3H), 1.25 (s, 6H), 2.76 (q, *J*=7.5, 5H), 3.12 (t, *J*=7.5, 2H), 4.10 (t, *J*=7.5, 2H), 4.32 (q, *J*=7.2, 3H), 7.08-7.20 (m, 4H).

[00956] Example 220: Synthesis of 2-[6-(ethoxycarbonyl)-1-[2-(2-methoxyphenyl)ethyl]-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-93).)

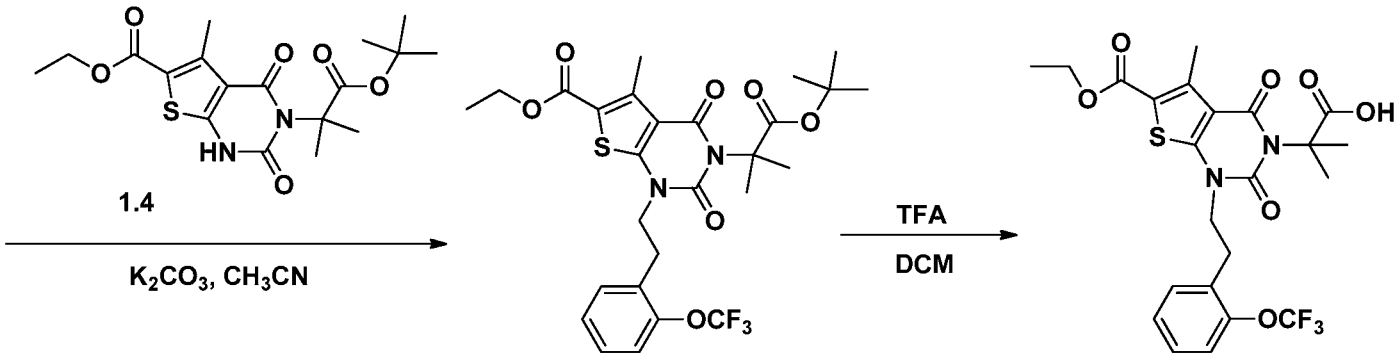


[00957] Compound **I-93** was prepared from **1.4** and commercially available 1-(2-bromoethyl)-2-methoxybenzene in a manner analogous to the synthesis of **136.2**. MS (ES): *m/z* 475 $(M+H)^+$. ^1H NMR (DMSO-d_6, 400 MHz): δ 1.29~1.32 (t, 3H), 1.64 (s, 6H), 2.70 (s, 3H), 2.96~2.95 (t, 2H), 3.76 (s, 3H), 4.03~4.07 (t, 2H), 4.25~4.30 (q, 2H), 6.84~6.87 (t, 1H), 6.91~6.93 (d, 1H), 7.12~7.14 (d, 1H), 7.19~7.23 (t, 1H).

[00958] Example 221: Synthesis of 2-[6-(ethoxycarbonyl)-5-methyl-2,4-dioxo-1-[2-[2-(trifluoromethoxy)phenyl]ethyl]-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-106).



221.1 221.2 221.3



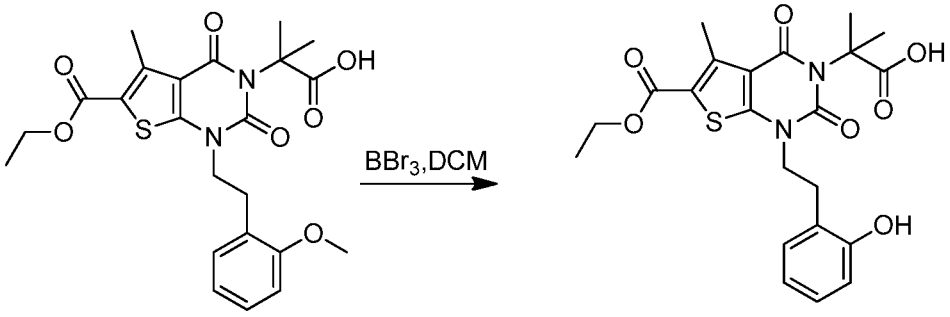
221.4 I-106

[00959] Synthesis of compound 221.2. Into a 100-mL round-bottom flask was placed 2-[2-(trifluoromethoxy)phenyl]acetic acid (1 g, 4.54 mmol, 1.00 equiv), THF (30 mL) and alumane lithium (173 mg, 4.55 mmol, 1.00 equiv). The resulting solution was stirred for 2 h at room temperature. The reaction was then quenched by the addition of 40 mL of NH_4Cl (aq). The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:20). This resulted in 300 mg (32%) of **221.2** as a colorless oil.

[00960] Synthesis of compound 221.3. 221.3 was prepared from **221.2** in a manner analogous to the synthesis of compound **9.3**. Isolated 300 mg of a colorless oil in 65% yield.

[00961] Synthesis of Compound I-106. Compound **I-106** was prepared from **221.3** and **1.4** in a manner analogous to the synthesis of **136.2**. Isolated 80 mg (60% overall yield) as a white solid. MS (ES): *m/z* 528.8 $(M+H)^+$, 591.8 $(M+Na+CH_3CN)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ1.26 (t, 3H), 1.56 (s, 6H), 2.67 (s, 3H), 3.05 (t, 2H), 4.04 (t, 2H), 4.26 (q, 2H), 7.24-7.40 (m, 4H).

[00962] Example 222: Synthesis of 2-[6-(ethoxycarbonyl)-1-[2-(2-hydroxyphenyl)ethyl]-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-99). .

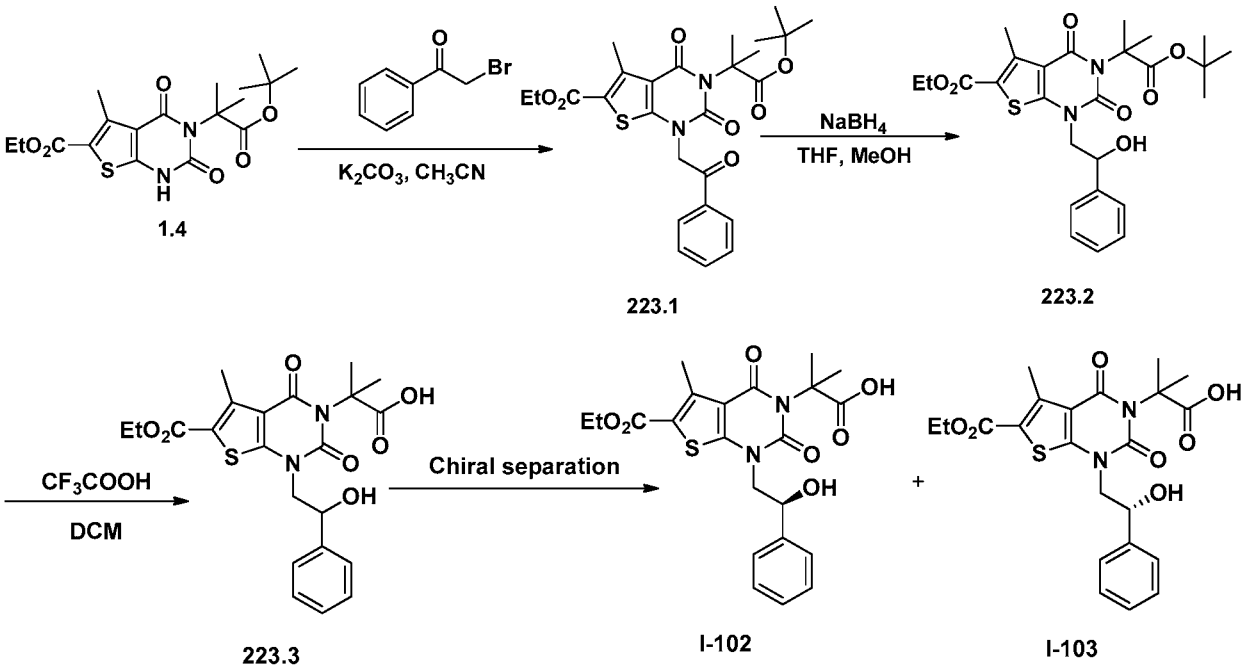


I-93 I-99

[00963] Into a 10-mL round-bottom flask was placed **I-93** (50 mg, 0.11 mmol, 1.00 equiv), BBr_3 (105 mg) and dichloromethane (5 mL). The resulting solution was stirred overnight at room temperature. The reaction was then quenched by the addition of 2 mL of water. The resulting solution was extracted with 3x5 mL of ethyl acetate and the organic layers combined and concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/hexane (1:2). This resulted in 4.6 mg (9%) of **I-99** as a colorless oil. MS (ES): *m/z* 461 $(M+H)^+$. ^1H NMR (CD_3OD, 300Mz): δ 1.29~1.37 (t, 3H), 1.77 (s, 6H), 2.73 (s, 3H), 3.04~3.09 (t, 2H), 4.13~4.17 (t, 2H), 4.26 ~4.33 (q, 2H), 6.68~6.72 (m, 2H), 6.98~7.03 (m, 2H).

[00964] Example 223: Synthesis of 2-[6-(ethoxycarbonyl)-1-[(2S)-2-hydroxy-2-phenylethyl]-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-102) and Example 224: Synthesis of 2-[6-(ethoxycarbonyl)-1-[(2S)-2-hydroxy-2-phenylethyl]-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-

methylpropanoic acid (I-103).



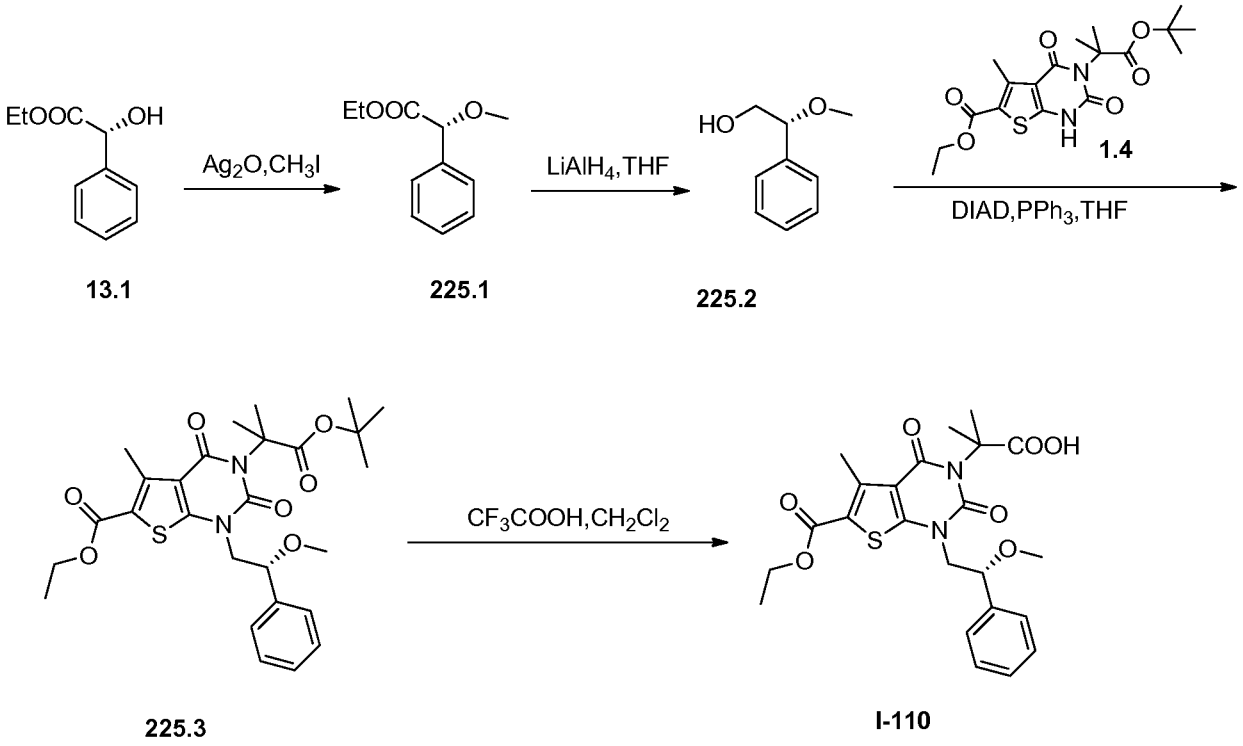
[00965] Synthesis of compound 223.3. Compound **223.3** was prepared from **1.4** and 2-bromo-1-phenylethan-1-one in a manner analogous to the synthesis of **I-60** (Example 203). Isolated 140 mg of a white solid in 60% overall yield from **1.4**.

[00966] Synthesis of Compound I-102 and I-103. The enantiomers of **223.3** (140 mg) were isolated by chiral preparative HPLC under the following conditions (Gilson Gx 281): column: Chiralpak IC(SFC), 2*25 cm, 5 μm; mobile phase: hexanes (0.1% TFA) and ethanol (hold at 10.0% ethanol in 16 min); detector: UV 220/254 nm. This resulted in 15.9 mg (11%) of **I-102** as a white solid and 15.2 mg (11%) of **I-103** as a white solid.

[00967] Analytical data for **I-102**: MS (ES): *m/z* 461 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 1.30 (t, 3H), 1.66 (s, 6H), 2.71 (s, 3H), 3.73 (m, 1H), 4.14 (m, 1H), 4.27 (m, 2H), 4.98 (q, 1H), 5.88 (d, 1H), 7.28-7.41 (m, 5H), 12.3 (s,1H).

[00968] Analytical data for **I-103**: MS (ES): *m/z* 461 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 1.30 (t, 3H), 1.66 (s, 6H), 2.71 (s, 3H), 3.73 (m, 1H), 4.14 (m, 1H), 4.27 (q, 2H), 4.98 (d, 1H), 5.88 (m,1H), 7.28-7.41 (m, 5H), 12.3 (br s, 1H).

[00969] Example 225: Synthesis of 2-[6-(ethoxycarbonyl)-1-[(2R)-2-methoxy-2-phenylethyl]-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-110).

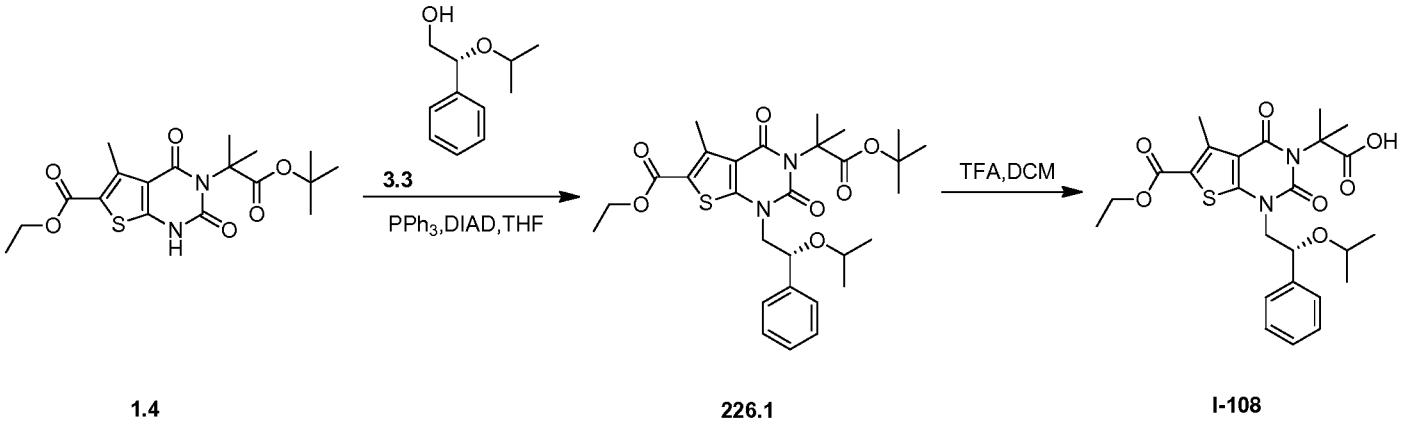


[00970] **Synthesis of compound 225.1. 225.1** was prepared from **13.1** in a manner analogous to the synthesis of **13.2.** Isolated 1.26 g (22%) of a colorless oil.

[00971] **Synthesis of compound 225.2.** Into a 100-mL 3-necked round-bottom flask was placed tetrahydrofuran (50 mL) and **225.1** (1.26 g, 6.49 mmol, 1.00 equiv). This was followed by the addition of $LiAlH_4$ (247 mg, 6.51 mmol, 1.00 equiv) in portions at 0°C. The resulting solution was stirred for 2 h at 0°C. The reaction was then quenched by the addition of 20 mL of NH_4Cl (aq.). The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/hexane (1:5). This resulted in 610 mg (62%) of **225.2** as a colorless oil.

[00972] **Synthesis of Compound I-110.** Compound **I-110** was prepared from **225.2** in a manner analogous to the synthesis of **2.5**. Isolated 70 mg (78%) of a white solid. MS (ES): *m/z* 475 $(M+H)^+$. ^1H NMR (CD_3OD, 300 MHz): δ 1.34 (m, 3H), 1.75 (s, 6H), 2.74 (s, 3H), 3.27 (s, 3H), 3.92 (m, 1H), 4.10 (m, 1H), 4.28 (m, 2H), 4.66 (m, 1H), 7.37 (m, 5H).

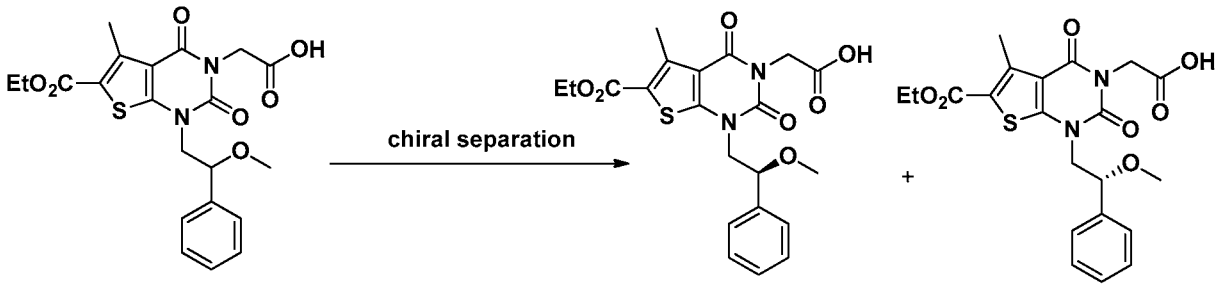
[00973] **Example 226: Synthesis of 2-[6-(ethoxycarbonyl)-5-methyl-2,4-dioxo-1-[(2R)-2-phenyl-2-(propan-2-yloxy)ethyl]-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-108).**



1.4 226.1 I-108

[00974] Compound **I-108** was prepared from **1.4** and **3.3** in a manner analogous to the synthesis of **2.5**. Isolated 51.6 mg (22% overall) of a white solid. MS (ES): *m/z* 503 $(M+H)^+$. ^1H NMR ($CDCl_3$, 400 MHz): δ 0.85 (d, 3H), 0.89 (d, 3H), 1.25~1.33 (t, 3H), 1.67~1.71 (d, 6H), 2.73 (s, 3H), 3.41~3.47 (m, 1H), 3.81~3.85 (m, 1H), 4.02~4.11 (m, 1H), 4.27~4.34 (m, 2H), 4.80~4.82 (m, 1H), 7.32 ~7.37 (m, 1H), 7.41 ~7.42 (d, 4H), 12.45 (s, 1H).

[00975] Example 227: Synthesis of 2-[6-(ethoxycarbonyl)-1-[(2S)-2-methoxy-2-phenylethyl]-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-104) and Example 228: Synthesis of 2-[6-(ethoxycarbonyl)-1-[(2S)-2-methoxy-2-phenylethyl]-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-105).



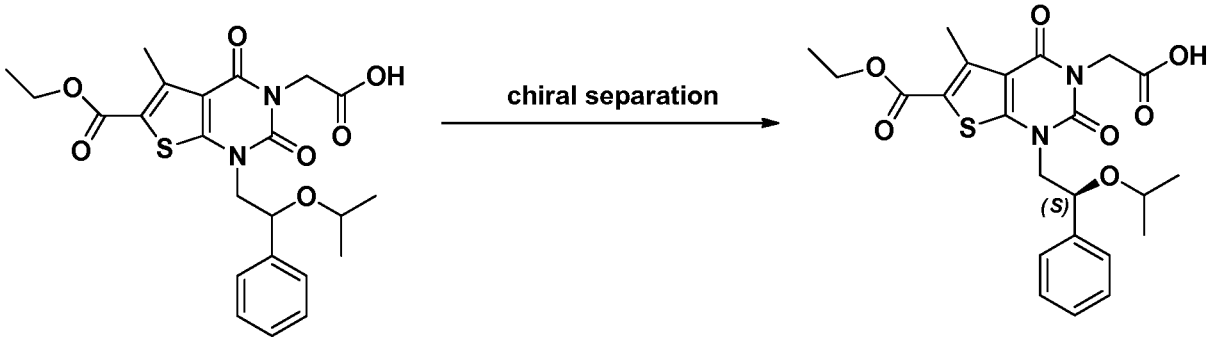
I-67 I-104 I-105

[00976] Synthesis of Compounds I-104 and I-105. The enantiomers of **I-67** were isolated by chiral preparative HPLC under the following conditions (Gilson Gx 281): column: Chiralpak IC(SFC), 2*25 cm, 5 μm; mobile phase: hexanes (0.1% TFA) and ethanol (hold at 30.0% ethanol over 15 min); detector: UV 220/254 nm. This resulted in 4.4 mg of **I-104** as a white solid (tR = 11.52 min) and 3.7 mg of **I-105** as a white solid (tR = 14.07 min).

[00977] Analytical data for **I-104**: MS (ES): *m/z* 446.9 $(M+H)^+$, 509.8 $(M+Na+CH_3CN)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.39 (t, 3H), 2.83 (s, 3H), 3.20 (s, 3H), 4.02 (m, 2H), 4.16 (q, 2H), 4.70 (m, 3H), 7.33-7.46 (m, 5H).

[00978] Analytical data for **I-105**: MS (ES): *m/z* 446.9 $(M+H)^+$, 509.8 $(M+Na+CH_3CN)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.39 (t, 3H), 2.83 (s, 3H), 3.21 (s, 3H), 4.02 (m, 2H), 4.16 (q, 2H), 4.70 (m, 3H), 7.33-7.46 (m, 5H).

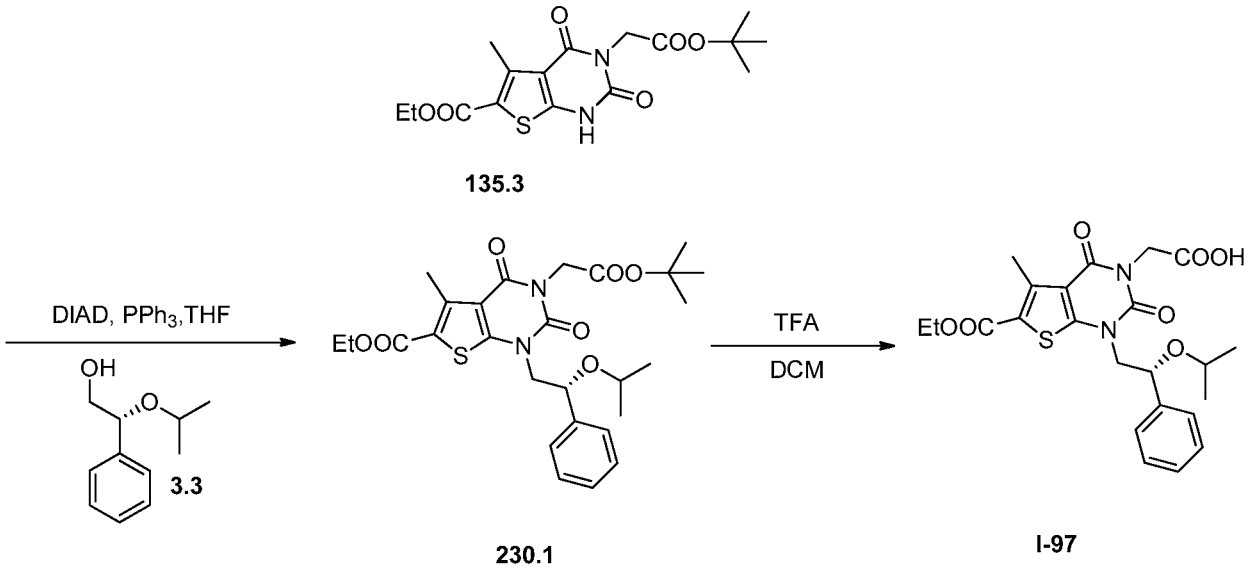
[00979] Example 229: Synthesis of (S)-2-(6-(ethoxycarbonyl)-1-(2-isopropoxy-2-phenylethyl)-5-methyl-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)acetic acid (I-96).



I-89 I-96

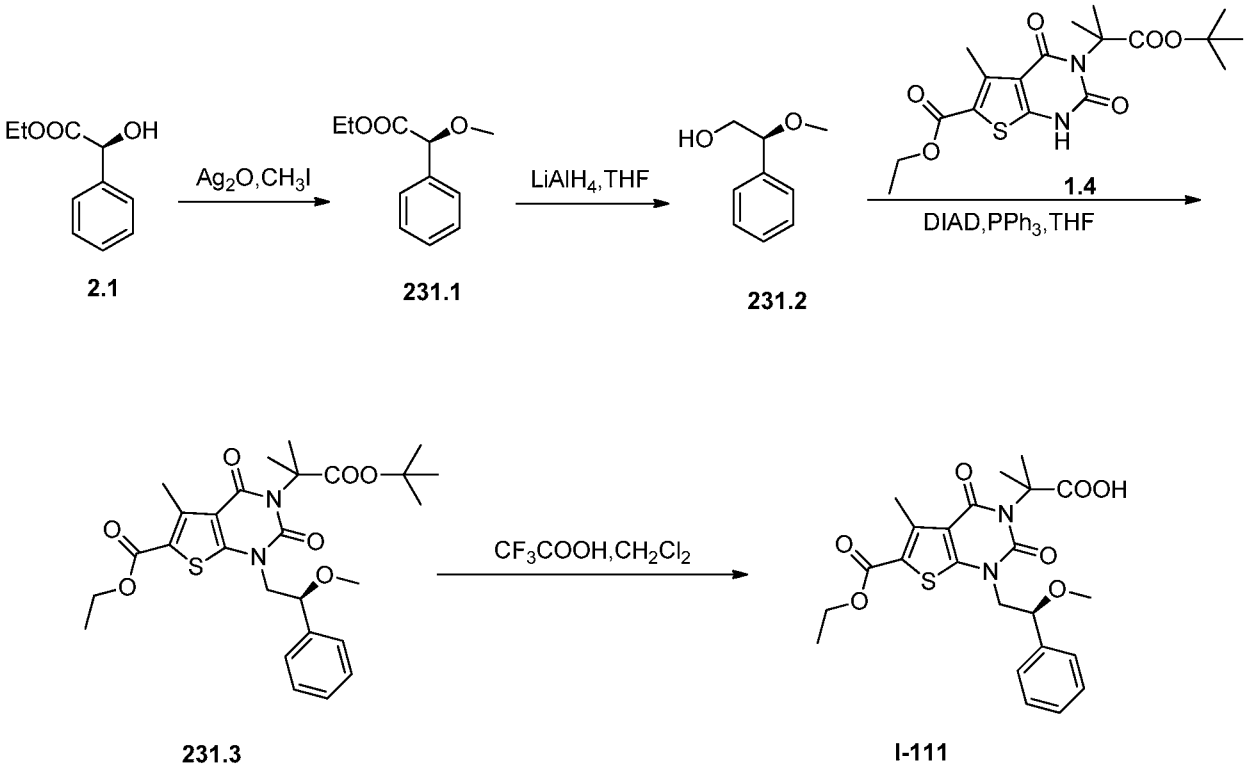
[00980] The (*S*) enantiomer of **I-89** was isolated by chiral preparative HPLC under the following conditions (Gilson Gx 281): column: Chiralpak IC(SFC), 2*25 cm, 5 μm; mobile phase: hexanes and ethanol (0.1% DEA) (hold at 10.0% ethanol(0.1% DEA) in 25 min); detector: UV 220/254 nm. 1.7 mg (tR = 14.9 min, 9%) of product were obtained as a white solid. MS (ES): *m/z* 475 $(M+H)^+$, 497 $(M+Na)^+$, 538 $(M+Na+CH_3CN)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 0.98 (d, 3H), 1.03 (d, 3H), 1.42 (t, 3H), 2.84 (s, 3H), 3.51 (m, 1H), 3.98 (m, 1H), 4.22 (m, 1H), 4.40 (m, 2H), 4.75 (m, 2H), 4.92 (m, 1H), 7.33-7.49 (m, 5H).

[00981] Example 230: Synthesis of (*R*)-2-(6-(ethoxycarbonyl)-1-(2-isopropoxy-2-phenylethyl)-5-methyl-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)acetic acid (I-97).



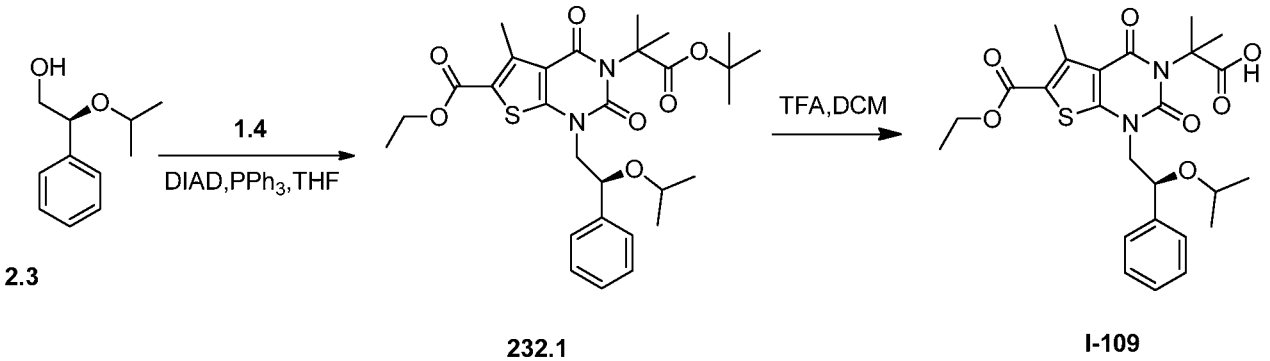
Compound **I-97** was prepared from **135.3** and **3.3** in a manner analogous to the synthesis of compound **2.5**. Isolated 180 mg of a white solid (tR = 17.8 min) in 21% overall yield. MS (ES): *m/z* $(M+H)^+$ 475. ^1H NMR (CD_3OD, 300 MHz): δ 0.90(d, *J* = 6.0 Hz, 3H), 0.97(d, *J* = 6.3 Hz, 3H), 1.35 (t, 3H), 2.80 (s, 3H), 3.48 (m, 1H), 3.88 (m, 1H), 4.16 (m,1H), 4.32 (m, 2H), 4.68 (m, 2H), 4.89 (m, 1H), 7.25-7.44 (m, 5H).

[00982] Example 231: 2-[6-(ethoxycarbonyl)-1-[(2S)-2-methoxy-2-phenylethyl]-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-111).



[00983] Compound **I-111** was prepared from **2.1** and **1.4** in a manner analogous to the synthesis of Compound **I-110** (Example 225). Isolated 65 mg of a white solid in 11% yield from **2.1**. MS (ES): *m/z* 475 $(M+H)^+$. ^1H NMR (CD_3OD, 300 MHz): δ 1.34 (t, 3H), 2.00 (s, 6H), 2.74 (s, 3H), 3.18 (s, 3H), 3.93 (m, 1H), 4.10 (m, 1H), 4.28 (q, 2H), 4.65 (m, 1H), 7.34 (m, 5H).

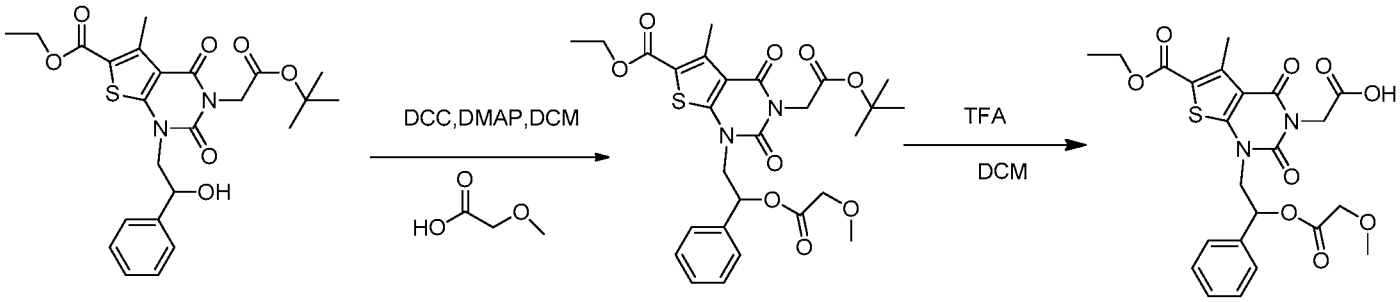
[00984] Example 232: Synthesis of 2-[6-(ethoxycarbonyl)-5-methyl-2,4-dioxo-1-[(2S)-2-phenyl-2-(propan-2-yloxy)ethyl]-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-109).



[00985] Compound **I-109** was prepared from **2.3** and **1.4** in a manner analogous to the synthesis of **2.5**. Isolated 11.3 mg of a white solid in 10% overall yield from **1.4**. MS (ES): *m/z*

503 $(M+H)^+$. ^1H NMR (CD_3OD, 400 MHz): δ 0.97~1.04 (m, 6H), 1.37~1.41 (t, 3H), 1.79~1.81 (d, 6H), 2.79 (s, 3H), 3.48~3.51 (m, 1H), 3.82~3.87 (m, 1H), 4.14~4.17 (m, 1H), 4.32~4.38 (m, 2H), 4.87~4.92 (m, 1H), 7.31~7.34 (m, 1H), 7.38~7.42 (t, 2H), 7.45~7.47 (d, 2H).

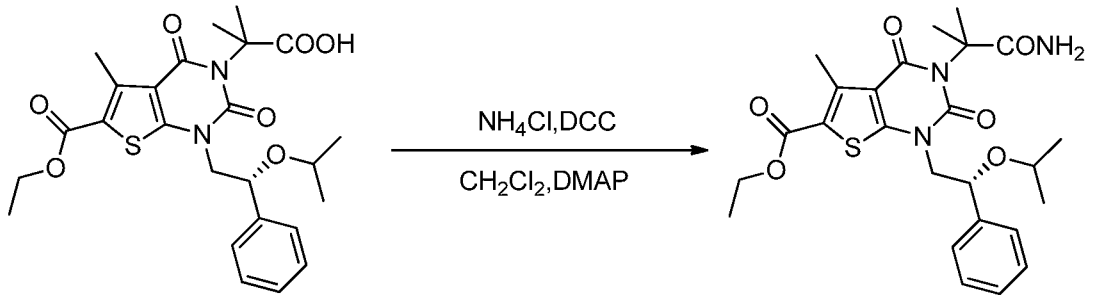
[00986] Example 233: Synthesis of 2-[6-(ethoxycarbonyl)-1-[2-[(2-methoxyacetyl)oxy]-2-phenylethyl]-5-methyl-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]acetic acid (I-101).



[00987] Synthesis of compound 233.1 Into a 50-mL round-bottom flask was placed **203.2** (200 mg, 0.41 mmol, 1.00 equiv), DCC (101 mg, 0.49 mmol, 1.20 equiv), 4-dimethylaminopyridine (90 mg, 0.74 mmol, 1.80 equiv), dichloromethane (10 mL) and 2-methoxyacetic acid (73 mg, 0.81 mmol, 1.98 equiv). The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). This resulted in 190 mg (85%) of **233.1.**

[00988] Synthesis of Compound I-101. Compound **I-101** was prepared from **233.1** in a manner analogous to the synthesis of compound **2.5**. Isolated 60.4 mg (67%) of a white solid. MS (ES): *m/z* 527 $(M+H)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 1.33 (t, 3H), 2.74 (s, 3H), 3.16 (s, 3H), 3.91 (d, 1H), 4.09 (d, 1H), 4.34 (m, 4H), 4.53 (s, 2H), 6.18 (m, 1H), 7.35-7.44 (m, 5H) 13.05 (br s, 1H).

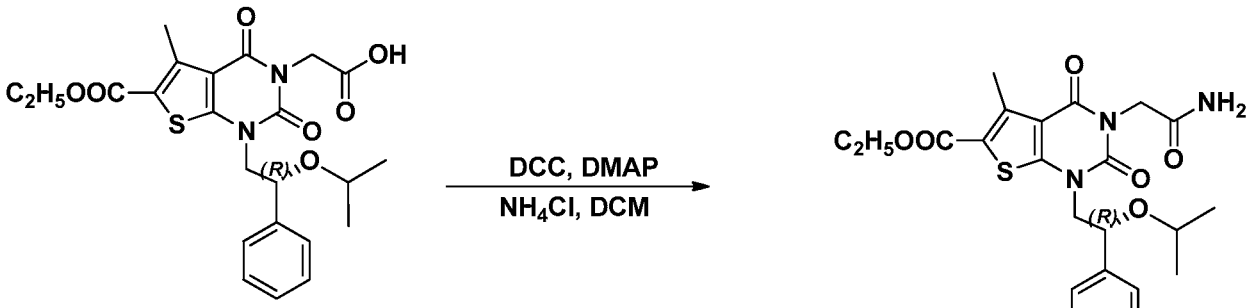
[00989] Example 234: Synthesis of ethyl 3-(1-carbamoyl-1-methylethyl)-5-methyl-2,4-dioxo-1-[(2R)-2-phenyl-2-(propan-2-yloxy)ethyl]-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-115).



I-108 I-115

[00990] Compound **I-115** was prepared from **I-108** (Example 226) and ammonium chloride in a manner analogous to the synthesis of **I-121** (Example 4). Isolated 0.059 g (42%) of a white solid. MS (ES): *m/z* 524 $(M+Na)^+$. ^1H NMR (DMSO-d_6, 300 MHz): δ 0.90 (m, 6H), 1.26 (t, 3H), 1.63 (d, J = 8.1 Hz, 6H), 3.29 (s, 3H), 3.40 (m, 1H), 3.73 (m, 1H), 4.03 (m, 1H), 4.26 (m, 2H), 4.74 (m, 1H), 7.23 (m, 5H).

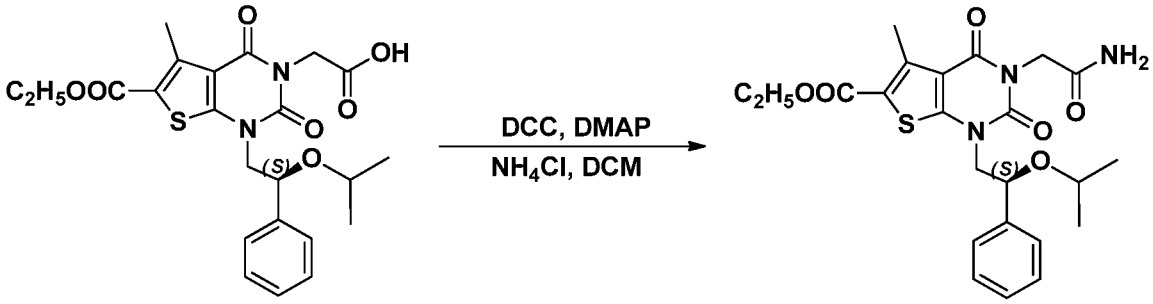
[00991] Example 235: Synthesis of ethyl 3-(carbamoylmethyl)-5-methyl-2,4-dioxo-1-[(2R)-2-phenyl-2-(propan-2-yloxy)ethyl]-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-112).



I-97 I-112

[00992] Compound **I-112** was prepared from **I-97** (Example 230) and ammonium chloride in a manner analogous to the synthesis of **I-121** (Example 4). Isolated 53.7 mg (41%) of a white solid. MS (ES): *m/z* 474 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ 0.97(d, 3H), 0.99 (d, 3H), 1.37 (t, 3H), 2.78 (s, 3H), 3.49 (m, 1H), 3.88 (m, 1H), 4.15 (dd, 1H), 4.32 (q, 2H), 4.65 (s, 2H) , 4.87 (m, 1H), 7.25-7.44 (m, 5H).

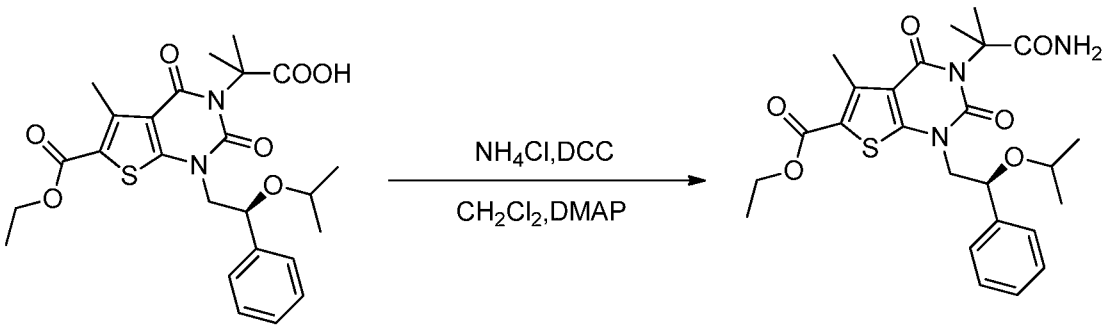
[00993] Example 236: Synthesis of ethyl 3-(carbamoylmethyl)-5-methyl-2,4-dioxo-1-[(2S)-2-phenyl-2-(propan-2-yloxy)ethyl]-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-113).



I-96 I-113

[00994] Compound **I-113** was prepared from **I-96** (Example 229) and ammonium chloride in a manner analogous to the synthesis of **I-121** (Example 4). MS (ES): *m/z* 474 $(M+H)^+$. ^1H NMR (300 MHz, CD_3OD): δ 0.97 (d, 3H), 0.99 (d, 3H), 1.37 (t, 3H), 2.78 (s, 3H), 3.49 (m, 1H), 3.88 (m, 1H), 4.15 (dd, 1H), 4.32 (q, 2H), 4.65 (s, 2H), 4.87 (m,1H), 7.25-7.44 (m, 5H).

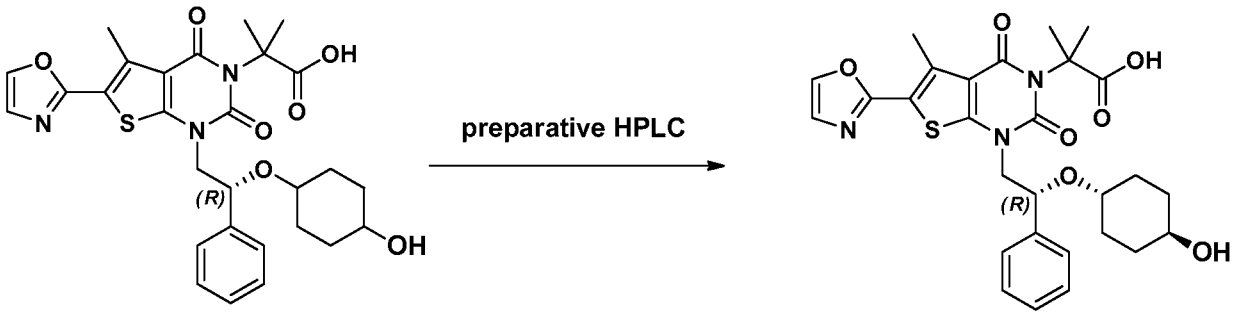
[00995] Example 237: Synthesis of ethyl 3-(1-carbamoyl-1-methylethyl)-5-methyl-2,4-dioxo-1-[(2S)-2-phenyl-2-(propan-2-yloxy)ethyl]-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-6-carboxylate (I-114).



I-109 I-114

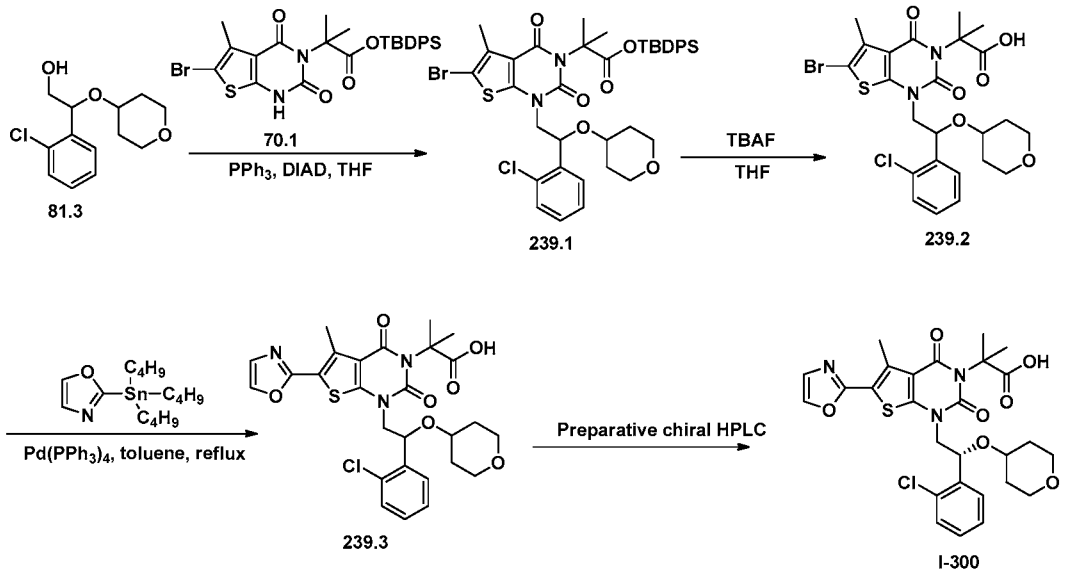
[00996] Compound **I-114** was prepared from **I-109** (Example 232) and ammonium chloride in a manner analogous to the synthesis of **I-121** (Example 4). Isolated 0.064 g (64%) of a white solid. MS (ES): *m/z* 524 $(M+H)^+$. ^1H NMR (DMSO-d_6, 300 MHz): δ 0.89 (m, 6H), 1.26 (q, 3H), 1.62 (d, J = 8.7 Hz, 6H), 2.67 (s, 3H), 3.38 (m, 1H), 3.76 (m, 1H), 4.03 (m, 1H), 4.26 (m, 2H), 4.75 (m, 1H), 7.35 (m, 5H).

[00997] Example 238: Synthesis of 2-[1-[(2R)-2-[(4-hydroxycyclohexyl)oxy]-2-phenylethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-165).



[00998] The (*R*)-enantiomer of compound **46.2** (30 mg) was isolated by preparative HPLC under the following conditions (Waters): Column: XBridge Shield RP18 OBD 5 μm, 19*150 mm; mobile phase: water (50 mM NH_4HCO_3) and CH_3CN (6.0% CH_3CN up to 50.0% in 14 min); detector: UV 254/220 nm. 11.1 mg of **I-165** (tR = 8.82) were obtained as a white solid. MS (ES): *m/z* 554 $(M+H)^+$, 576 $(M+Na)^+$, 617 $(M+Na+CH_3CN)^+$. ^1H NMR (300MHz, CD_3OD): δ 1.29-1.38 (m, 6H), 1.44-1.64 (m, 2H), 1.75 (s, 6H), 2.77 (s, 3H), 3.50 (m, 1H), 3.81 (m, 1H), 4.19 (m, 1H), 4.95 (m, 1H), 7.24-7.45 (m, 6H), 7.94 (s, 1H).

[00999] Example 239: Synthesis of 2-[1-[(2R)-2-(2-chlorophenyl)-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-300).

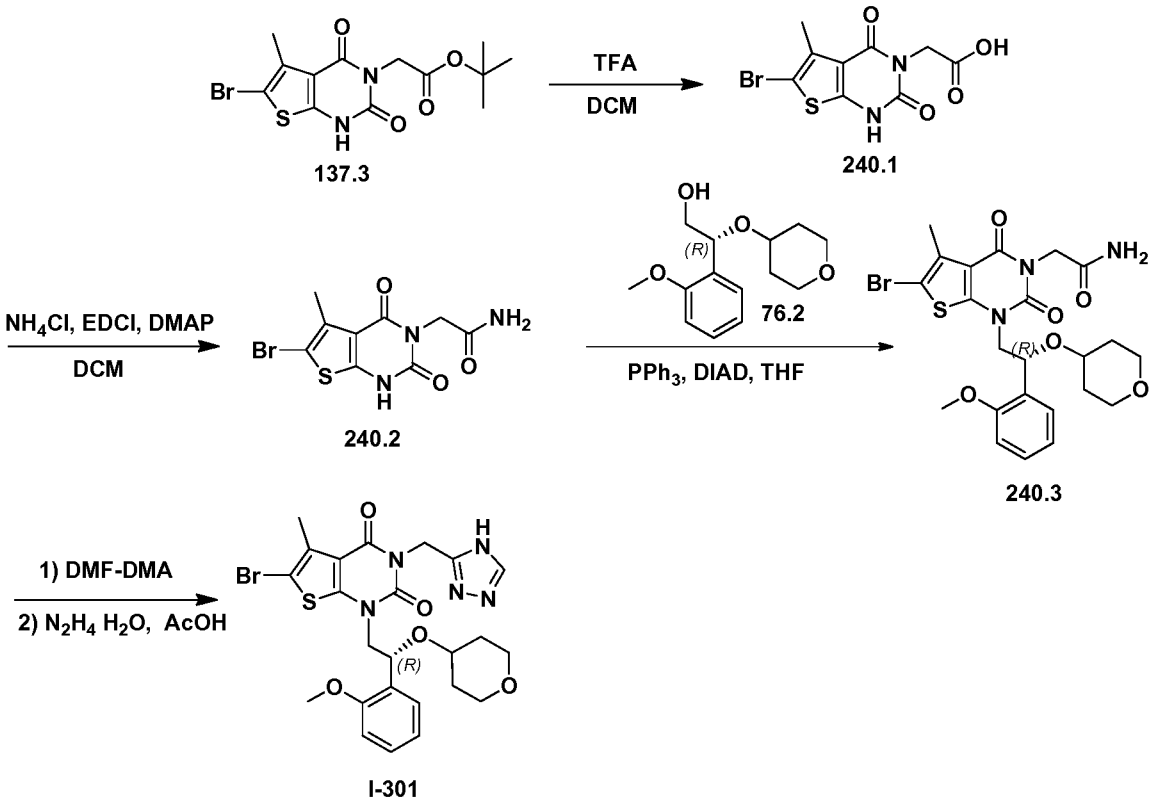


[001000] **Synthesis of compound 239.2.** Compound **239.2** was prepared from **70.1** and **81.3** in a manner analogous to **I-264** (Example 96). Isolated 180 mg of a colorless oil in 36% yield from **70.1**.

[001001] **Synthesis of compound 239.3.** Compound **239.3** was prepared from **239.2** in a manner analogous to the synthesis of **I-120** (Example 2). Isolated a 40 mg (23%) of a colorless oil.

[001002] **Synthesis of Compound I-300.** The crude product (41 mg) was purified by chiral preparative HPLC under the following conditions (Gilson Gx 281): Column: Chiralpak IA, 2*25 cm, 5 μm; mobile phase: hexanes and IPA (hold at 20% IPA over 22 min); detector: UV 220/254 nm. Purification afforded 2.8 mg (7%) of Compound **I-300** as a white solid. MS (ES): *m/z* 574 $(M+H)^+$. ^1H NMR (300MHz, CD_3OD): δ 8.00 (s, 1H), 7.75 (d, 1H, *J* = 6.0 Hz), 7.45 (m, 2H), 7.35 (d, 1H, *J* = 5.1 Hz), 7.29 (s, 1H), 5.49 (q, 1H, *J* = 5.1Hz), 4.32 (m, 1 H), 3.99 (m, 1H), 3.70 (m, 2 H), 3.50 (m, 1H), 3.40 (m, 2H), 2.83 (s, 3H), 1.82 (s, 3H), 1.80 (s, 3H), 1.75 (m, 2H), 1.52 (m, 2H).

[001003] **Example 240: Synthesis of 6-bromo-1-[(2R)-2-(2-methoxyphenyl)-2-(oxan-4-yloxy)ethyl]-5-methyl-3-(4H-1,2,4-triazol-3-ylmethyl)-1H,2H,3H,4H-thieno[2,3-d]pyrimidine-2,4-dione (I-301).**

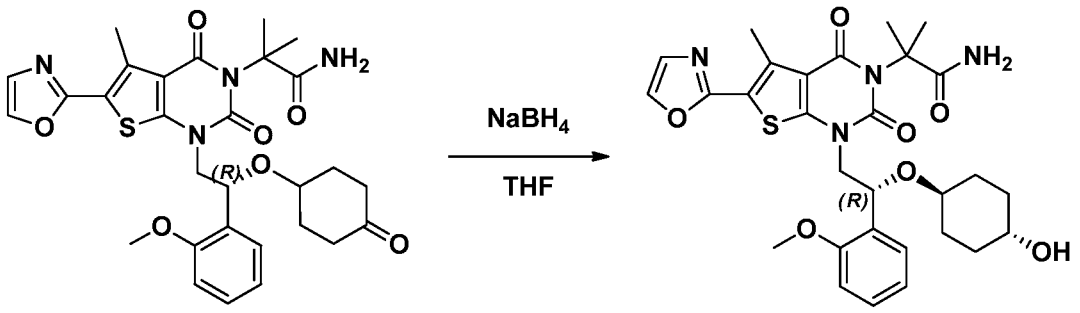


[001004] **Synthesis of compound 240.1.** Compound **240.1** was prepared from **137.3** in a manner analogous to the synthesis of **136.2** from **136.1**. Isolated 1.9 g of a white solid in 97% yield.

[001005] **Synthesis of compound 240.3.** Compound **240.3** was prepared from **240.1** and **76.2** in a manner analogous to the synthesis of **I-285** from **141.1** (Example 141). Isolated 106 mg of a white solid in 6% overall yield.

[001006] **Synthesis of Compound I-301.** Compound **I-301** was prepared from **240.3** in a manner analogous to the synthesis of **I-289** from **I-285** (Example 145). Isolated 40 mg of a white solid in 43% yield. MS (ES): *m/z* 576 $(M+H)^+$. ^1H NMR (300MHz, d_6-DMSO): δ 13.81 (1H, br s), 8.42 (1H, s), 7.49-7.46 (1H, dd, J_1 = 7.2 Hz, J_2 = 1.5 Hz), 7.31 (1H, m), 7.05-6.98 (2H, m), 5.23-5.16 (3H, m), 4.15-4.09 (1H, m), 3.77-3.75 (4H, m), 3.53-3.48 (2H, m), 3.29-3.24 (2H, m), 2.36 (3H, s), 1.59 (2H, m), 1.28-1.15 (2H, m).

[001007] **Example 241: Synthesis of 2-[1-[(2R)-2-[(4-hydroxycyclohexyl)oxy]-2-(2-methoxyphenyl)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanamide (I-302).**



129.1 I-302

[001008] Compound **I-302** was prepared from **129.1** in a manner analogous to the synthesis of **I-279** from **129.1**. The desired enantiomer was isolated by preparative HPLC under the following conditions (Waters): Column: HPrepC-012(T) Xbridge Prep Phenyl 5 μm, 19*150 mm; mobile phase: water (50 mM NH_4HCO_3) and CH_3CN (30.0% CH_3CN up to 70.0% in 15 min); detector: 254/220 nm. This resulted in 17.4 mg (3%) of **I-302** (9.34 min) as a white solid. MS (ES): *m/z* 605 $(M+Na)^+$. ^1H NMR (300 MHz, DMSO-d_6): δ 1.02-1.08 (m, 4H), 1.21 (m, 1H), 1.59 (m, 4H), 1.66 (d, 6H), 2.74 (s, 3H), 3.17 (m,1H), 3.78 (s, 3H), 3.99 (m, 2H), 4.29 (s, 1H), 5.28 (t, 1H), 6.79-7.28 (m, 4H), 7.30 (m,1H), 7.37 (s,1H), 7.47 (m, 1H), 8.21 (s, 1H).

[001009] Example 242: Synthesis of (*S*)-2-(1-(2-(2-(cyanomethyl)phenyl)-2-((tetrahydro-2H-pyran-4-yl)oxy)ethyl)-5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)-2-methylpropanoic acid (I-303).

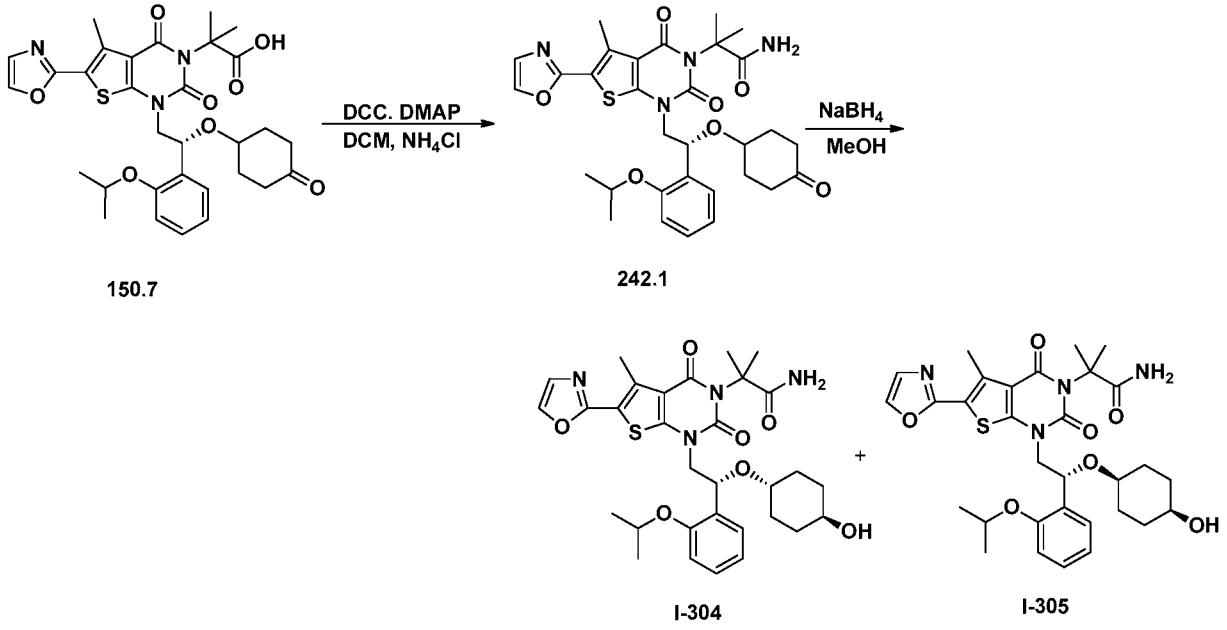


154.7 I-303

[001010] The *S* enantiomer of **154.7** was isolated by chiral preparative HPLC under the following conditions: column: CHIRALPK IC-3; mobile phase: hexanes (0.1% AcOH):IPA = 70:30; detector: UV 254 nm; retention time: 23.375 min. 11.4 mg (white solid) of the desired product were obtained. MS (ES): *m/z* 579 $(M+H)^+$, 601 $(M+Na)^+$. ^1H NMR (400 MHz, DMSO-

d_6): δ 12.41 (br s, 1 H) , 8.26 (s, 1H), 7.63 (d, 1H), 7.49-7.42 (m, 4H), 5.12 (d, 1H), 4.31-4.16 (m, 3H), 3.70 (s, 1H), 3.53 (d, 1H), 3.43-3.32 (m, 2H), 3.25-3.20 (m, 2H), 2.78 (s, 3H), 1.72-1.62 (m, 8H), 1.33-1.21 (m, 2H).

[001011] Example 243: Synthesis of 2-(1-((R)-2-(((1r,4R)-4-hydroxycyclohexyl)oxy)-2-(2-isopropoxyphenyl)ethyl)-5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)-2-methylpropanamide (I-304) and Example 244: Synthesis of 2-(1-((R)-2-(((1s,4S)-4-hydroxycyclohexyl)oxy)-2-(2-isopropoxyphenyl)ethyl)-5-methyl-6-(oxazol-2-yl)-2,4-dioxo-1,2-dihydrothieno[2,3-d]pyrimidin-3(4H)-yl)-2-methylpropanamide (I-305).



[001012] Synthesis of compound 242.1. Compound **242.1** was prepared from **150.7** in a manner analogous to **I-121** (Example 4). Isolated 1.6 g (84%) of a white solid.

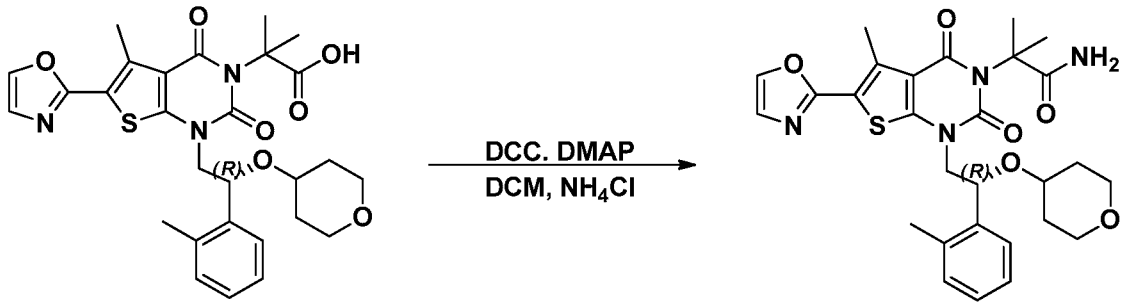
[001013] Synthesis of Compounds I-304 and **I-305**. Into a 50-mL round-bottom flask was placed **242.1** (1.6 g, 2.63 mmol, 1.00 equiv) and methanol (20 mL). This was followed by the addition of $NaBH_4$ (208 mg, 5.50 mmol, 2.09 equiv) at 0 °C. The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified by thin layer chromatography developed with dichloromethane/MeOH/HOAc (30:1:0.15). This resulted in 86.4 mg (5%) of **I-304** as a white solid and 270 mg (17%) of **I-305** as a white solid.

[001014] Analytical data for I-304: MS (ES): *m/z* 633 $(M+Na)^+$. ^1H NMR (400 MHz,

CD_3OD): δ 1.15-1.39 (m, 10H), 1.69-1.80 (m, 10H), 2.82 (s, 3H), 3.17 (m, 1H), 3.52 (m, 1H), 3.95 (m, 1H), 4.18 (m, 1H), 4.69 (m, 1H), 5.42 (t, 1H), 6.99 (m, 2H), 7.28 (m, 2H), 7.52 (m, 1H), 8.01 (s, 1H).

[001015] **Analytical data for I-305**: MS (ES): *m/z* 633 $(M+Na)^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.31-1.49 (m, 12H), 1.70-1.83 (m, 8H), 2.82 (s, 3H), 3.50 (m, 1H), 4.02-4.22 (m, 2H), 4.69 (m, 1H), 5.43 (t, 1H), 6.99 (m, 2H), 7.28 (m, 2H), 7.55 (m, 1H), 7.98 (s, 1H).

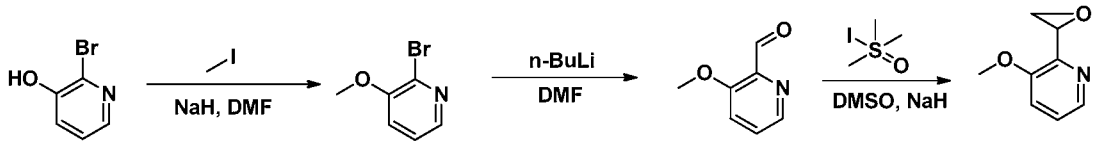
[001016] **Example 244: Synthesis of 2-[1-[(2R)-2-[(4-hydroxycyclohexyl)oxy]-2-[2-(propan-2-yloxy)phenyl]ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanamide (I-306).**



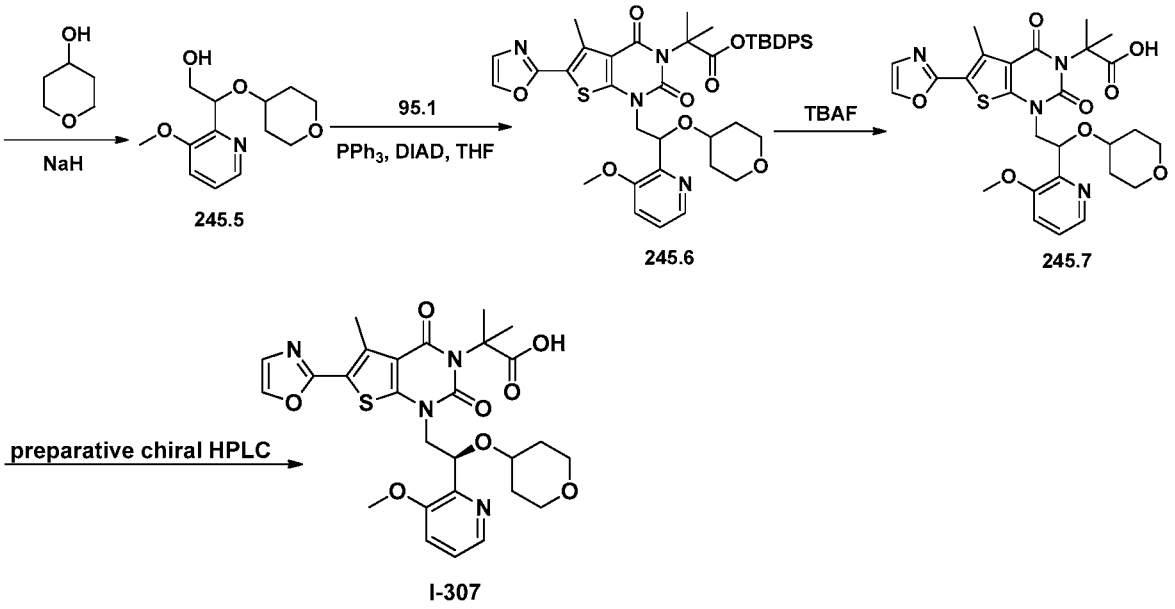
I-282 I-306

[001017] Compound **I-306** was prepared from **I-282** in a manner analogous to the synthesis of **I-121** (Example 4). MS (ES): *m/z* 575 $(M+Na)^+$. ^1H NMR (400 MHz, DMSO-d_6): δ 1.12-1.30 (m, 2H), 1.58-1.71 (m, 8H), 2.43-2.51 (s, 3H), 2.75 (s, 3H), 3.19-3.24 (m, 2H), 3.33-3.49 (m, 2H), 3.51-353 (m, 1H), 4.17-4.20 (m, 1H), 5.10-5.13 (m, 1H), 6.80 (br s, 1H), 7.20 (br s, 1H), 7.21-7.31 (m, 3H) , 7.40 (s, 1H), 7.54 (m, 1H), 8.24 (s, 1H).

[001018] **Example 245: Synthesis of 2-[1-[(2R)-2-(3-methoxypyridin-2-yl)-2-(oxan-4-yloxy)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-307).**



245.1 245.2 245.3 245.4

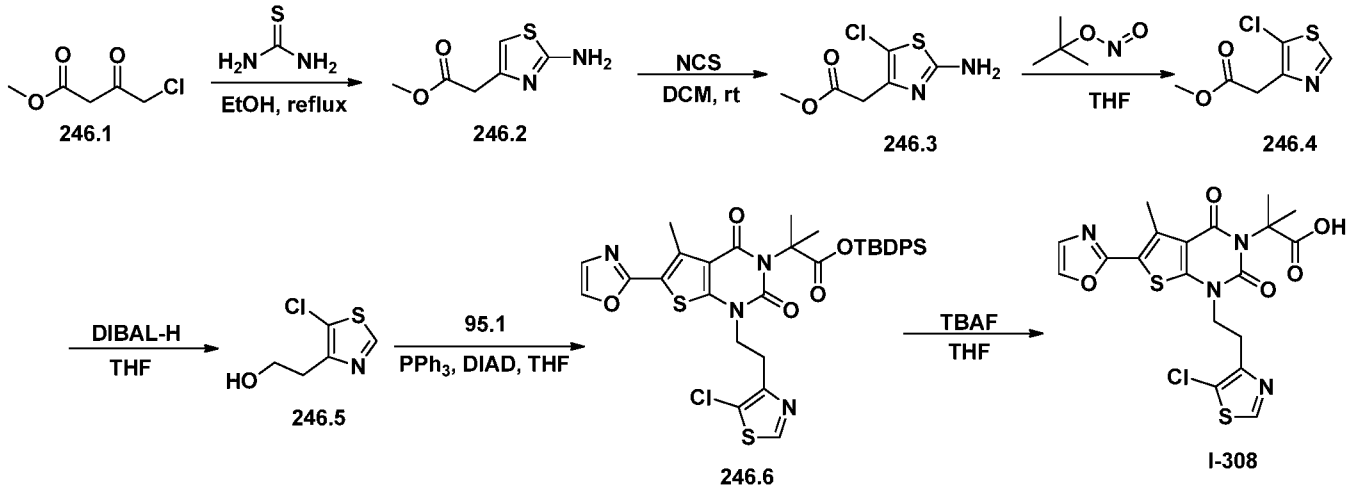


[001019] **Synthesis of compound 245.4.** Compound **245.4** was prepared from **245.1** in a manner analogous to the synthesis of **149.4** from **149.1**. Isolated 500 mg of a yellow oil in 5% overall yield.

[001020] **Synthesis of compound 245.5.** Compound **245.5** was prepared from **245.4** in a manner analogous to the synthesis of **73.2** from **73.1**. Isolated 200 mg (24%) of a colorless oil.

[001021] **Synthesis of Compound I-307.** Compound **I-307** was prepared from **245.4** in a manner analogous to the synthesis of Compound **I-265** (Example 97). Purification: **I-307** (20 mg) was isolated by chiral preparative HPLC under the following conditions (Gilson Gx 281): Column: Chiralpak IC, 2*25 cm, 5 μm; mobile phase: hexanes and EtOH (0.1% HAC) (hold at 30.0% EtOH (0.1% HAC) for 13 min); detector: UV 254/220 nm. Isolated 2.4 mg of **I-307** (retention time 10.9 min) as a white solid. MS (ES): *m/z* 571 $(M+H)^+$, 593 $(M+Na)^+$. ^1H NMR (300 MHz, CD_3OD): δ 1.33-1.48 (m, 2H), 1.67-1.75 (m, 8H), 2.67 (s, 3H), 3.21 (m, 2H), 3.63-3.70 (m, 6H), 4.32 (m, 1H), 4.57 (m, 1H), 6.20 (m, 1H), 7.11 (m, 1H), 7.29 (d, 2H), 7.82 (s, 1H), 8.09 (m, 1H).

[001022] **Example 246: Synthesis of 2-[1-[2-(5-chloro-1,3-thiazol-4-yl)ethyl]-5-methyl-6-(1,3-oxazol-2-yl)-2,4-dioxo-1H,2H,3H,4H-thieno[2,3-d]pyrimidin-3-yl]-2-methylpropanoic acid (I-308).**



[001023] **Synthesis of 246.2.** Into a 1000-mL 3-necked round-bottom flask was placed methyl 4-chloro-3-oxobutanoate (28 g, 185.97 mmol, 1.00 equiv), thiourea (15.2 g, 199.68 mmol, 1.07 equiv) and ethanol (400 ml, 46.69 equiv). The resulting solution was heated to reflux for 4 hr. The solids were collected by filtration. 20 g (62%) of **246.2** were obtained as a light yellow solid.

[001024] **Synthesis of 246.3.** Into a 50-mL 3-necked round-bottom flask was placed **246.2** (10 g, 58.07 mmol, 1.00 equiv) and dichloromethane (40 mL). This was followed by the addition of NCS (7.76 g, 58.11 mmol, 1.00 equiv) dropwise with stirring at 0 °C. The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). Purification afforded 1 g (crude) of **246.3** as a yellow solid.

[001025] **Synthesis of 246.4.** Into a 100-mL 3-necked round-bottom flask was placed **246.3** (1 g, 4.84 mmol, 1.00 equiv), tetrahydrofuran (40 mL) and tert-butyl nitrite (8.98 g, 87.08 mmol, 18.00 equiv). The resulting solution was stirred for 0.5 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:10). Purification afforded 200 mg (22%) of **246.4** as a yellow oil.

[001026] **Synthesis of 246.5.** Into a 100-mL 3-necked round-bottom flask, purged and maintained with an inert atmosphere of nitrogen, was placed **246.4** (200 mg, 1.04 mmol, 1.00 equiv) and tetrahydrofuran (50 mL). This was followed by the addition of DIBAL-H (5 mL, 25% in toluene) dropwise with stirring at -78 °C. The resulting solution was stirred for 0.5 h at -78 °C.

The reaction was then quenched by the addition of 50 mL of NH_4Cl (aq). The resulting solution was extracted with 3x100 mL of ethyl acetate and the organic layers combined. The residue was applied onto a silica gel column with ethyl acetate/petroleum ether (1:5). Purification afforded 40 mg (23%) of **246.5** as a yellow oil.

[001027] **Synthesis of Compound I-308.** Compound **I-308** was prepared from **246.5** and **95.1** in a manner analogous to the synthesis of Compound **I-264** (Example 96). 11.2 mg (14% from **95.1**) of **I-308** were isolated as a white solid. MS (ES): *m/z* 481 $(M+H)^+$. ^1H NMR (400 MHz, DMSO): δ 1.67 (s, 6H), 2.75 (s, 3H), 3.09-3.13 (t, 2H), 4.14-4.18 (t, 2H), 7.40 (s, 1H), 7.48 (s, 1H), 8.24 (s, 1H).

[001028] Additional compounds of formula **I** were prepared in a manner substantially similar to that described above. Mass spectroscopy data are provided in Table 1, *supra*.

[001029] In certain embodiments, compounds of the present invention are assayed as inhibitors of ACC using methods known in the art including those contained in Harwood et al. Isozyme-nonselective *N*-Substituted Bipiperidylcarboxamide Acetyl-CoA Carboxylase Inhibitors Reduce Tissue Malonyl-CoA Concentrations, Inhibit Fatty Acid Synthesis, and Increase Fatty Acid Oxidation in Cultured Cells and in Experimental Animals, J. Biol. Chem., 2003, vol. 278, 37099-37111. In some embodiments the assays used are selected from an *in vitro* ACC enzyme inhibition assays, *in vitro* cell culture assays, and *in vivo* efficacy assays in animals. In some embodiments, assay results for compounds of the present invention are compared to results obtained for known inhibitors of ACC or related enzymes. In some embodiments, the ACC inhibitor used for comparison is CP-640186 or soraphen A.

[001030] Compounds of the present invention were evaluated in an *in vitro* ACC inhibition assay as described by Harwood, et al, 2003, the entirety of which is incorporated herein by reference.

Example 247

In Vitro Acetyl-CoA Carboxylase (ACC) Inhibition Assay

[001031] An exemplary procedure for the *in vitro* ACC inhibition assay, which can be used to determine the inhibitory action of compounds of the invention toward either ACC1 or ACC2, follows. The ADP-Glo™ Kinase Assay kit from Promega was used. The ADP-Glo™ Kinase Assay is a luminescent ADP detection assay to measure enzymatic activity by quantifying the amount of ADP produced during an enzyme reaction. The assay is performed in two steps; first,

after the enzyme reaction, an equal volume of ADP-Glo™ Reagent is added to terminate the reaction and deplete the remaining ATP. Second, the Kinase Detection Reagent is added to simultaneously convert ADP to ATP and allow the newly synthesized ATP to be measured using a luciferase/luciferin reaction. Luminescence can be correlated to ADP concentrations by using an ATP-to-ADP conversion curve. The detailed procedure is as follows. 50 μL of the compound being tested (600 uM in DMSO) was added to a 384-well dilution plate. The compound was diluted 1:3 in succession in DMSO for each row for 11 wells. .5 μL ACC2 working solution was added to 384-well white Optiplate assay plate. 0.5 μL diluted compound solution in each column from step 2 to assay plate, each row containing 2 replicates. For the last 2 rows, add 0.5 μL negative control (DMSO) in one row and 0.5 μL positive control (compound I-97) in the other. The plates were incubated at room temperature for 15 minutes. 5 μL substrate working solution was added to each well to initiate reaction. Final ACC2 reaction concentrations consist of: 5 nM ACC2, 20 μM ATP, 20 μM acetyl-CoA, 12 mM NaHCO3, 0.01% Brij35, 2 mM DTT, 5% DMSO, test compound concentrations: 30 μM, 10 μM, 3.33 μM, 1.11 μM, 0.37 μM, 0.123 μM, 0.0411 μM, 0.0137 μM, 0.00457 μM, 0.00152 μM, and 0.00051 μM. Plates were incubated at room temperature for 60 minutes. 10 μL ADP glo reagent was added. Plates were incubated at room temperature for 40 minutes. 20 μL kinase detection reagent was added. Plates were incubated at room temperature for 40 minutes, then read on a Perkin Elmer EnVision 2104 plate reader for luminescence as Relative Light Units (RLU).

[001032] Data for each concentration, as well as the positive and negative controls were averaged, and the standard deviation calculated. Percent inhibition was calculated by the formula: 100 x (average negative control – compound) / (average negative control – average positive control). The IC50 for each compound was calculated by fitting the data with a non-linear regression equation: Y=Bottom + (Top-Bottom)/(1+10^((LogIC50-X)*HillSlope)), where X is the log of compound concentration and Y is percent inhibition.

[001033] The results of the *in vitro* ACC1 and ACC2 inhibition assays are set forth in **Table 2**. The compound numbers correspond to the compound numbers in **Table 1**. Compounds having an activity designated as "AAA" provided an $IC_{50} \leq 0.1$ μM; compounds having an activity designated as "AA" provided an $IC_{50} \leq 1$ μM; compounds having an activity designated as "A" provided an $IC_{50} \leq 5$ μM; compounds having an activity designated as "B" provided an IC_{50} of 5-20 μM; compounds having an activity designated as "C" provided an IC_{50}

of 20-50 μM; and compounds having an activity designated as "D" provided an $IC_{50} \geq 50$ μM. "NA" stands for "not assayed." Enzyme inhibition curves for compound I-158 against ACC1 and ACC2 are shown in **Figure 1**. Enzyme inhibition curves for compound I-181 against ACC1 and ACC2 are shown in **Figure 6.**

Table 2. Results of *in vitro* ACC1 and ACC2 inhibition assays.

Compound ID	ACC1	ACC2
I-1	A	B
I-2	NA	D
I-3	NA	C
I-4	NA	C
I-5	NA	D
I-6	NA	C
I-7	NA	D
I-8	NA	B
I-9	NA	D
I-10	NA	D
I-11	NA	D
I-12	NA	D
I-13	A	A
I-14	A	A
I-15	NA	D
I-16	NA	D
I-17	NA	D
I-18	NA	D
I-19	A	B
I-20	B	A
I-21	NA	D
I-22	NA	D

Compound ID	ACC1	ACC2
I-23	NA	C
I-24	NA	D
I-25	NA	D
I-26	NA	B
I-27	NA	D
I-28	NA	D
I-29	NA	D
I-30	NA	D
I-31	A	A
I-32	A	A
I-33	B	B
I-34	NA	B
I-35	NA	D
I-36	NA	C
I-37	NA	B
I-38	NA	D
I-39	NA	C
I-40	NA	D
I-41	NA	D
I-42	NA	C
I-43	NA	B
I-44	NA	D

Compound ID	ACC1	ACC2
I-45	A	A
I-46	A	A
I-47	NA	D
I-48	NA	B
I-49	NA	D
I-50	NA	D
I-51	NA	D
I-52	D	D
I-53	NA	B
I-54	NA	B
I-55	A	A
I-56	NA	A
I-57	NA	D
I-58	NA	D
I-59	NA	D
I-60	A	A
I-61	A	A
I-62	NA	B
I-63	NA	C
I-64	NA	D
I-65	NA	D
I-66	NA	A
I-67	NA	A
I-68	NA	B
I-69	NA	A
I-70	AA	AA
I-71	NA	D
I-72	NA	D

Compound ID	ACC1	ACC2
I-73	NA	C
I-74	NA	B
I-75	NA	B
I-76	NA	A
I-77	NA	B
I-78	NA	A
I-79	NA	B
I-80	NA	A
I-81	NA	B
I-82	NA	B
I-83	NA	A
I-84	NA	D
I-85	NA	A
I-86	NA	B
I-87	NA	A
I-88	NA	D
I-89	AA	AA
I-90	NA	C
I-91	NA	B
I-92	NA	A
I-93	AA	AA
I-94	NA	A
I-95	NA	C
I-96	AAA	B
I-97	AAA	AA
I-98	NA	C
I-99	NA	A
I-100	AAA	AA

Compound ID	ACC1	ACC2
I-101	NA	B
I-102	NA	B
I-103	NA	AA
I-104	NA	C
I-105	NA	AA
I-106	NA	A
I-107	NA	A
I-108	AAA	AA
I-109	NA	B
I-110	AA	AA
I-111	NA	B
I-112	AAA	AA
I-113	NA	C
I-114	NA	C
I-115	AA	AA
I-116	NA	A
I-117	NA	A
I-118	NA	C
I-119	AAA	AA
I-120	NA	B
I-121	AA	AA
I-122	NA	AA
I-123	AAA	AA
I-124	NA	B
I-125	NA	B
I-126	NA	C
I-127	NA	C
I-128	NA	C

Compound ID	ACC1	ACC2
I-129	NA	B
I-130	AAA	AA
I-131	AA	AA
I-132	NA	C
I-133	AAA	AA
I-134	AA	AA
I-135	AAA	AA
I-136	NA	A
I-137	NA	AA
I-138	NA	B
I-139	AA	AA
I-140	AAA	AA
I-141	NA	A
I-142	NA	AA
I-143	AA	AA
I-144	NA	B
I-145	AAA	AA
I-146	NA	AA
I-147	AA	AA
I-148	NA	A
I-149	NA	AA
I-150	NA	B
I-151	NA	AA
I-152	NA	AA
I-153	NA	AA
I-154	NA	AA
I-155	NA	AA
I-156	NA	A

Compound ID	ACC1	ACC2
I-157	NA	C
I-158	AAA	AAA
I-159	NA	AA
I-160	AAA	AAA
I-161	NA	A
I-162	AAA	AA
I-163	AA	AA
I-164	AAA	AAA
I-165	AAA	AAA
I-166	NA	AA
I-167	NA	A
I-168	NA	AA
I-169	NA	AAA
I-170	NA	AA
I-171	NA	AA
I-172	NA	AA
I-173	NA	AA
I-174	AAA	AAA
I-175	NA	AA
I-176	NA	A
I-177	AAA	AAA
I-178	NA	A
I-179	AAA	AAA
I-180	AAA	AAA
I-181	AAA	AAA
I-182	NA	C
I-183	NA	AAA
I-184	NA	AA

Compound ID	ACC1	ACC2
I-185	NA	AA
I-186	NA	AA
I-227	NA	
I-229	NA	
I-228	NA	
I-249	AAA	AAA
I-230	NA	A
I-235	AAA	AAA
I-236	AAA	AAA
I-231	NA	A
I-234	NA	A
I-246	AAA	AAA
I-243	AAA	AAA
I-233	NA	A
I-257	NA	A
I-277	AAA	AAA
I-278	AAA	AAA
I-254	AAA	AAA
I-258	AAA	AAA
I-244	AAA	AAA
I-245	AAA	AAA
I-256	AAA	AAA
I-237	AAA	AAA
I-238	AAA	AAA
I-239	AAA	AAA
I-242	AAA	AAA
I-255	AAA	AAA
I-263	NA	AA

Compound ID	ACC1	ACC2
I-240	NA	AAA
I-241	AAA	AAA
I-286	AAA	AAA
I-251	NA	A
I-261	NA	A
I-262	NA	A
I-285	NA	A
I-259	AAA	AAA
I-290	AAA	AAA
I-287	AAA	AAA
I-247	AAA	AAA
I-270	A	NA
I-267	AAA	AAA
I-260	AAA	AAA
I-275	AAA	NA
I-266	AA	NA
I-265	AA	NA
I-271	AAA	AAA
I-253	AA	NA
I-272	AAA	AAA
I-268	AAA	AAA
I-252	AA	NA
I-248	AA	NA
I-264	AAA	AAA
I-276	AAA	NA
I-274	AAA	AAA
I-269	A	NA
I-273	AAA	NA

Compound ID	ACC1	ACC2
I-283	AAA	NA
I-284	AAA	NA
I-288	AAA	AAA
I-289	AAA	AAA
I-291	AAA	AAA
I-279	AAA	AAA
I-282	AAA	AAA
I-296	NA	AAA
I-293	NA	AAA
I-297	AAA	AAA
I-303	AAA	AAA
I-292	AAA	AAA
I-294	AAA	AAA
I-295	AAA	AAA

Example 248

Thermal Shift Assay

[001034] Compounds of the present invention were evaluated in a thermal shift assay using methods substantially similar to those described by Vedadi *et al.* "Chemical screening methods to identify ligands that promote protein stability, protein crystallization , and structure determination." PNAS (2006) vol. 103, 43, 15835-15840, the entirety of which is incorporated herein by reference.

[001035] The results of the thermal shift assay showing the ability of compound I-97 to bind effectively to and elicit a conformational change on the protein resulting in its allosteric inhibition mechanism is highlighted by the data in **Figure 2**. **Figure 2** shows the results from a Thermal Shift Assay (TSA) comparing I-97 and Soraphen A (IC50 = 4 nM), and illustrating the ability of compound I-97 to change the tertiary structure of the target protein, resulting in a thermal melting point change of more than 14˚C.

[001036] The results of the thermal shift assay showing the ability of compound I-97 to bind effectively to and elicit a conformational change on the protein resulting in its allosteric inhibition mechanism is highlighted by the data in **Figure 3**. **Figure 3** shows the results from a Thermal Shift Assay (TSA) comparing compounds I-1, I-158, I-174, and Soraphen A (IC50 = 4 nM), and illustrating the ability of compounds I-158 and I-174 to change the tertiary structure of the target protein, resulting in a thermal melting point change equivalent to that of Soraphen A.

Example 249

[^{14}C] Acetate Incorporation Assay

[001037] Compounds of the present invention were evaluated in a [^{14}C] Acetate Incorporation Assay. An exemplary procedure for the assay, which measures the incorporation of isotopically labeled acetate into fatty acids, follows. HepG2 cells were maintained in T-75 flasks containing DMEM supplemented with 2mM l-glutamine, penicillin G (100 units/ml), streptomycin 100µg/ml with 10% FBS and incubated in a humidified incubator with 5% CO2 at 37°C. Cells were fed every 2-3 days. On Day 1. cells were seeded in 24 well plates at a density of 1.2 X 105 cells/ml/well with the growth medium. On Day 3 the medium was replaced with fresh medium containing10% FBS. On Day 4 the medium was replaced with 0.5 ml of fresh medium containing test compound (in DMSO; final [DMSO] is 0.5 %) and the cells were incubated at 37°C for 1 hour. To one copy of plate, 4 ul of [2-^{14}C] acetate

(56mCi/mmol; 1 mCi/ml; PerkinElmer) was added and the cells were incubated at 37°C, 5% CO2 for 5 hrs. To a second copy of plate, 4 ul of cold acetate were added and the cells were incubated at 37°C, 5% CO2 for 5 hrs. This plate was used for protein concentration measurement. Medium was removed and placed in a 15 ml centrifuge tube (BD, Falcon/352096). Cells were rinsed with 1ml PBS, then aspirated, and the rinse and aspiration steps were repeated. 0.5ml of 0.1N NaOH were added to each well and let sit at RT to dissolve cell monolayer. The remaining cell suspension was pooled with medium. For the protein determination plate, an aliquot was removed for protein determination (25 ul). 1.0 ml of EtOH and 0.17 ml 50% KOH were added to tubes containing medium and cell suspensions. Cells were incubated at 90°C for 1 hr, then cooled to room temperature. 5 ml petroleum ether was added per tube, shaken vigorously, centrifuged at 1000 rpm for 5 min, and 500 uL of the petroleum ether layer was transferred to tubes for Microbeta reading, then 2 ml Aquasol-2 were added to each tube, the tubes were shaken and counted with a Microbeta Liquid Scintillation Counter (Perkin Elmer).

[001038] The remaining petroleum ether layer was discarded and the aqueous phase reserved for fatty acid extractions. The aqueous phase was acidified with 1 ml of concentrated HCl, checking pH of one or two extracts to make sure pH was below 1. 5 ml of petroleum ether was added per tube, shaken vigorously, centrifuged at 1000 rpm for 5 min, and 4 ml of the petroleum ether layer was transferred to a new glass tube (10*18 mm). 5 ml of petroleum ether was added per tube, shaken vigorously, centrifuged at 1000 rpm for 5 min, and 5 ml of the petroleum ether layer was transferred to the glass tube, and the extraction repeated again. The petroleum ether extracts were pooled and evaporated to dryness overnight. On Day 5 the residue from the petroleum ether fractions was resuspended in 120 uL of chloroform-hexane (1:1) containing 200 ug of linoleic acid as a carrier. 5 uL of this was spotted onto silica gel sheets, and the plates developed using heptane-diethyl ether-acetic acid (90:30:1) as eluent. The fatty acid band was visualized with iodine vapor and the corresponding bands were cut out into scintillation vials. 2 ml of Aquasol-2 was added to each vial, and the vials were shaken and counted on a scintillation counter.

[001039] The results of the [^{14}C] Acetate Incorporation Assay are shown in **Figure 4** and **Figure 7**. **Figure 4** illustrates the ability of compounds I-158 and I-174 to inhibit incorporation of isotopically labeled acetate into fatty acids with an IC_{50} of less than 100 nM. Another inhibitor, CP-640186 (at a single concentration of 3 uM) is shown for comparison.

Figure 7 illustrates the ability of compound I-181 to inhibit incorporation of isotopically labeled acetate into fatty acids in Hep-G2 cells.

Example 250

[001040] Compounds of the present invention were evaluated in an Anti-Fungal Activity Assay. An exemplary procedure for the assay, which measures the susceptibility of various Candida species to anti-fungal compounds, follows. Compounds to be tested (including fluconazole and amphotericin B) were dissolved in DMSO to obtain a solution having a concentration of 1 mg/mL. These stock solutions were sterile filtered using a 0.22 um nylon syringe filter, then diluted in sterile water to achieve a final concentration of 128 ug/mL.

[001041] All species were grown from frozen stock by directly plating on to freshly prepared Sabouraud Dextrose agar (BD, Difco) and incubated overnight in ambient air at 35°C for 24h. A direct suspension was prepared in RPMI 1640 + MOPS (Lonza, Biowhittaker) by taking individual colonies from the overnight cultures using sterile swabs soaked in sterile saline. The concentration of the suspension was determined using pre-determined standard curves. These suspensions were then diluted down to 5 x 10^3 CFU/mL to achieve a final concentration of 2.5 x 10^3 CFU/mL once added to the microtiter plate as per CLSI guidelines (M27-A3, Vol.28 No.14).

[001042] Broth microtiter MIC challenge plates were prepared following CLSI guidelines (M27-A3, Vol. 28 No. 14). The original CLSI guidelines focused on reading *Candida* MICs after 48h of incubation. As reading after only 24h offers a clear advantage of patient care, QC limits are being established for all drugs at 24h. That being said there are no known interpretive breakpoints for amphotericin B at 24h and the current fluconazole interpretive breakpoints are based on a 48h reading. The MIC breakpoints for the Pharmaron test compounds were recorded at 48h, and for the soraphen the 24h time-point was added. All MIC determinations were achieved by visually comparing the growth found in the antibiotic challenged wells to that of the growth control. The first well found in the dilution scheme that showed no growth (or complete inhibition) was recorded as the MIC.

[001043] The results of the Anti-Fungal Activity Assay are shown in **Table 3**. **Table 3** illustrates that compound **I-158**, **I-159**, **I-174, I-235, I-236,** and **I-246** have anti-fungal activity MICs in the low ug/mL range.

Table 3. Anti-Fungal Activity Assay Results

	MIC (ug/mL; 3 replicates)											
Candida species	**Amph. B**	**Fluc.**	**I-158**	**I-174**	**I-181**	**I-235**	**I-236**	**I-246**	**I-159**	**I-160**	**I-162**	**I-165**
C. albicans	0.5	1	2	2	>64	8	8	4	8	>64	>64	>64
ATCC	0.5	1	2	2	>64	8	8	4	8	>64	>64	>64
90028	1	2	2	2	>64	8	8	4	8	>64	>64	>64
C.	1	2	8	8	>64	8	2	4	>64	>64	>64	>64
parapsilosis	1	2	8	8	>64	8	2	4	>64	>64	>64	>64
ATCC	1	4	8	8	>64	8	2	4	>64	>64	>64	>64
22019												
C. krusei	1	32	2	2	>64	8	8	16	16	>64	>64	>64
ATCC 6258	1	32	2	2	>64	8	4	16	16	>64	>64	>64
	1	2	2	2	>64	8	4	16	32	>64	>64	>64

Example 251

[001044] Compounds of the invention were also assayed in a Cancer Cell Viability Assay as described by Beckers et al. "Chemical Inhibition of Acetyl-CoA Carboxylase Induces Growth Arrest and Cytotoxicity Selectively in Cancer Cells" Cancer Res. (2007) 67, 8180-8187. An exemplary procedure for the assay, which measures the percentage of cancer cells surviving following administration of inhibitor compounds, follows.

[001045] LNCaP (prostate cancer cell line) cells plated at 4 x 10^5 per 6 cm dish were incubated at 37°C, and the following day they were treated with increasing concentrations of inhibitor compounds and incubated. Viable cells and the percentage of dead cells was counted and calculated every day for 5 days from day 0, using trypan blue staining.

[001046] The results of the Cancer Cell Viability Assay are shown in **Figure 5**, which shows the ability of compound I-158 to completely inhibit cell population growth at a concentration of 5 uM.

Example 252

[001047] Compounds of the present invention were also assayed in an *In Vivo* Fatty Acid Synthesis Study as described by Harwood *et al.* "Isozyme-nonselective N-Substituted Bipiperidylcarboxamide Acetyl-CoA Carboxylase Inhibitors Reduce Tissue Malonyl-CoA Concentrations, Inhibit Fatty Acid Synthesis, and Increase Fatty Acid Oxidation in Cultured Cells and in Experimental Animals" Journal of Biological Chemistry (2008) 278, 37099-

37111. An exemplary procedure for the assay, which measures the amount of radioactive [C^{14}]-acetate incorporated into rat liver tissue, follows.

[001048] Animals given food ad water *ad libitum* were treated orally at a volume of 1.0 mL/200g body weight (rat) with either an aqueous solution containing 0.5% methylcellulose (vehicle), or an aqueous solution containing 0.5% methylcellulose plus test compound. One to four hours after compound administration, animals received an intraperitoneal injection of 0.5 mL of [C^{14}]-acetate (64 uCi/mL; 56 uCi/mL). One hour after radiolabeled acetate administration, animals were sacrificed by CO_2 asphyxiation and two 0.75 g liver pieces were removed and saponified at 70 degrees C for 120 minutes in 1.5 mL of 2.5M NaOH. After saponification, 2.5 mL of absolute ethanol were added to each sample and the solutions were mixed and allowed to stand overnight. Petroleum ether (4.8 mL) was then added to each sample, and the mixtures were first shaken vigorously for 2 minutes and then centrifuged at 1000 x g in a benchtop Sorvall for 5 minutes. The resultant petroleum ether layers, which contain non-saponifiable lipids, were removed and discarded. The remaining aqueous layer was acidified to pH < 2 by the addition of 12M HCl and extracted two times with 4.8 mL of petroleum ether. The pooled organic fractions were transferred to liquid scintillation vials, dried under nitrogen, dissolved in 7 mL of Aquasol liquid scintillation fluid, and assessed for radioactivity using a Beckman 6500 liquid scintillation counter. Results were recorded as disintigrations per minute (DPM) per milligram of tissue.

[001049] Results of the *In Vivo* Fatty Acid Synthesis Study are shown in **Figure 8** and **Figure 16**, which show that the ED_{50} of each of compounds I-181 and I-278 is less than 0.3 mg/Kg body weight.

Example 253

[001050] Compounds of the present invention were also assayed in a Respiratory Quotient Measurement Assay, as described by Harwood *et al.* "Isozyme-nonselective N-Substituted Bipiperidylcarboxamide Acetyl-CoA Carboxylase Inhibitors Reduce Tissue Malonyl-CoA Concentrations, Inhibit Fatty Acid Synthesis, and Increase Fatty Acid Oxidation in Cultured Cells and in Experimental Animals" Journal of Biological Chemistry (2008) 278, 37099-37111. An exemplary procedure for the assay, which measures the ratio of carbon dioxide production to oxygen consumption in rats, follows.

[001051] Male Sprague-Dawley rats (350–400 g) housed under standard laboratory conditions, either fed chow, fasted, or fasted and refed a diet high in sucrose for 2 days prior to experimentation were removed from their home cages, weighed, and placed into sealed chambers (43 " 43 " 10 cm) of the calorimeter (one rat per chamber). The chambers were

placed in activity monitors. The calorimeter was calibrated before each use, air flow rate was adjusted to 1.6 liters/min, and the system settling and sampling times were set to 60 and 15 s, respectively. Base-line oxygen consumption, CO_2 production, and ambulatory activity were measured every 10 min for up to 3 h before treatment. After collecting base-line data, the chambers were opened and rats were given a 1.0-ml oral bolus of either an aqueous 0.5% methylcellulose solution (vehicle control) or an aqueous 0.5% methylcellulose solution containing test compound and then returned to the Oxymax chambers. Measurements were made every 30 min for an additional 3–6 h after dose. Fed vehicle controls were used to assess effects produced by vehicle administration and by drift in the RQ measurement during the course of the experimentation (if any). Overnight-fasted, vehicle-treated controls were used to determine maximal potential RQ reduction. Results were plotted as their absolute RQ value (± SEM) over time.

[001052] Results of the *In Vivo* Fatty Acid Synthesis Study are shown in **Figure 9** and **Figure 10**, which shows that the compound I-181 decreases RQ to approximately 80-90% of its baseline value and shows dose-dependent decreases in RQ upon treatment with I-181.

Example 254

[001053] Compounds of the present invention were also assayed in a propidium iodide (PI) cell death assay, based on the procedure described by van Engeland *et al.* "A novel assay to measure loss of plasma membrane asymmetry during apoptosis of adherent cells in culture" Cytometry (1996) 24 (2), 131-139. An exemplary procedure for the assay, which measures the number of intact mitotic cells following drug application follows.

[001054] Hepatocellular carcinoma cells (such as HepG2 or Hep3B) were seeded in a 24-well plate at a density of 1.106/ml in 0.5 ml of culture medium, and incubated for 3 hours to allow time for cells to adhere. Cells were treated with experimental compounds, 1 uM doxorubicin (1,2) or vehicle (DMSO) control for 120 hours after treatment: a. First removed culture supernatant into 2mL polypropylene tube and place on ice; b. Washed wells with 0.5mL PBS, transferring the wash volume to the 2mL tube containing culture supernatant (floating cells). Kept cells on ice. Harvested by adding into the wells 200uL of accutase for 5 min. Inactivated with 300uL media. Pipetted up and down and transfered trypsinized cells from the well into the 2mL tube with the floating cells (total volume: 1.5mL). Kept cells on ice. Spun cells 0.6 rcf for 10 min at 4 degrees. Aspirated medium. Resuspended in 500uL of Media by vortexing in pulses for about 15s. Kept cells on ice.

[001055] For cell counting: added 20uL of cells to a plate after vortexing in pulses for 15s. Kept the plate on ice. Then added 20uL trypan blue right before counting. Counted

cells with TC10 biorad cell counter. Spun cells 0.6 rcf for 10 min at 4 degrees. Aspirated the medium carefully. Resuspended in 500uL of annexin binding buffer 1X by vortexing. Transfered the cell suspension in a 5 ml FACS tube then added 5ul of Propidium Iodide. Gently mixed the cells and incubated for 15 min at RT in the dark.

[001056] For the flow cytometric analysis, unstained/untreated samples were used at each time point as negative control, and doxorubicin treated samples were used at each time point as a positive control. A FACScan flow cytometer was used, and FL2-A histograms were analyzed with FlowJo software. The results of a PI cell death assay are depicted in **Figure 14**.

Example 255

[001057] Compounds of the present invention were also assayed in high fat diet induced obesity (DIO) studies. A representative protocol for the assay follows.

[001058] The compounds of the present invention are readily adapted to clinical use as anti-obesity agents, insulin sensitizing agents, hyperinsulinemia-reversing agents, and hepatic steatosis-reversing agents. Such activity was determined by assessing the amount of test compound that reduces body weight and percentage body fat, reduces plasma insulin levels, blunts the rise and/or accelerates the reduction in plasma insulin and glucose levels in response to an oral glucose challenge, and reduces hepatic lipid content relative to a control vehicle without test compound in mammals. Sprague Dawley rats were fed either chow, a diet high in sucrose (for example AIN76A rodent diet; Research diets Inc. Cat #10001) or a diet high in fat (for example Research diets Inc. Cat #12451), for from 3-8 weeks prior to and during test compound administration.

[001059] The anti-obesity, insulin sensitizing, hyperinsulinemia-reversing, and hepatic steatosis-reversing potential of compounds of the present invention were demonstrated by evaluating modifications to a variety of parameters of lipid and carbohydrate metabolism using methods based on standard procedures known to those skilled in the art. For example, after a 3-8 week period of ad libitum feeding of either a chow, high-fat, or high-sucrose diet, animals that continued to receive the diet were treated for 1-8 weeks with test compound administered either by oral gavage in water or saline or water or saline containing 0.5% methylcelulose using a Q.D., B.I.D, or T.I.D. dosing regimen. At various times during study and at sacrifice (by CO_2 asphyxiation), blood was collected either from the tail vein of an unanesthesized rat or from the vena cava of animals at sacrifice into heparin or EDTA containing tubes for centrifugal separation to prepare plasma. Plasma levels of parameters of lipid and carbohydrate metabolism known by those skilled in the art to be altered coincident

with anti-obesity, insulin sensitizing, hyperinsulinemia-reversing, and hepatic steatosis-reversing actions, including but not limited to cholesterol and triglycerides, glucose, insulin, leptin, adiponectin, ketone bodies, free fatty acids, and glycerol, are measured using methods known to those skilled in the art.

[001060] The anti-obesity potential of compounds of the present invention can also be demonstrated by evaluating their potential to produce a reduction in body weight, a reduction in percentage body fat (measured by for example dual-energy x-ray absorptiometry (DEXA) analysis), and a reduction in plasma leptin levels. The anti-obesity and hepatic steatosis-reversing potential of compounds of the present invention can also be demonstrated by evaluating their potential to reduce the concentration of triglycerides in the liver, using extraction and quantitation procedures known to those skilled in the art. The insulin sensitizing and hyperinsulinemia-reversing potential of compounds of the present invention can also be demonstrated by evaluating their potential to blunt the rise and/or accelerate the reduction in plasma insulin and glucose levels in response to an oral glucose challenge, using procedures known to those skilled in the art.

[001061] The anti-obesity, insulin sensitizing, hyperinsulinemia-reversing, and hepatic steatosis-reversing potential of compounds of the present invention are exemplified through the actions of example compound I-181. When compound I-181 was administered once daily by oral gavage in 0.5% methylcellulose in saline at doses of 0, 3, 10, and 30 mg/kg to Sprague Dawley rats that had been consuming a high-fat diet for 4 weeks prior to initiation of dosing and continued to consume the same high-fat diet throughout the 2-weeks of test compound administration, compound I-181 produced a dose-dependent reduction in total body weight relative to vehicle-treated control animals with no concomitant reduction in food consumption. Results of the reduction in total body weight measurements after treatment of high fat diet-fed DIO rats with compound I-181 are shown in **Figure 11**. The degree of body weight reduction paralleled plasma drug levels measured at the end of the study. Plasma leptin levels, which are known to be an indicator of whole-body fat mass and which were increased by administration of the high-fat diet, were reduced by all compound I-181 doses evaluated, indicating that the body weight reduction was the result of a reduction in body fat. The plasma leptin levels for animals receiving the standard chow diet (lean controls) were also evaluated to determine the extent of parameter normalization produced by compound I-181. Plasma insulin levels, which were increased by the high-fat diet, were reduced to near lean control levels by all three compound I-181 doses with no concomitant reduction in plasma glucose levels, indicating an improvement in insulin sensitivity after treatment with

compound I-181. Results of the reduction in plasma insulin measurements after treatment of high fat diet-fed DIO rats with compound I-181 are shown in **Figure 12**. Hepatic triglycerides, which were elevated by the high-fat diet, were reduced in a dose-dependent manner after compound I-181 treatment and were normalized to lean control levels by the highest dose evaluated. Results of the reduction in hepatic triglyceride and cholesterol measurements after treatment of high fat diet-fed DIO rats with compound I-181 are shown in **Figure 13**. Treatment with compound I-181 did not increase either liver weight or the markers of liver function, ALT and AST. In studies where compound I-181 was administered once daily by oral gavage in 0.5% methylcellulose in salin at doses of 0, 3, 10, and 30 mg/kg to Sprague Dawley rats that had been consuming a high sucrose diet for 4 weeks prior to initiation of dosing and continued to consume the same high sucrose diet throughout the two weeks of test compound administration, compound I-181 produced a dose-dependent reduction in plasma cholesterol and triglyceride levels. Results of diet-induced obesity studies measuring the effect of compound I-181 on plasma cholesterol and plasma triglycerides are shown in **Table 4** below. Data shown are mean values for n = 14 animals per group ± SEM.

Table 4. Plasma cholesterol and triglyceride lowering in high sucrose-fed DIO rats after treatment with I-181.

Dose I-181	Plasma Cholesterol* (mg/dL)			Plasma Triglycerides* (mg/dL)		
	Prebleed	Day 7	Day 14	Prebleed	Day 7	Day 14
0 mg/kg	100 ± 3	106 ± 3	110 ± 6	170 ± 11	226 ± 16	195 ± 15
3 mg/kg	96 ± 2	94 ± 3	96 ± 3	144 ± 12	154 ± 15	171 ± 16
10 mg/kg	96 ± 3	82 ± 3	87 ± 3	183 ± 18	139 ± 10	165 ± 15
30 mg/kg	99 ± 3	78 ± 3	78 ± 2	166 ± 13	116 ± 9	118 ± 14
Chow-fed controls	109 ± 2	107 ± 3	107 ± 3	61 ± 5	69 ± 5	67 ± 5

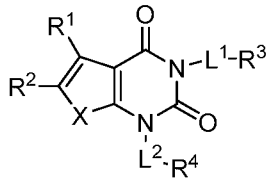
[001062] While we have described a number of embodiments of this invention, it is apparent that our basic examples may be altered to provide other embodiments that utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of

this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example.

CLAIMS

We claim:

1. A compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

X is –O-, -S-, or –NR-;

R^1 is hydrogen or C_{1-4} aliphatic, optionally substituted with one or more halogen, -OR, -SR, -$N(R)_2$, -N(R)C(O)R, -$C(O)N(R)_2$, -N(R)C(O)$N(R)_2$, -N(R)C(O)OR, -$OC(O)N(R)_2$, -N(R)SO_2R, -$SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or -SO_2R;

R^2 is halogen, -R, -OR, -SR, -$N(R)_2$, -N(R)C(O)R, -$C(O)N(R)_2$, -N(R)C(O)$N(R)_2$, -N(R)C(O)OR, -$OC(O)N(R)_2$, -N(R)SO_2R, -$SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or -SO_2R, or Hy, where Hy is selected from 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

or R^1 and R^2 are taken together to form an optionally substituted 4-7 membered partially unsaturated carbocyclo-, or heterocyclo-, benzo-, or 5-6 membered heteroarylo- fused ring;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring; a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each of L^1 and L^2 is independently a covalent bond or an optionally substituted 1-6 membered straight or branched bivalent hydrocarbon chain; or a cyclopropylenyl, cyclobutylenyl, or oxetanyl group;

R^3 is hydrogen, halogen, -CN,-OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-C(O)N(R)S(O)_2R$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, $-SO_2R$, $-B(OH)_2$, or an optionally substituted ring selected from phenyl or 5-6 membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

R^4 is hydrogen or an optionally substituted ring selected from a 3-8 membered monocyclic saturated or partially unsaturated carbocyclic ring, a 4-8 membered monocyclic saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, phenyl, an 8-10 membered bicyclic aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

wherein if L^2 is a covalent bond, then R^4 is not hydrogen; and

wherein the group $-L^2-R^4$ is not alkyl when R^2 is unsubstituted alkyl; and

wherein the group $-L^1-R^3$ taken together is not unsubstituted alkyl.

2. The compound according to claim 1, wherein X is –S-.

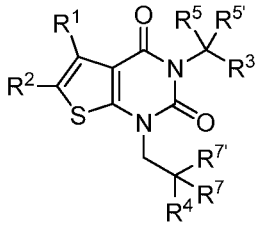
3. The compound according to claim 2, wherein R^1 is methyl or trifluoromethyl.

4. The compound according to claim 3, wherein R^2 is halogen, -C(O)OR, $–C(O)N(R)_2$, or oxazolyl.

5. The compound according to claim 3, wherein R^1 and R^2 are taken together to form a 5-6 membered partially unsaturated carbocyclic ring.

6. The compound according to claim 3, wherein R^3 is tetrazolyl, -C(O)OR, $-C(O)N(R)_2$, or -OR.

7. A compound of formula **II**:



II

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen or C_{1-4} aliphatic, optionally substituted with one or more halogen, -OR, -SR, -$N(R)_2$, -N(R)C(O)R, -C(O)$N(R)_2$, -N(R)C(O)$N(R)_2$, -N(R)C(O)OR, -OC(O)$N(R)_2$, -$N(R)SO_2R$, -$SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or -SO_2R;

R^2 is halogen, -R, -OR, -SR, -$N(R)_2$, -N(R)C(O)R, -C(O)$N(R)_2$, -N(R)C(O)$N(R)_2$, -N(R)C(O)OR, -OC(O)$N(R)_2$, -$N(R)SO_2R$, -$SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or -SO_2R, or Hy, where Hy is selected from 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or R^1 and R^2 are taken together to form an optionally substituted 4-7 membered partially unsaturated carbocyclo-, or heterocyclo-, benzo-, or 5-6 membered heteroarylo- fused ring;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring; a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

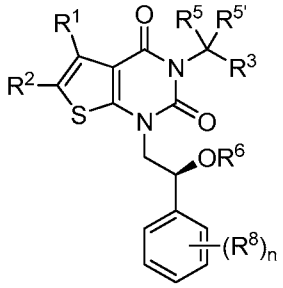
R^3 is hydrogen, halogen, -CN, -OR, -SR, -$N(R)_2$, -N(R)C(O)R, -C(O)$N(R)_2$, -N(R)C(O)$N(R)_2$, -N(R)C(O)OR, -OC(O)$N(R)_2$, -$N(R)SO_2R$, -$SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, -SO_2R, -$B(OH)_2$, or an optionally substituted ring selected from phenyl or 5-6 membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^4 is an optionally substituted phenyl or naphthyl ring;

each of R^5 and $R^{5'}$ is independently -R, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or $-SO_2R$; or R^5 and $R^{5'}$ are taken together to form a cyclopropylenyl, cyclobutylenyl, or oxetanyl group; and

each of R^7 and $R^{7'}$ is independently hydrogen, -R, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or $-SO_2R$; or R^7 and $R^{7'}$ are taken together to form a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

8. A compound of formula **III**:



III

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen or C_{1-4} aliphatic, optionally substituted with one or more halogen, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or $-SO_2R$;

R^2 is halogen, -R, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or $-SO_2R$, or Hy, where Hy is selected from 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or R^1 and R^2 are taken together to form an optionally substituted 4-7 membered partially unsaturated carbocyclo-, or heterocyclo-, benzo-, or 5-6 membered heteroarylo- fused ring;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring; a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^3 is hydrogen, halogen, -CN, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, $-SO_2R$, $-B(OH)_2$, or an optionally substituted ring selected from phenyl or 5-6 membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

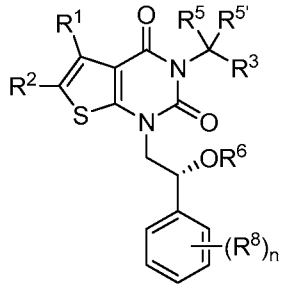
each of R^5 and $R^{5'}$ is independently -R, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or $-SO_2R$; or R^5 and $R^{5'}$ are taken together to form a cyclopropylenyl, cyclobutylenyl, or oxetanyl group;

R^6 is -R, $-C(O)N(R)_2$, or -C(O)R;

each R^8 is independently selected from halogen, -R, -OR, -SR, $-N(R)_2$ or deuterium; and

n is 0-5.

9. A compound of formula **IV**:



IV

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen or C_{1-4} aliphatic, optionally substituted with one or more halogen, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or $-SO_2R$;

R^2 is halogen, -R, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or $-SO_2R$, or Hy, where Hy is selected from 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or R^1 and R^2 are taken together to form an optionally substituted 4-7 membered partially unsaturated carbocyclo-, or heterocyclo-, benzo-, or 5-6 membered heteroarylo- fused ring;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring; a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^3 is hydrogen, halogen, -CN, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, $-SO_2R$, $-B(OH)_2$, or an optionally substituted ring selected from phenyl or 5-6 membered heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each of R^5 and $R^{5'}$ is independently -R, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, or $-SO_2R$; or R^5 and $R^{5'}$ are taken together to form a cyclopropylenyl, cyclobutylenyl, or oxetanyl group;

R^6 is -R, $-C(O)N(R)_2$, or -C(O)R;

each R^8 is independently selected from halogen, -R, -OR, -SR, $-N(R)_2$ or deuterium; and

n is 0-5.

10. A composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

11. A method of inhibiting ACC in a patient in need thereof, comprising administering to said patient the composition according to claim 10.

12. A method of inhibiting ACC in a biological sample, comprising contacting the biological sample with the compound according to claim 1.

13. A method for treating a metabolic disorder in a patient in need thereof, comprising administering to said patient the composition according to claim 10.

14. The method according to claim 13, wherein the metabolic disorder is obesity.

15. The method according to claim 13, wherein the metabolic disorder is dyslipidemia or hyperlipidemia.

16. The method according to claim 14, wherein the obesity is a symptom of Prader-Willi syndrome, Bardet-Biedl syndrome, Cohen syndrome or MOMO syndrome.

17. The method according to claim 14, wherein the obesity is a side effect of the administration of another medication, including but not limited to insulin, sulfunylureas, thiazolidinediones, antipsychotics, antidepressants, steroids, anticonvulsants (including phenytoin and valproate), pizotifen, or hormonal contraceptives.

18. A method of treating a cancer or other proliferative disorder in a patient in need thereof, comprising administering to said patient the composition according to claim 10.

19. A method of treating a fungal, parasitic, or bacterial infection in a patient in need thereof, comprising administering to said patient the composition according to claim 10.

20. A method of inhibiting ACC in a plant, comprising contacting the plant with the compound according to claim 1.

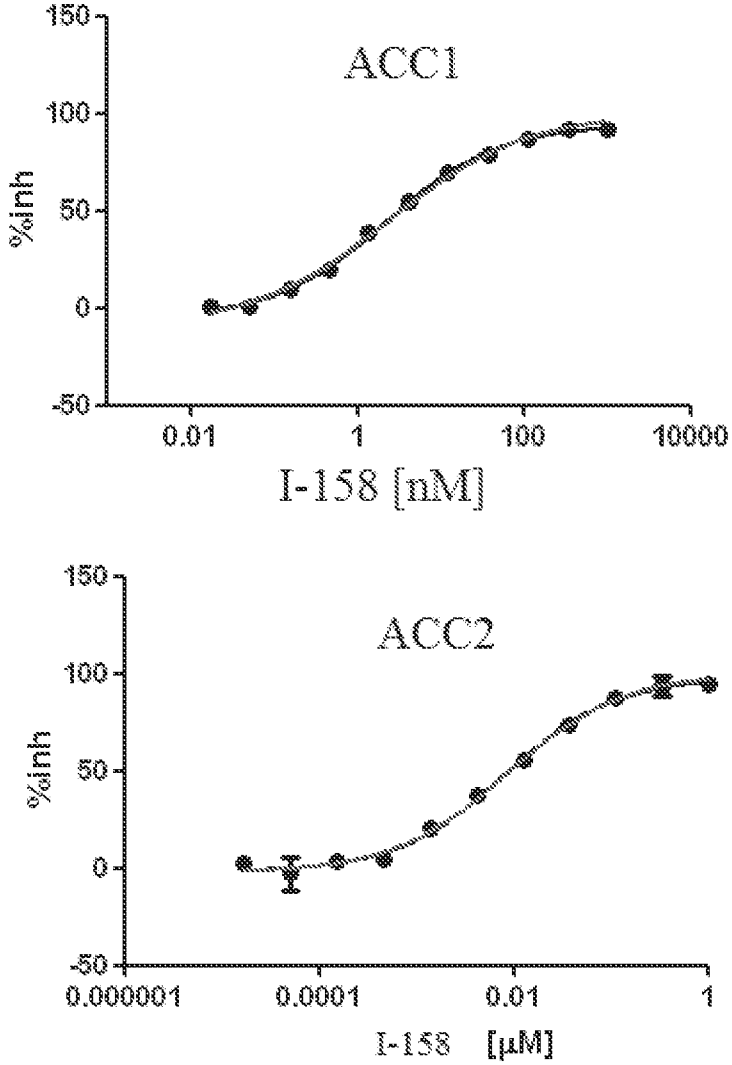


Figure 1. ACC1 and ACC2 enzyme inhibition curves for compound I-158.

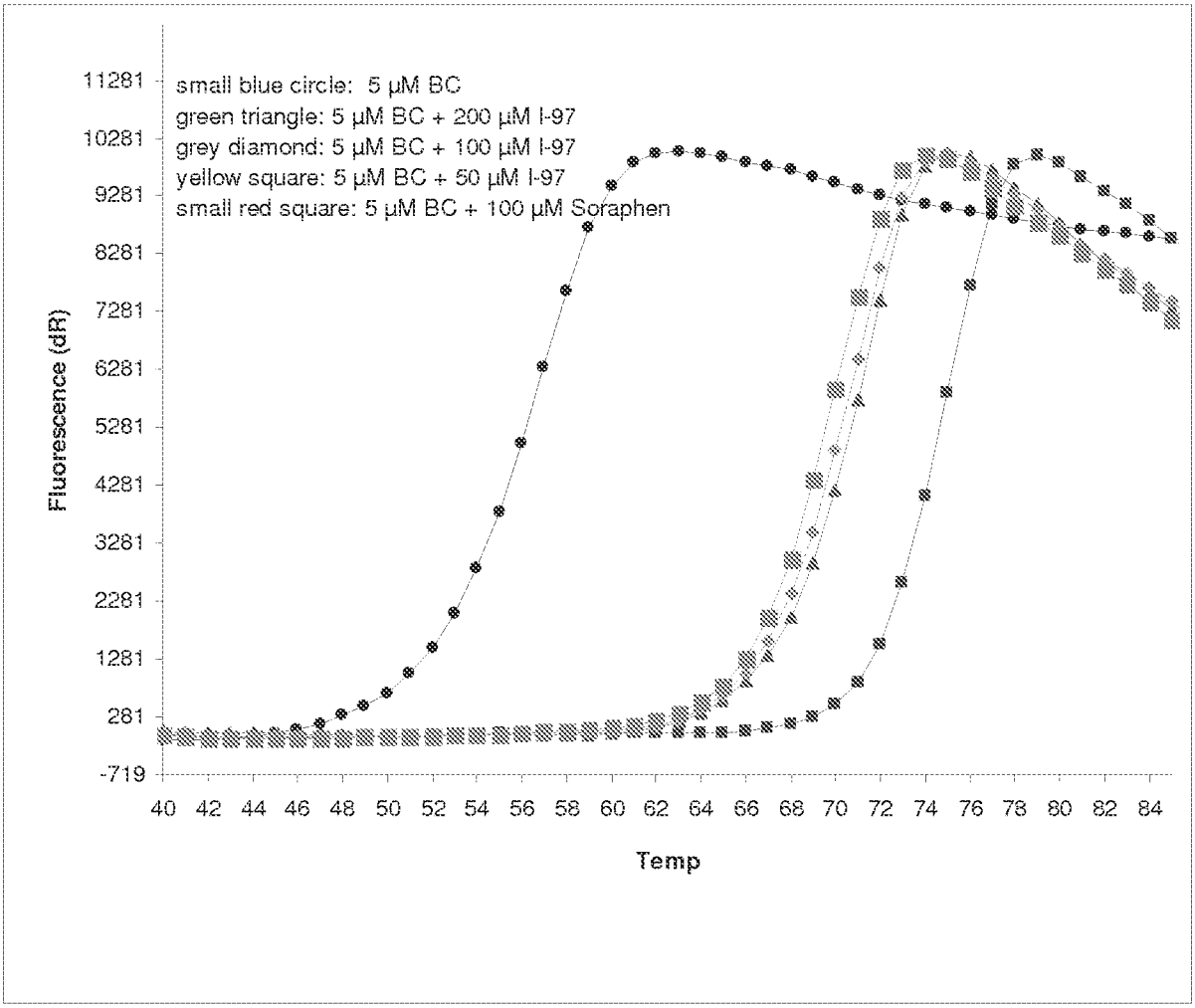


Figure 2. Results of the thermal shift assay of compound I-97 against the Biotin Carboxylase domain of ACC2.

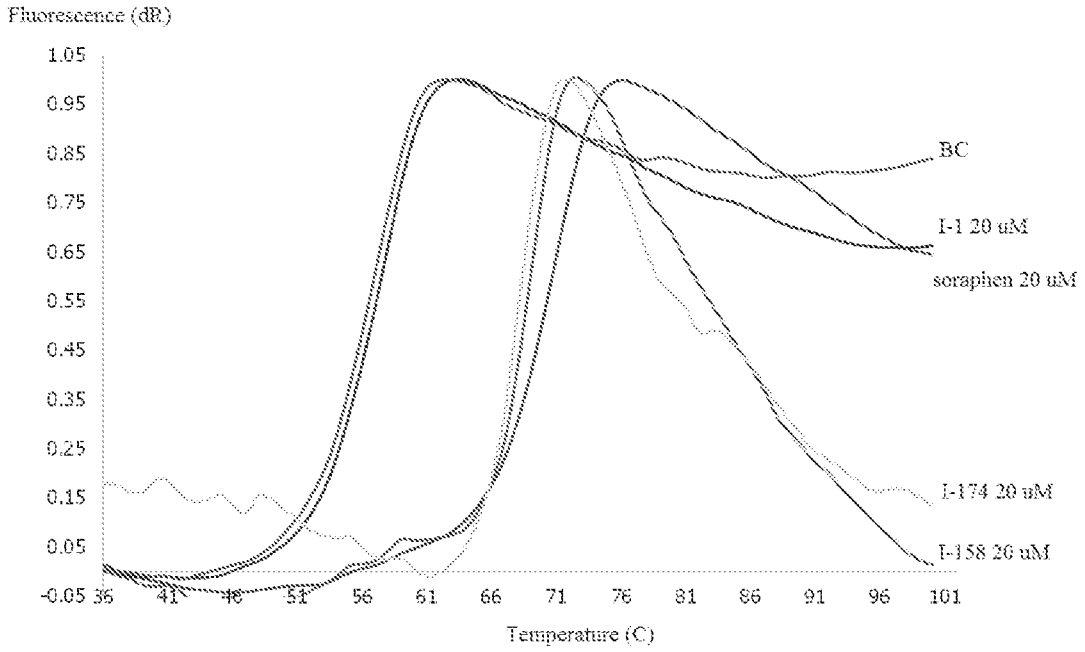
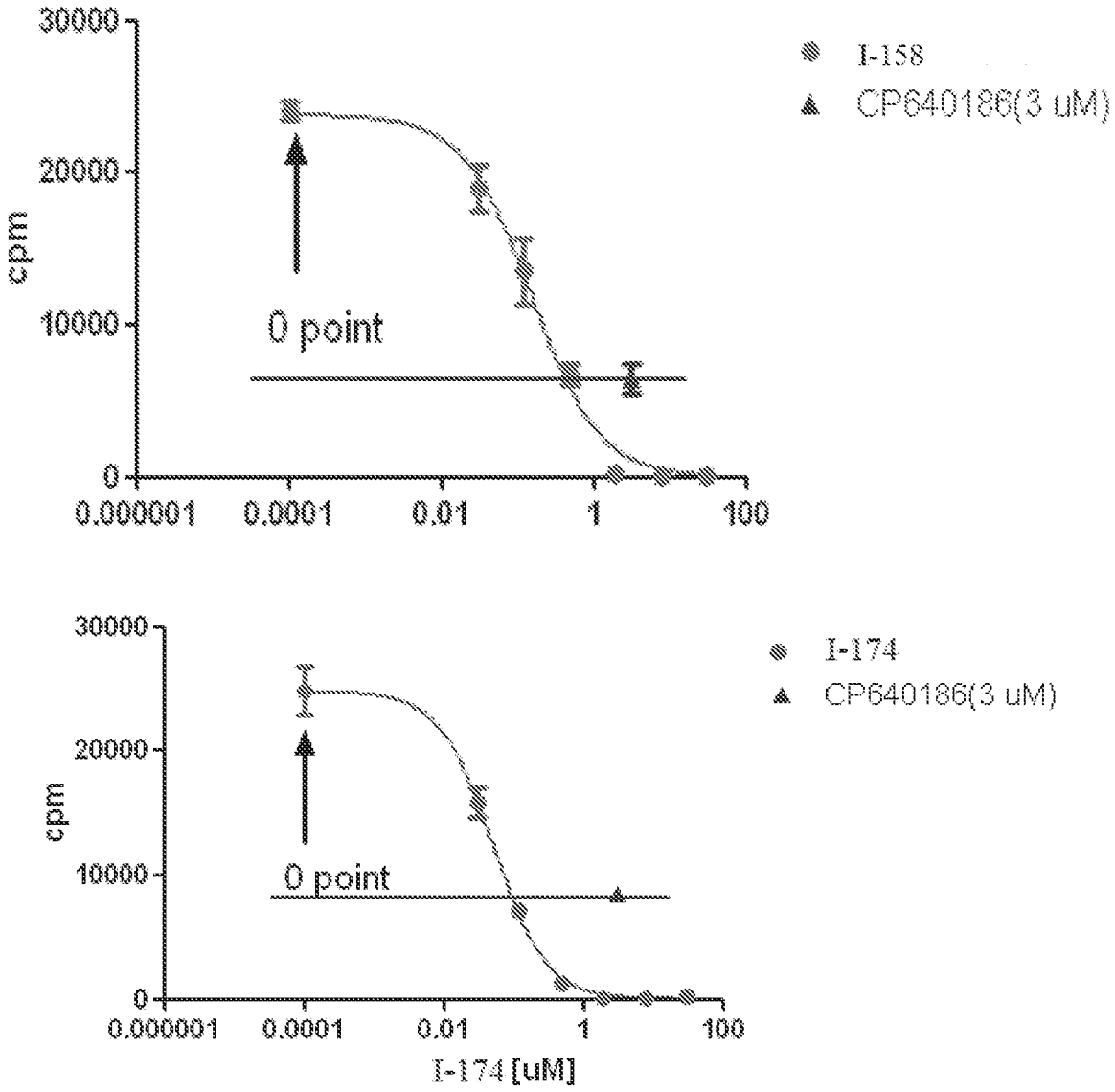
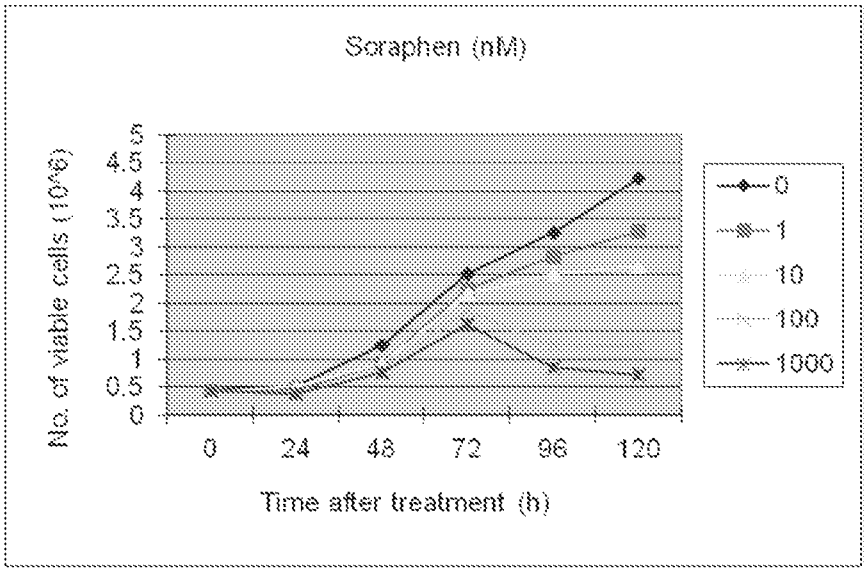


Figure 3. Results of the thermal shift assay of compounds I-1, I-158, I-174, and soraphen A against the Biotin Carboxylase domain of ACC2.



Bottom	= 0.0	HillSlope	-1.138
Top	24797	IC50	0.04978

Figure 4. Results of the [^{14}C] Acetate Incorporation HepG2 Cellular Assay for compounds I-158, I-174, and CP640186.



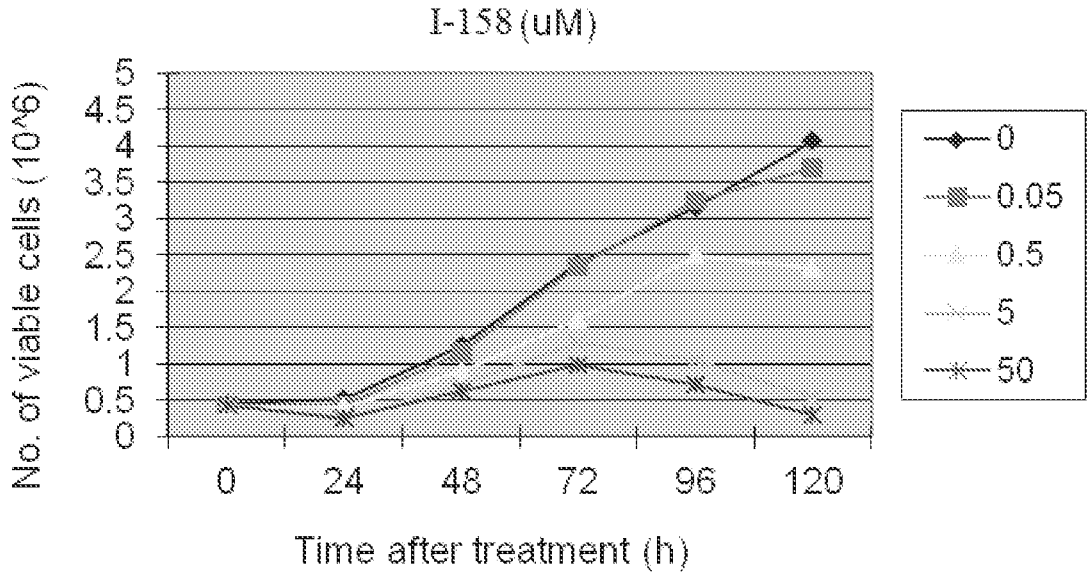


Figure 5. Results of LnCaP (Prostate) Cancer Cell Viability Assay for I-158 and Soraphen A.

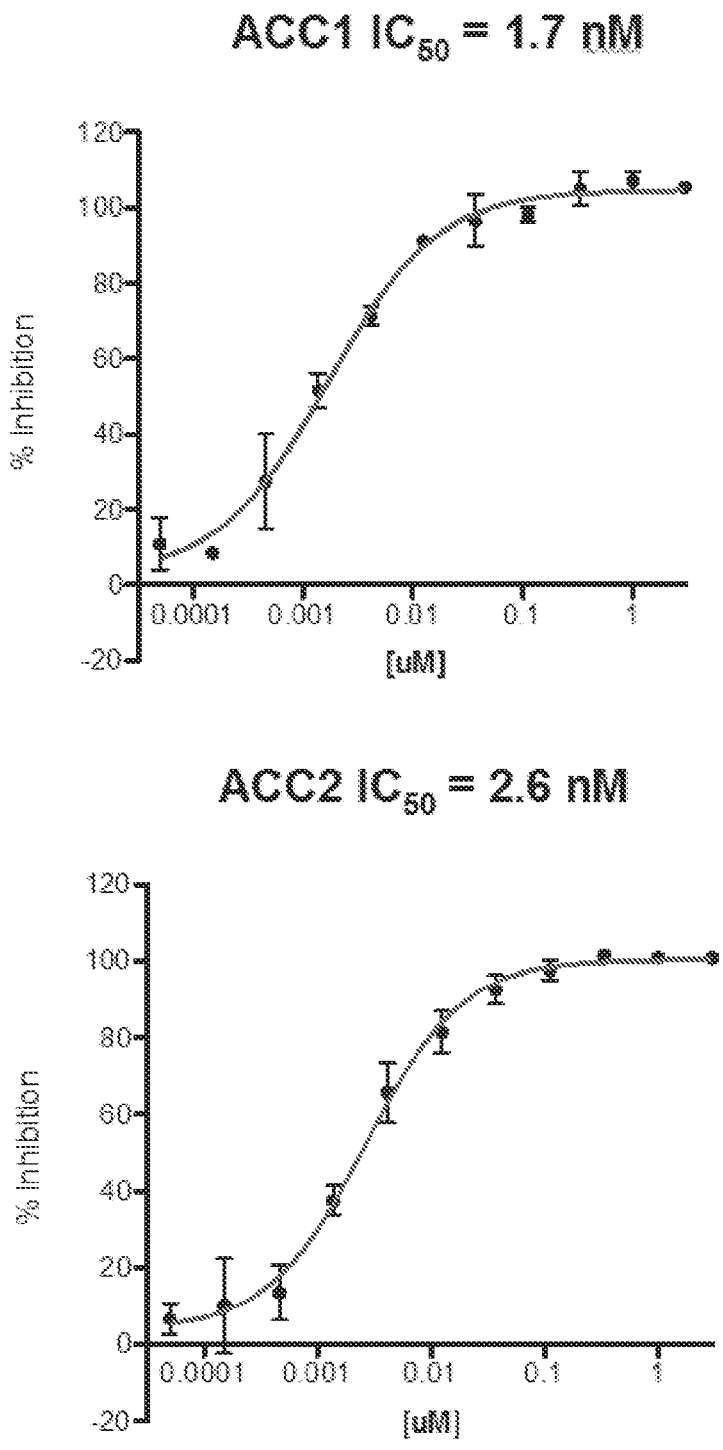


Figure 6. Enzyme inhibition curves for compound I-181 against ACC1 and ACC2 in vitro.

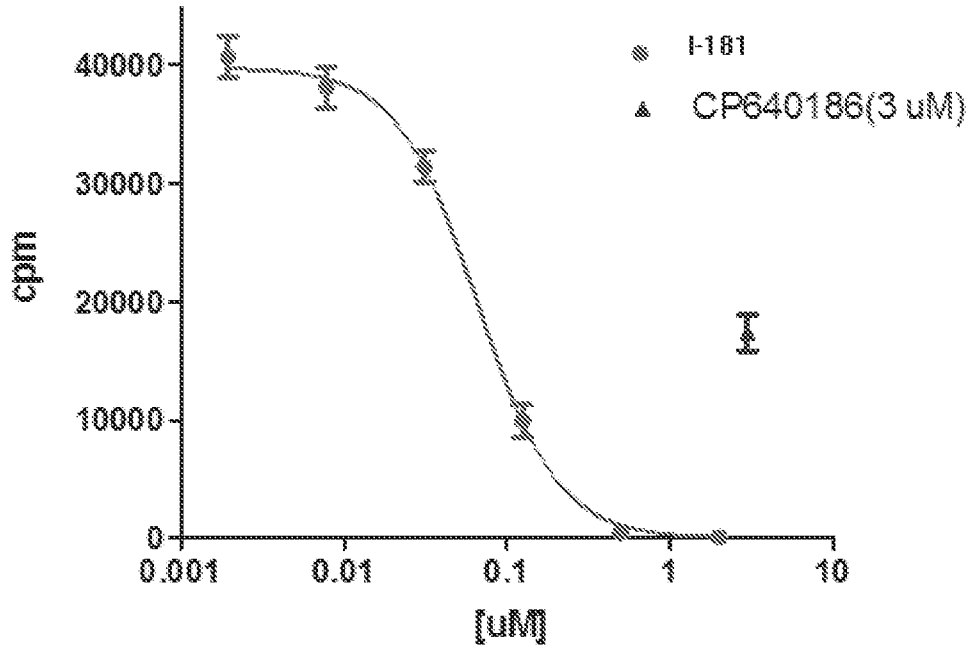
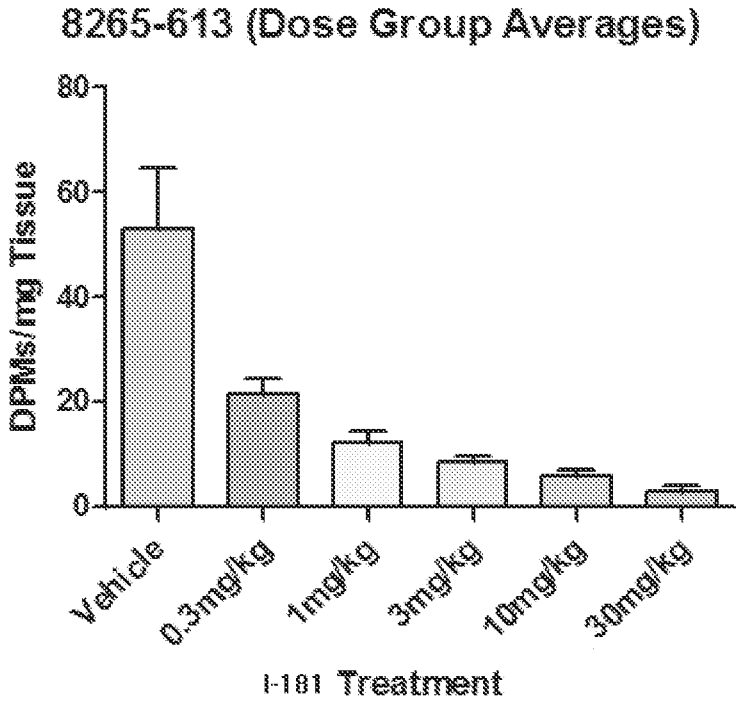


Figure 7. Inhibition of fatty acid synthesis in Hep-G2 cells by compound I-181, measured by [^{14}C]-acetate incorporation.



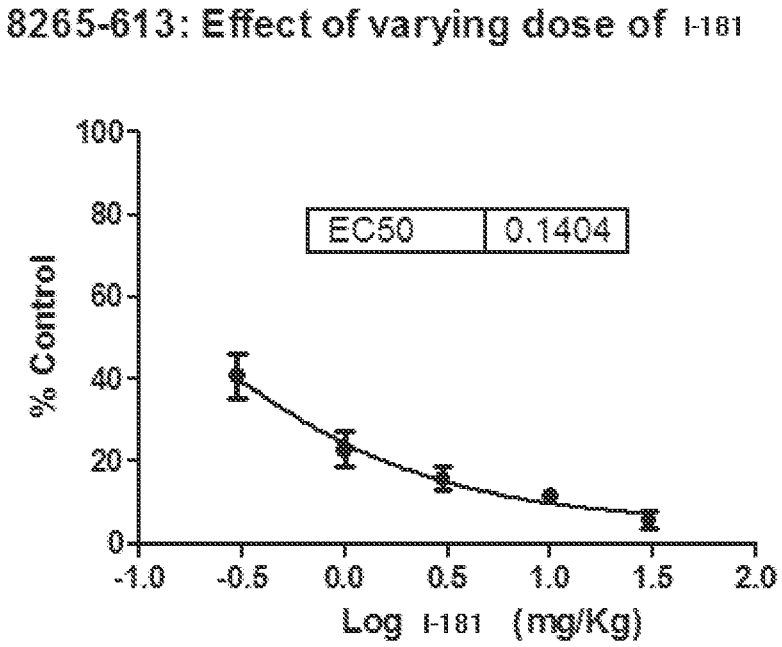


Figure 8 depicts inhibition of fatty acid synthesis in rats by compound I-181, showing an ED_{50} of less than 0.3 mg/kg.

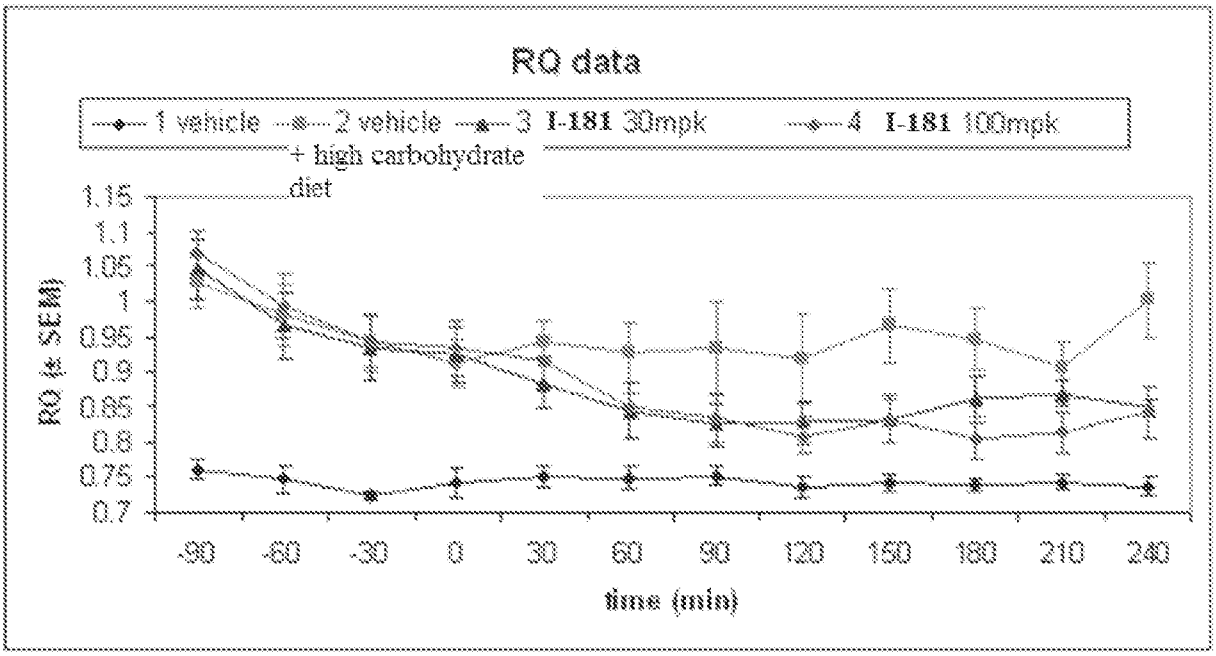


Figure 9 depicts results of a respiratory quotient (RQ) study measuring the ratio of CO_2 production to O_2 consumption in rats, using compound I-181 at doses of 30 and 100 mg/kg bodyweight.

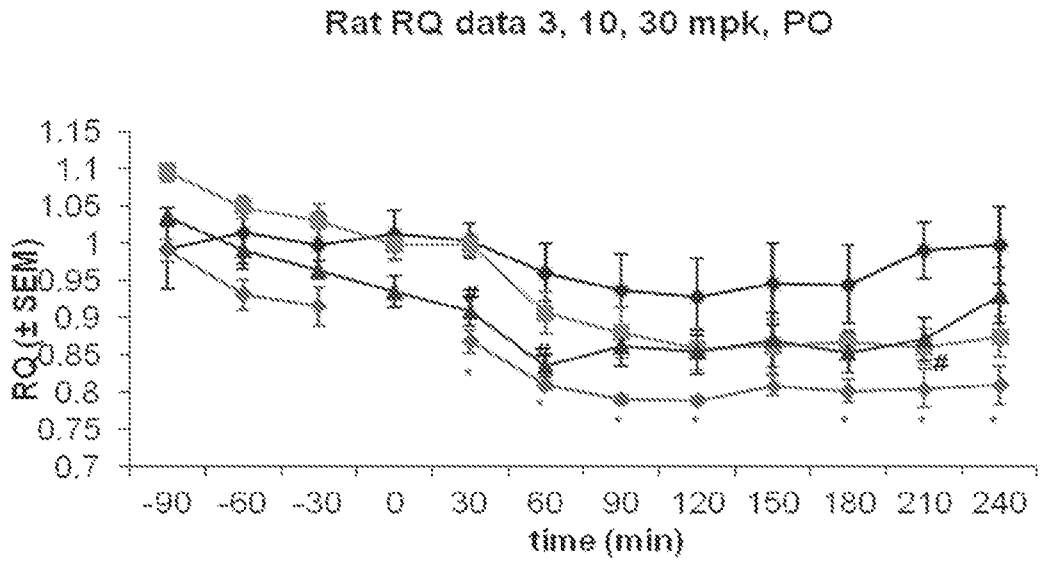


Figure 10 depicts results of a respiratory quotient (RQ) study measuring the ratio of CO_2 production to O_2 consumption in rats, using vehicle only (dark blue diamond), or compound I-181 at doses of 3 mg/kg (pink square), 10 mg/kg (blue triangle), and 30 mg/kg (red diamond) bodyweight administered PO.

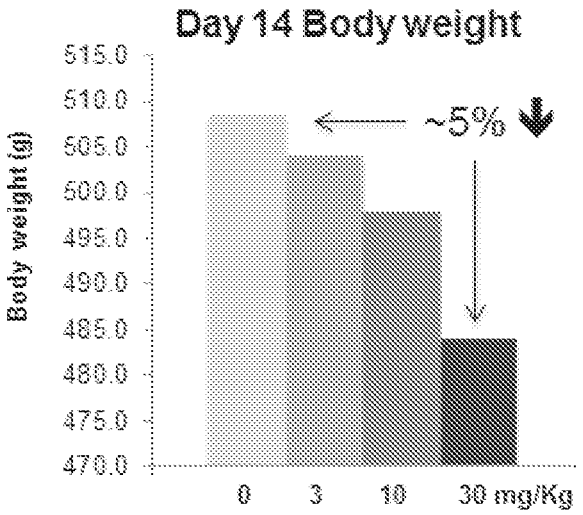


Figure 11 depicts results of a high fat diet-induced obesity (DIO) weight gain experiment, wherein rats were treated with 3, 10, or 30 mg/Kg of I-181. The results show that rats treated with a dose of 30 mg/Kg, p.o., q.i.d. gained approximately 5% less body weight after 14 days than control rats.

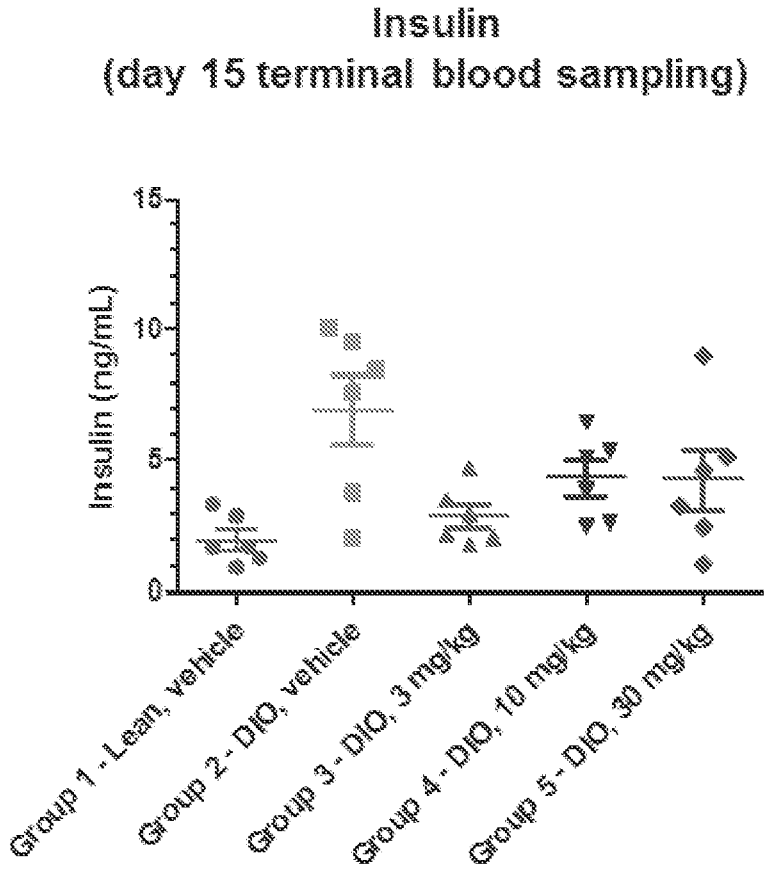


Figure 12 depicts results of an insulin level reduction experiment, wherein rats on a high fat diet-induced obesity (DIO) diet were treated with 3, 10, or 30 mg/Kg of I-181. The results show that rats treated with a dose of 30 mg/Kg of I-181, p.o., q.i.d showed lower insulin levels after 15 days than control rats.

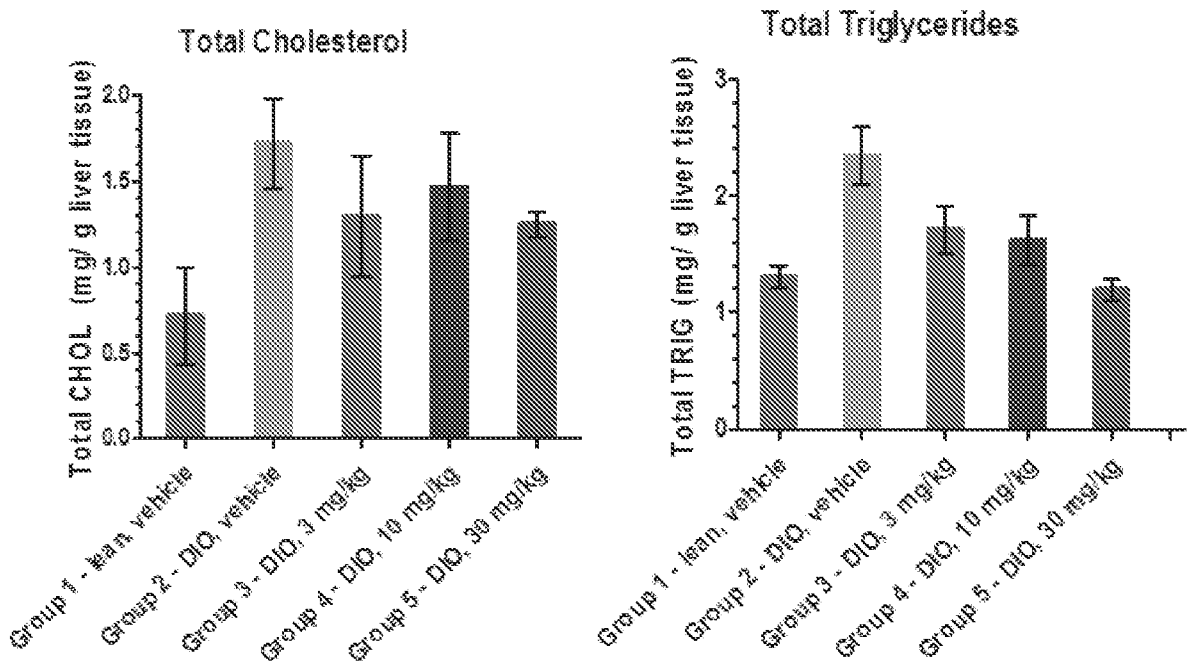


Figure 13 depicts results of a hepatic cholesterol and triglyceride measurement experiment, wherein rats on a high fat diet-induced obesity (DIO) diet were treated with 3, 10, or 30 mg/Kg of I-181. The results show that rats treated with a dose of 30 mg/Kg of I-181, p.o., q.i.d showed lower levels of liver cholesterol and triglycerides than control rats.

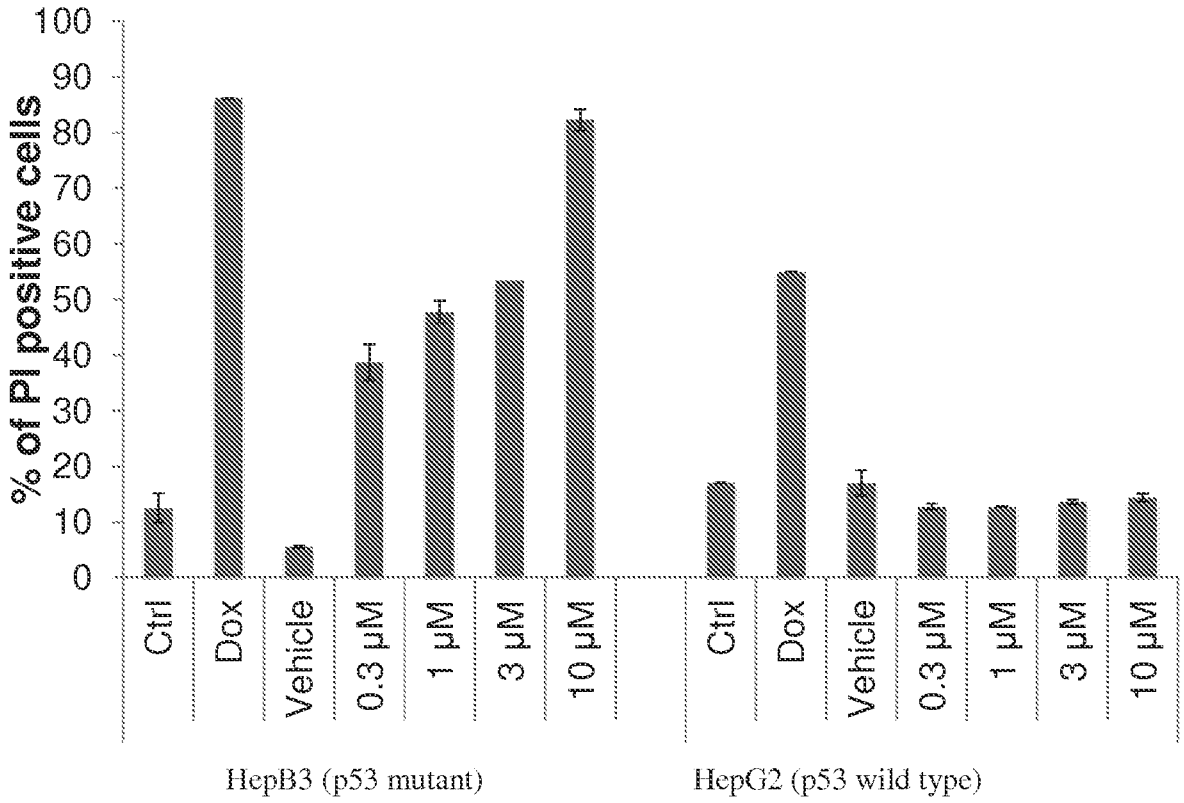


Figure 14 depicts results of an experiment measuring cell death induction in wild type and p53 mutant hepatocellular tumor lines (HepG2 and HepB3) following administration of compound I-246 and doxycycline as positive control. These results show differential sensitivity to ACC1 and ACC2 inhibition and that compound I-246 shows an EC_{50} of 8 nM in wild type HepG2 cells.

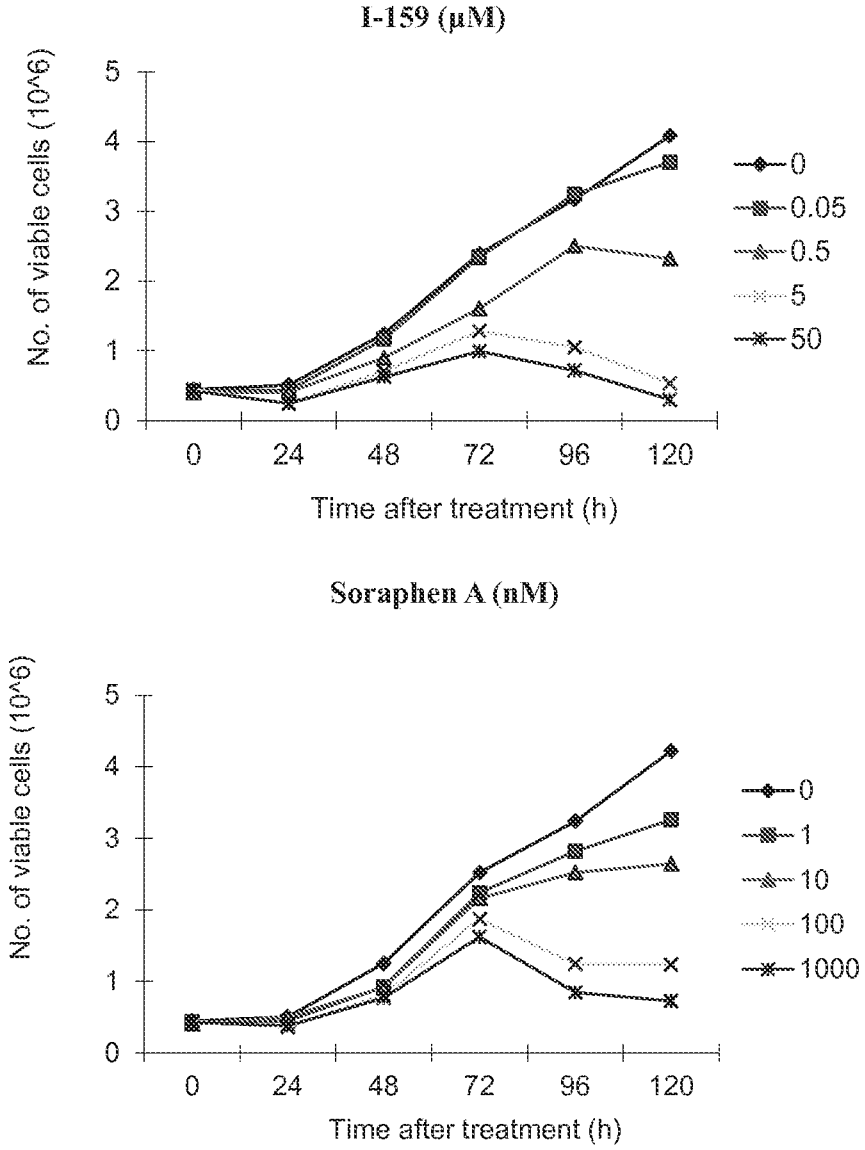


Figure 15 depicts results of an experiment measuring cell death in an androgen-sensitive human prostate adenocarcinoma (LNCaP) tumor line following administration of compound I-159 or Soraphen A. These results show dose-dependent cell death for both compounds.

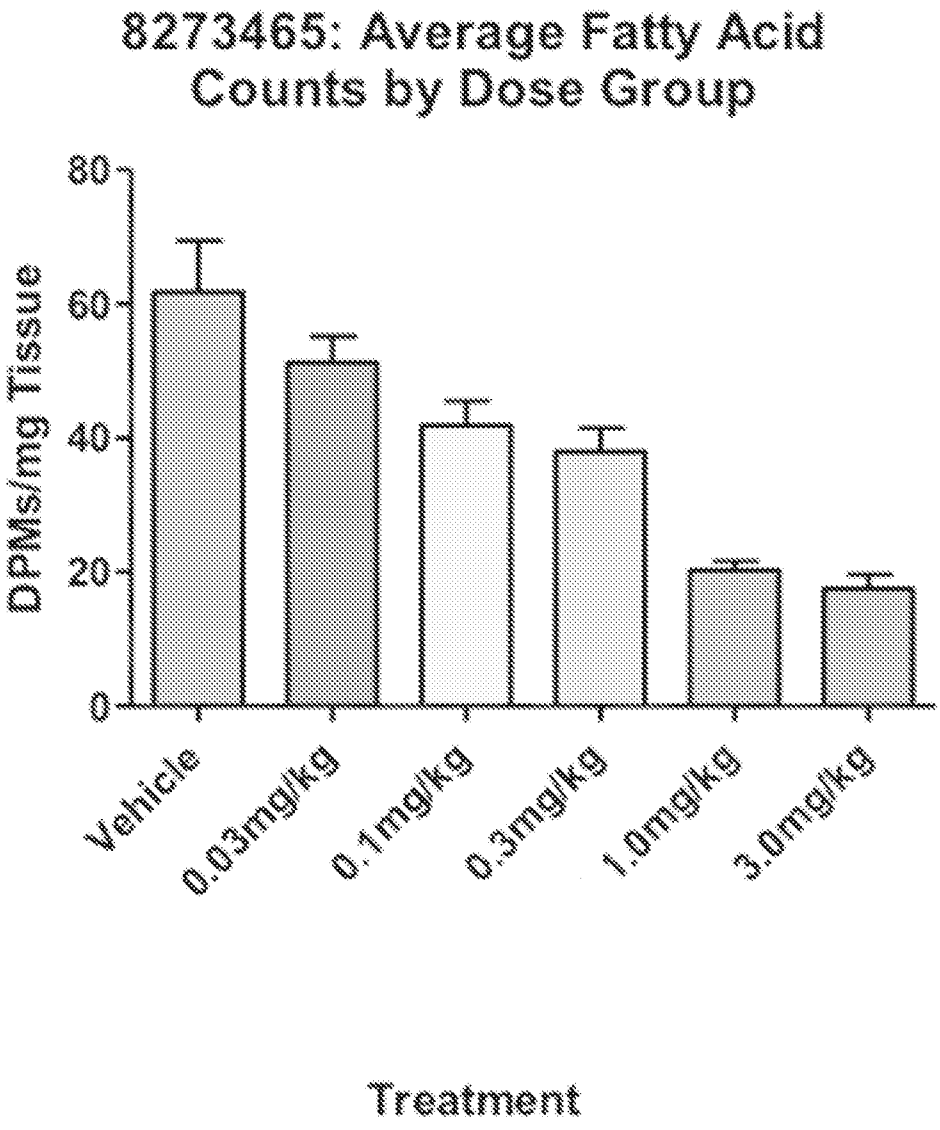


Figure 16 depicts results of an experiment measuring fatty acid (FA) synthesis in rats following administration of compound I-278. These results show a dose-dependent decrease in FA synthesis.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/64528

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/519; A61K 31/38 (2012.01)
USPC - 514/260.1; 514/443
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): A61K 31/519; A61K 31/38 (2012.01)
USPC: 514/260.1; 514/443 (text search)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/258.1; 514/265.1; 544/117 (text search) Find search terms below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB,USPT,USOC,EPAB,JPAB), Google Scholar/Patents, WIPO, SureChem, PatBase
thienopyrimidine, thieno[2,3-d]pyrimidine-2,4-dione, acetyl-CoA carboxylase, obesity, dyslipidemia, hyperlipidemia, metabolic, treat$,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2008/0287465 A1 (TUMEY et al.) 20 November 2008 (20.11.2008) para [0006]-[0007], [0009], [0014], [0048], [0166], [0237]	1-3, 5-6, 10 and 18 --- 4, 11-17 and 19-20
Y	US 2007/0208040 A1 (ELZEIN et al.) 06 September 2007 (06.09.2007) para [0020]-[0024], [0088]-[0089], [0112], [0185], [0334]	4 and 7-9
Y	EP 2 351 743 A1 (KAMATA et al.) 03 August 2011 (03.08.2011) para [0056]-[0058], [0111], [0115]-[0119], [0122]-[0128], [0251], [0258], claim 18	7-9, 11-17 and 19-20
Y	US 2006/0039943 A1 (APPLEBAUM et al.) 23 February 2006 (23.02.2006) para [0016]-[0022]	20
A	US 2005/0124636 A1 (SHARMA et al.) 09 June 2005 (09.06.2005) para [0011]-[0069]	1-20
A	US 6,180,635 B1 (CHESHIRE et al.) 30 January 2001 (30.01.2001) col 1, ln 27 - col 8, ln 8	1-20
A	US 2003/0187254 A1 (PERRY et al.) 02 October 2003 (02.10.2003) para [0017]-[0242]	1-20

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
02 January 2013 (02.01.2013)	04 FEB 2013
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INHIBIDORES DE ACC Y USOS DE LOS MISMOS

ANTECEDENTES DE LA INVENCION

La obesidad es una crisis de salud de proporciones extraordinarias. La carga de salud de la obesidad, medida en años de vida de calidad ajustada perdidas por adulto ha sobrepasado al hábito de fumar volviéndose la causa prevenible más grave de muerte. En los Estados Unidos, aproximadamente 34% de los adultos presentan obesidad, hasta 31% en 1999 y hasta 15% en los años 1960 a 1980. La obesidad incrementa la tasa de mortalidad de todas las causas tanto para hombres como para mujeres de todas las edades y en todos los grupos raciales y étnicos. La obesidad también lleva a estigmatización y discriminación raciales lo que disminuye la calidad de vida notablemente. Las enfermedades crónicas que resultan del costo de obesidad en la economía en Estados Unidos es mayor de 150 miles de millones de dólares en facturas médicas relacionadas con el peso cada año. Además, aproximadamente la mitad de esta población obesa y 25% de la población en general presentan síndrome metabólico, una condición asociada con obesidad abdominal, hipertensión, triglicéridos plasmáticos aumentados, colesterol HDL disminuido y resistencia a insulina lo que incrementa el riesgo de diabetes tipo 2 (T2DM), apoplejía y enfermedad cardíaca coronaria. [Hardwood, *Expert Opin. Ther. Targets*

9:267, 2005].

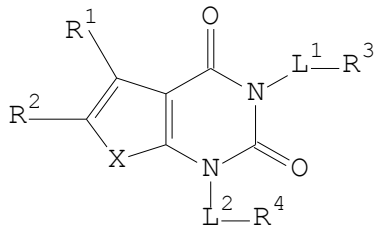
La dieta y el ejercicio, incluso cuando se utilizan junto con la farmacoterapia actual, no proporcionan una pérdida de peso sostenible necesaria para beneficio de salud a largo plazo. Actualmente solo algunos medicamentos contra la obesidad han sido aprobados en los Estados Unidos. El inhibidor de absorción de grasa orlistat (Xenical^{MR}), el antagonista de 5-TH_{2C} lorcaserina (Belviq^{MR}) y el tratamiento combinado de fentermina/topiramato (Qsymia^{MR}). Desafortunadamente, la poca eficacia y los efectos secundarios gastrointestinales desagradables limitan el uso de orlistat. La cirugía ha sido efectiva pero está limitada a pacientes con índice de masa corporal (BMI, por sus siglas en inglés) extremadamente altos y un bajo rendimiento de la cirugía limita el impacto de esta modalidad a aproximadamente 200,000 pacientes al año. La mayor parte de los fármacos contra la obesidad en desarrollo clínico están diseñados para reducir la ingestión calórica mediante acción central en el SNC (por ejemplo, anorécticos y agentes para la saciedad). No obstante, la FDA (siglas en inglés para Administración de Alimentos y Medicamentos) ha tomado una posición desfavorable contra agentes activos en el SNC debido a su modestia eficacia y sus perfiles de efectos secundarios observados/potenciales.

El problema continuo e incremento de obesidad y la carencia actual de fármacos inocuos y eficaces para tratarla

resalta la necesidad abrumadora de fármacos nuevos para tratar esta condición y sus causas subyacentes.

SUMARIO DE LA INVENCION

Ahora se ha encontrado que los compuestos de esta invención y las composiciones farmacéuticamente aceptables de los mismos son eficaces como inhibidores de acetil-COA carboxilasa (ACC, por sus siglas en inglés). Estos compuestos tienen la fórmula general I:



I

o una sal farmacéuticamente aceptable del mismo, en donde cada variable es como se define y se describe en la presente.

Los compuestos de la presente invención y las composiciones farmacéuticamente aceptables de los mismos son útiles para tratar una diversidad de enfermedades, trastornos o condiciones asociados con la regulación de la producción u oxidación de ácidos grasos. Estas enfermedades, trastornos o condiciones incluyen aquellos descritos en la presente.

Los compuestos proporcionados por esta invención también son útiles para el estudio de enzimas de ACC en fenómenos biológicos y patológicos; el estudio de las vías de

transducción de señal intracelular que se produce en tejidos lipogénicos; y la evaluación comparativa de inhibidores nuevos de ACC u otros reguladores de niveles de ácidos grasos *in vitro* o *in vivo*.

BREVE DESCRIPCION DE LAS FIGURAS

La figura 1 muestra curvas de inhibición de enzima para el compuesto I-158 contra ACC1 y ACC2.

La figura 2 muestra los resultados del análisis de desplazamiento térmico del compuesto I-97.

La figura 3 muestra los resultados del análisis de desplazamiento térmico de los compuestos I-1, I-158, I-174 y Soraphen A.

La figura 4 muestra los resultados del análisis celular en HepG2 de incorporación de acetato [^{14}C] para los compuestos I-158, I-174 y CP640186.

La figura 5 muestra los resultados de un análisis de viabilidad de células cancerosas LnCAP para I-158 y Soraphen A.

La figura 6 muestra las curvas de inbibición de enzima para el compuesto I-158 contra ACC1 y ACC2 *in vitro*.

La figura 7 muestra la inhibición de síntesis de ácido graso en células Hep-G2 por el compuesto I-181, medido por incorporación de acetato [^{14}C].

La figura 8 muestra la inhibición de síntesis de ácido graso en ratas por el compuesto I-181, que muestra una

DE_{50} de menos de 0.3 mg/kg.

La figura 9 muestra los resultados de un estudio de cociente respiratorio (RQ) que mide la relación de producción de CO_2 respecto al consumo de O_2 en ratas, utilizando el compuesto I-181 a dosis de 30 y 100 mg/kg de peso corporal.

La figura 10 muestra los resultados de un estudio de cociente respiratorio (RQ) que mide la relación de producción de CO_2 respecto al consumo de O_2 en ratas, utilizando el compuesto I-181 a dosis de 3, 10 y 30 mg/kg de peso corporal.

La figura 11 muestra los resultados de un experimento de ganancia de peso de obesidad inducida por dieta (DIO, por sus siglas en inglés) alta en grasa, en donde las ratas son tratadas con 3, 10 ó 30 mg/kg de I-181.

La figura 12 muestra los resultados de un experimento de reducción en el nivel de insulina, en donde ratas con una dieta de obesidad inducida por dieta alta en grasa (DIO) son tratadas con 3, 10 ó 30 mg/kg de I-181.

La figura 13 muestra los resultados de un experimento de medición de colesterol hepático y triglicéridos en donde las ratas con una dieta para obesidad inducida por dieta alta en grasa (DIO) son tratadas con 3, 10 ó 30 mg/kg de I-181.

La figura 14 muestra los resultados de un experimento que mide la inducción de muerte celular en líneas de tumor hepatocelular naturales y mutante p53 (HepG2 y HepB3)

después de la administración del compuesto I-246.

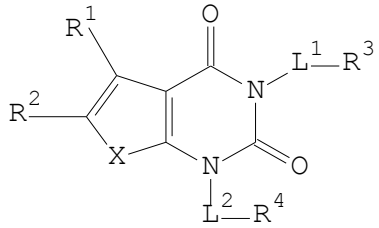
La figura 15 muestra los resultados de un experimento que mide la muerte celular en una línea de tumor de adenocarcinoma de próstata humano sensible a andrógeno (LNCaP) después de la administración del compuesto I-159 o Soraphen A.

La figura 16 muestra los resultados de un experimento que mide la síntesis de ácido graso (FA, por sus siglas en inglés) en ratas después de la administración del compuesto I-278. Estos resultados muestran una disminución dependiente de la dosis en la síntesis de FA.

DESCRIPCION DETALLADA DE LA INVENCION

I. DESCRIPCION GENERAL DE LOS COMPUESTOS DE LA INVENCION

En ciertas modalidades, la presente invención proporciona inhibidores de ACC, en algunas modalidades, estos compuestos incluyen aquellos de fórmula I:



I

o una sal farmacéuticamente aceptable de los mismos, en donde:

X es -O-, -S- o -NR-;

R^1 es hidrógeno o un grupo alifático de 1 a 4 átomos

de carbono, opcionalmente sustituido con uno o más de halógeno, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -C(O)OR, -S(O)R o $-SO_2R$;

R^2 es halógeno, -R, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o $-SO_2R$ o Hy, en donde Hy se selecciona de un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre; o

R^1 y R^2 se toman juntos para formar un anillo opcionalmente sustituido de 4 a 7 miembros parcialmente insaturado carbociclo- o heterociclo-, benzo- o heteroarilo-fusionado de 5 a 6 miembros;

cada R es independientemente hidrógeno, deuterio o un grupo opcionalmente sustituido que se selecciona de un grupo alifático de 1 a 6 átomos de carbono, un anillo carbocíclico monocíclico saturado o parcialmente insaturado de

3 a 8 miembros, fenilo, un anillo carbocíclico aromático bicíclico de 8 a 10 miembros; un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

cada uno de L^1 y L^2 es independientemente, un enlace covalente o una cadena de hidrocarburo divalente lineal o ramificada de 1 a 6 miembros opcionalmente sustituida;

R^3 es hidrógeno, halógeno, -CN, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)RN(R)_2$, $-C(O)N(R)S(O)_2R$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, $-C(O)R$, $-C(O)OR$, $-OC(O)R$, $-S(O)R$, $-SO_2R$, o un anillo opcionalmente sustituido que se selecciona de fenilo o un heteroarilo de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

R^4 es hidrógeno o un anillo opcionalmente sustituido que se selecciona de un anillo carbocíclico saturado o parcialmente insaturado monocíclico de 3 a 8 miembros, un anillo heterocíclico saturado o parcialmente insaturado

monocíclico de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, fenilo, un anillo arilobicíclico de 8 a 10 miembros, un anillo heteroarilo monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se selecciona independientemente de nitrógeno, oxígeno o azufre o un anillo heteroarilo bicíclico de 8 a 10 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre.

2. COMPUESTOS Y DEFINICIONES

Los compuestos de esta invención incluyen aquellos descritos de manera general en lo anterior y se ilustran adicionalmente por las clases, subclases y especies descritas en la presente. Como se utiliza en la presente, se aplicarán las siguientes definiciones a menos que se indique en otro sentido. Para propósitos de esta invención, los elementos químicos se identifican de acuerdo con la tabla periódica de los elementos, versión CAS, Handbook of Chemistry and Physics, 75ª edición. De manera adicional, los principios generales de química orgánica se describen en "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5ª edición., Editores Smith, M.B. y March, J., John Wiley & Sons, New York: 2001, los contenidos completos de los cuales se incorporan en la presente como referencia.

El término "alifático" o "grupo alifático", como se

utiliza en la presente, significa una cadena de hidrocarburo sustituida o no sustituida de cadena lineal (es decir, no ramificada) o ramificada, que está completamente saturada o que contiene una o más unidades de insaturación, o un hidrocarburo monocíclico o un hidrocarburo bicíclico que está completamente saturado o que contiene una o más unidades de insaturación pero la cuales son no aromáticas (también denominado en la presente como "carbociclo" "cicloalifático" o "cicloalquilo"), que tiene un solo punto de unión al resto de la molécula. A menos que se especifique en otro sentido, los grupos alifáticos contienen 1 a 6 átomos de carbono alifáticos. En algunas modalidades, los grupos alifáticos contienen 1 a 5 átomos de carbono alifáticos. En otras modalidades, los grupos alifáticos contienen 1 a 4 átomos de carbono alifáticos. En otras modalidades adicionales, los grupos alifáticos contienen 1 a 3 átomos de carbono alifáticos y en otras modalidades aún adicionales los grupos alifáticos contienen 1 a 2 átomos de carbono alifáticos. En algunas modalidades, ("cicloalifático" o "carbociclo" o "cicloalquilo") se refiere a un hidrocarburo monocíclico de 3 a 8 átomos de carbono que está completamente saturado o que contiene una o más unidades de insaturación pero el cual es no aromático, que tiene un único punto de unión al resto de la molécula. Los grupos alifáticos adecuados incluyen, pero no se limitan a grupos alquilo, alquenilo, alquinilo lineales o

ramificados, sustituidos o no sustituidos e híbridos de los mismos tales como (cicloalquil)alquilo, (cicloalquenil)alquilo o (cicloalquil)alquenilo.

El término "alquilo inferior" se refiere a un grupo alquilo lineal o ramificado de 1 a 4 átomos de carbono. Los grupos alquilo inferior ejemplares son metilo, etilo, propilo, isopropilo, butilo, isobutilo y terbutilo.

El término "haloalquilo inferior" se refiere a un grupo alquilo lineal o ramificado de 1 a 4 átomos de carbono que está sustituido con uno o más átomos de halógeno.

El término "heteroátomo" significa uno o más de oxígeno, azufre, nitrógeno, fósforo o silicio (que incluye cualquier forma oxidada de nitrógeno, azufre, fósforo o silicio; la forma cuaternizada de cualquier nitrógeno básico o un nitrógeno sustituible de un anillo heterocíclico, por ejemplo N (como en 3,4-dihidro-2H-pirrolilo), NH (como en pirrolidinilo) o NR^+ (como en pirrolidinilo N-sustituido)).

El término "insaturado", como se utiliza en la presente, significa que una porción tiene una o más unidades de insaturación.

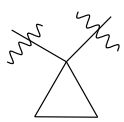
Como se utiliza en la presente, el término "cadena de hidrocarburo lineal o ramificada, saturada o insaturada de 1 a 8 átomos de carbono (o de 1 a 6 átomos de carbono) bivalente", se refiere a cadenas bivalentes alquileno, alquenileno y alquinileno que son lineales o ramificadas como

se define en la presente.

El término "alquileno" se refiere a un grupo alquilo bivalente. Una "cadena alquileno" es un grupo polimetileno, es decir, $-(CH_2)_n-$, en donde n es un número entero positivo, preferiblemente de 1 a 6, de 1 a 4, de 1 a 3, de 1 a 2 o de 2 a 3. Una cadena alquileno sustituida es un grupo polimetileno en el cual uno o más átomos de hidrógeno metileno están sustituidos con un sustituyente. Los sustituyentes adecuados incluyen aquellos descritos en lo siguiente para un grupo alifático sustituido.

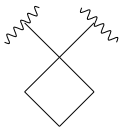
El término "alquenileno" se refiere a un grupo alquenilo bivalente. Una cadena alquenileno sustituida es un grupo polimetileno que contiene por lo menos un enlace doble en el cual uno o más átomos de hidrógeno están sustituidos con un sustituyente. Los sustituyentes adecuados incluyen aquellos descritos más adelante para un grupo alifático sustituido.

Como se utiliza en la presente, el término "ciclopropilenilo" se refiere a un grupo ciclopropilo bivalente de la siguiente estructura:



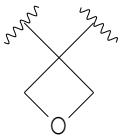
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Como se utiliza en la presente, el término "ciclobutilenilo" se refiere a un grupo ciclobutilo bivalente de la siguiente estructura:



.

Como se utiliza en la presente, el término "oxetanilo" se refiere a un grupo oxetanilo bivalente de la siguiente estructura:



El término "halógeno" significa F, Cl, Br o I.

El término "arilo" utilizado solo o como parte de una porción más grande, como en "aralquilo", "aralcoxi" o "ariloxialquilo" se refiere a sistemas de anillos monocíclicos o bicíclicos que tienen un total de 5 a 14 miembros en el anillo, en donde por lo menos un anillo en el sistema es aromático y en donde cada anillo en el sistema contiene 3 a 7 miembros en el anillo. El término "arilo" se puede utilizar de manera intercambiable con el término "anillo arilo". El término "arilo" utilizado solo o como parte de una porción más grande como en "aralquilo", "aralcoxi" o "ariloxialquilo" se refiere a sistemas de anillos monocíclicos o bicíclicos que tienen un total de 5 a 10 miembros en el anillo, en donde por lo menos un anillo en el sistema es aromático y en donde cada anillo en el sistema contiene 3 a 7 miembros en el anillo. El término "arilo" se puede utilizar de manera intercambiable con el término "anillo arilo".

En ciertas modalidades de la presente invención, "arilo" se refiere a un sistema de anillo aromático el cual incluye, pero no se limita a fenilo, bifenilo, naftilo, antracilo y similares, los cuales pueden presentar uno o más sustituyentes. También se incluyen dentro del alcance del término "arilo", como se utiliza en la presente, un grupo en el cual un anillo aromático está fusionado a uno o más anillos no aromáticos tales como indanilo, ftalimidilo, naftimidilo, fenantridinilo o tetrahidronaftilo y similares.

Los términos "heteroarilo" y "heteroar-", utilizados solos o como parte de una porción más grande, por ejemplo "heteroaralquilo" o "heteroaralcoxi" se refieren a grupos que tienen 5 a 10 átomos en el anillo preferiblemente 5, 6 ó 9 átomos en el anillo; que tienen 6, 10 ó 14 electrones π compartidos en una distribución cíclica; y que tienen, además de átomos de carbono, de 1 a 5 heteroátomos. El término "heteroátomo" se refiere a nitrógeno, oxígeno o azufre e incluye cualquier forma oxidada de nitrógeno o azufre y cualquier forma cuaternizada de un nitrógeno básico. Los grupos heteroarilo incluyen, sin limitación, tienilo, furanilo, pirrolilo, imidazolilo, pirazolilo, triazolilo, tetrazolilo, oxazolilo, isoxazolilo, oxadiazolilo, tiazolilo, isotiazolilo, tiadiazolilo, piridilo, piridazinilo, pirimidinilo, pirazinilo, indolizinilo, purinilo, naftiridinilo y pteridinilo. Los términos "heteroarilo" y

"heteroar-", como se utilizan en la presente, también incluyen grupos en los cuales el anillo heteroaromático está fusionado a uno o más anillos arilo, cicloalifático o heterociclilo, en donde el radical o punto de unión está sobre el anillo heteroaromático. Los ejemplos no limitantes incluyen indolilo, isoindolilo, benzotienilo, benzofuranilo, dibenzofuranilo, indazolilo, bencimidazolilo, benztiazolilo, quinolilo, isoquinolilo, cinnolinilo, ftalazinilo, quinazolinilo, quinoxalinilo, 4H-quinozilinilo, carbazolilo, acridinilo, fenazinilo, fenotiazinilo, fenoxazinilo, tetrahidroquinolinilo, tetrahidroisoquinolinilo y pirido[2,3-b]-1,4-oxazin-3(4H)-ona. Un grupo heteroarilo puede ser mono- o bicíclico. El término "heteroarilo" se puede utilizar de manera intercambiable con los términos "anillo heteroarilo", "grupo heteroarilo" o "heteroaromático" cualquiera de los términos los cuales incluyen anillos que están opcionalmente sustituidos. El término "heteroarilo" se refiere a un grupo alquilo sustituido por un heteroarilo en donde las porciones alquilo y heteroarilo están independientemente opcionalmente sustituidas.

Como se utiliza en la presente, los términos "heterociclo", "heterociclilo", "radical heterocíclico" y "anillo heterocíclico" se utilizan de manera intercambiable y se refieren a una porción heterocíclica estable monocíclica de 5 a 7 miembros o bicíclica de 7 a 10 miembros que está

saturada o parcialmente insaturada y que tiene, además de átomos de carbono, uno o más, preferiblemente uno a cuatro heteroátomos, como se define en lo anterior. Cuando se utiliza con referencia a un átomo en el anillo de un heterociclo, el término "nitrógeno" incluye un nitrógeno sustituido. Como un ejemplo, en un anillo saturado o parcialmente insaturado que tiene 0 a 3 heteroátomos que se seleccionan de oxígeno, azufre o nitrógeno, el nitrógeno puede ser N (como en 3,4-dihidro-2H-pirrolilo), NH (como en pirrolidinilo) o $^{+}$NR (como en pirrolidinilo N-sustituido).

Un anillo heterocíclico se puede unir a su grupo pendiente en cualquier heteroátomo o átomo de carbono que resulte en una estructura estable y cualquiera de los átomos del anillo opcionalmente puede estar sustituido. Los ejemplos de los radicales heterocíclicos saturados o parcialmente insaturados incluyen, sin limitación, tetrahidrofuranilo, tetrahidrotiofenilo, pirrolidinilo, piperidinilo, pirrolinilo, tetrahidroquinolinilo, tetrahidroisoquinolinilo, decahidroquinolinilo, oxazolidinilo, piperazinilo, dioxanilo, dioxolanilo, diazepinilo, oxazepinilo, tiazepinilo, morfolinilo y quinuclidinilo. Los términos "heterociclo", "heterociclilo", "anillo heterociclilo", "grupo heterocíclico", "porción heterocíclica" y "radical heterocíclico" se utilizan de manera intercambiable en la presente y también incluyen grupos en los cuales un anillo

heterociclilo está fusionado a uno o más anillos arilo, heteroarilo o cicloalifáticos tales como indolinilo, 3H-indolilo, cromanilo, fenantridinilo o tetrahidroquinolinilo, en donde el radical o punto de unión está sobre el anillo heterociclilo. Un grupo heterociclilo puede ser mono- o bicíclico. El término "heterociclilalquilo" se refiere a un grupo alquilo sustituido por un heterociclilo, en donde las porciones alquilo y heterociclilo independientemente están opcionalmente sustituidas.

Como se utiliza en la presente, el término "parcialmente insaturado" se refiere a una porción del anillo que incluye por lo menos un enlace doble o triple. El término "parcialmente insaturado" se pretende que abarque anillos que tienen sitios de insaturación múltiples pero no se pretende que incluya porciones arilo o heteroarilo, como se definen en la presente.

Como se describe en la presente, los compuestos de la invención pueden contener porciones "opcionalmente sustituidas". En general, el término "sustituido" cuando está presente por el término "opcionalmente" o no significa que uno o más hidrógenos de la porción designada están sustituidos con un sustituyente adecuado. A menos que se indique en otro sentido, un grupo "opcionalmente sustituido" puede tener un sustituyente adecuado en cada posición sustituible del grupo y cuando más de una posición en cualquier estructura dada puede

estar sustituida con más de un sustituyente que se selecciona de un grupo especificado, el sustituyente puede ser el mismo o diferente en cada posición. Las combinaciones de sustituyentes considerados por está invención preferiblemente son aquellas que resultan en la formación de compuestos estables o químicamente factibles. El término "estable", como se utiliza en la presente, se refiere a compuestos que no han sido alterados sustancialmente cuando se someten a condiciones para permitir su producción, detección y, en algunas modalidades, su recuperación, purificación y el uso de uno o más de los propósitos descritos en la presente.

Los sustituyentes monovalentes adecuados sobre un átomo de carbono sustituible de un grupo "opcionalmente sustituido" son independientemente halógeno; $-(CH_2)_{0-4}R^{\circ}$; $-(CH_2)_{0-4}OR^{\circ}$; $-O(CH_2)_{0-4}R^{\circ}$, $-O-(CH_2)_{0-4}C(O)OR^{\circ}$; $-(CH_2)_{0-4}CH(OR^{\circ})_2$; $-(CH_2)_{0-4}SR^{\circ}$; $-(CH_2)_{0-4}Ph$, los cuales puede estar sustituido con R°; CH=CHPh, el cual puede estar sustituido con R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}$-piridilo el cual puede estar sustituido con R°; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^{\circ})_2$; $-(CH_2)_{0-4}N(R^{\circ})C(O)R^{\circ}$; $N(R^{\circ})C(S)R^{\circ}$; $-(CH_2)_{0-4}N(R^{\circ})C(O)NR^{\circ}_2$; $-N(R^{\circ})C(S)NR^{\circ}_2$; $-(CH_2)_{0-4}N(R^{\circ})C(O)OR^{\circ}$; $-N(R^{\circ})N(R^{\circ})C(O)R^{\circ}_2$; $-N(R^{\circ})N(R^{\circ})C(O)NR^{\circ}_2$; $-N(R^{\circ})N(R^{\circ})C(O)OR^{\circ}$; $-(CH_2)_{0-4}C(O)R^{\circ}$; $-C(S)R^{\circ}$; $-(CH_2)_{0-4}C(O)OR^{\circ}$; $-(CH_2)_{0-4}C(O)SR^{\circ}$; $-(CH_2)_{0-4}C(O)OSiR^{\circ}$; $-(CH_2)_{0-4}OC(O)R^{\circ}$, $-OC(O)(CH_2)_{0-4}SR-$, $-SC(S)SR^{\circ}$; $-(CH_2)_{0-4}SC(O)R^{\circ}$; $-(CH_2)_{0-4}C(O)NR^{\circ}_2$; $-C(S)NR^{\circ}_2$; $-C(S)SR^{\circ}$; $-SC(S)SR^{\circ}$; $-(CH_2)_{0-4}OC(O)NR^{\circ}_2$; $-C(O)N(OR^{\circ})R^{\circ}$;

$-C(O)C(O)R^{\circ}$; $-C(O)CH_2C(O)R^{\circ}$; $-C(NOR^{\circ})R^{\circ}$; $-(CH_2)_{0-4}SSR^{\circ}$; $-(CH_2)_{0-4}S(O)_2R^{\circ}$; $-(CH_2)_{0-4}S(O)_2OR^{\circ}$; $-(CH_2)_{0-4}OS(O)_2R^{\circ}$; $-S(O)_2NR^{\circ}_2$; $-(CH_2)_{0-4}S(O)R^{\circ}$; $-N(R^{\circ})S(O)_2NR^{\circ}_2$; $-N(R^{\circ})S(O)_2R^{\circ}$; $-N(OR^{\circ})R^{\circ}$; $-P(O)_2R^{\circ}$; $-P(O)R^{\circ}_2$; $-OP(O)R^{\circ}_2$; $-OP(O)(OR^{\circ})_2$; SiR°_3; -(alquileno lineal o ramificado de 1 a 4 átomos de carbono)-$O-N(R^{\circ})_2$; o -(alquileno lineal o ramificado de 1 a 4 átomos de carbono)$(C(O)O-N(R^{\circ})_2$, en donde cada R° puede estar sustituido como se define más adelante y es independientemente hidrógeno, alifático de 1 a 6 átomos de carbono, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2$-(anillo heteroarilo de 5-6 miembros), o un anillo arilo de 5 a 6 miembros saturado, parcialmente insaturado que tiene 0 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, o, sin importar la definición anterior, las dos presentaciones independientes de R°, tomadas junto con uno o varios de los átomos intermedios, forma un anillo de 3 a 12 miembros saturado, parcialmente insaturado o arilo mono- o bicíclico que tiene 0 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, los cuales pueden estar sustituido como se define más adelante.

Los sustituyentes monovalentes adecuados en R° (o el anillo formado al tomar dos presentaciones independientes de R° junto con sus átomos intermedios) son independientemente halógeno, $-(CH_2)_{0-2}R^{\bullet}$, -(halo$R^{\bullet}$), $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}CH(OR^{\bullet})_2$; $-(CH_2)_{0-2}OR^{\bullet}$, $-(CH_2)_{0-2}CH(OR)_2{}^{\bullet}$, -O(halo$R^{\bullet}$), -CN, $-N_3$, $-(CH_2)_{0-}$

$_2$C(O)R$^\bullet$; -(CH$_2$)$_{0-2}$C(O)OH, -(CH$_2$)$_{0-2}$C(O)OR$^\bullet$, -(CH$_2$)$_{0-2}$SR$^\bullet$, -(CH$_2$)$_{0-2}$SH, -(CH$_2$)$_{0-2}$NH$_2$, -(CH$_2$)$_{0-2}$NHR$^\bullet$, -(CH$_2$)$_{0-2}$NR$^\bullet_2$, -NO$_2$, -SiR$^\bullet_3$, -OSiR$^\bullet_3$, -C(O)SR$^\bullet$, -(alquileno de 1 a 4 átomos de carbono lineal o ramificado)C(O)OR$^\bullet$ o -SSR$^\bullet$, en donde cada R$^\bullet$ está no sustituido o cuando está precedido por "halo" está sustituido únicamente con uno o más halógenos, y se selecciona independientemente de alifático de 1 a 4 átomos de carbono, -CH$_2$Ph, -O(CH$_2$)$_{0-1}$Ph o un anillo de 5 a 6 miembros saturado, parcialmente insaturado o arilo que tiene 0 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre. Los sustituyentes divalentes adecuados sobre un átomo de carbono saturado de R$^\circ$ incluyen =O y =S.

Los sustituyentes divalentes adecuados sobre un átomo de carbono saturado de un grupo "opcionalmente sustituido" incluyen los siguientes: =O, =S, =NRR$^*_2$; =NNHC(O)R*, =NNHC(O)OR*, =NNHS(O)$_2$R*, =NR*, =NOR*, -O(C(R$^*_2$))$_{2-3}$O-, o -S(C(R$^*_2$))$_{2-3}$S-, en donde cada presentación independiente de R* se selecciona de hidrógeno, alifático de 1 a 6 átomos de carbono el cual puede estar sustituido como se define más adelante o un anillo no sustituido de 5 a 6 miembros, saturado, parcialmente insaturado o arilo que tiene 0 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre. Los sustituyentes divalentes adecuados que se unen a carbonos sustituibles vecinales de un grupo "opcionalmente sustituido" incluyen: -O(CR$^*_2$)$_{2-3}$O-, en

donde cada presentación independiente de R^* se selecciona de hidrógeno, alifático de 1 a 6 átomos de carbono el cual puede estar sustituido como se define más adelante o un anillo no sustituido de 5 a 6 miembros, saturado, parcialmente insaturado o arilo que tiene 0 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre.

Los sustituyentes adecuados en el grupo alifático de R^* incluyen halógeno, $-R^\bullet$, $-(haloR^\bullet)$, $-OH$, $-OR^\bullet$, $-O(haloR^\bullet)$, $-CN$, $-C(O)OH$, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$ o $-NO_2$, en donde cada $R^\bullet$ está no sustituido o cuando está precedido por "halo" está sustituido únicamente con uno o más halógenos y es independientemente un grupo alifático de 1 a 4 átomos de carbono, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$ o un anillo de 5 a 6 miembros saturado, parcialmente insaturado o arilo que tiene 0 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre.

Los sustituyentes adecuados sobre un nitrógeno sustituible de un grupo "opcionalmente sustituido" incluyen $-R^\dagger$, $-NR^\dagger_2$, $-C(O)R^\dagger$, $-C(O)OR^\dagger$, $-C(O)C(O)R^\dagger$, $-C(O)CH_2C(O)R^\dagger$, $-S(O)_2R^\dagger$, $-S(O)_2NR^\dagger_2$, $-C(S)NR^\dagger_2$, $-C(NH)NR^\dagger_2$ o $-N(R^\dagger)S(O)_2R^\dagger$; en donde cada $R^\dagger$ es independientemente hidrógeno, un grupo alifático de 1 a 6 átomos de carbono el cual puede estar sustituido como se define más adelante no sustituido $-OPh$ o un anillo no sustituido de 5 a 6 miembros saturado, parcialmente insaturado o arilo que tiene 0 a 4 heteroátomos que se

seleccionan independientemente de nitrógeno, oxígeno o azufre, o, sin importar la definición anterior, dos presentaciones independientes de $R^{\dagger}$, tomadas junto con uno o varios de sus átomos intermedios forman un anillo no sustituido de 3 a 12 miembros saturado, parcialmente insaturado o arilo mono- o bicíclico que tiene 0 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre.

Los sustituyentes adecuados en el grupo alifático de $R^{\dagger}$ son independientemente halógeno, $-R^{\bullet}$, $-(haloR^{\bullet})$, $-OH$, $-OR^{\bullet}$, $-O(haloR^{\bullet})$, $-CN$, $-C(O)OH$, $-C(O)OR^{\bullet}$, $-NH_2$, $-NHR^{\bullet}$, $-NR^{\bullet}_2$ O $-NO_2$, en donde cada $R^{\bullet}$ está no sustituido o cuando está precedido por "halo" está sustituido únicamente con uno o más halógenos y es independientemente un grupo alifático de 1 a 4 átomos de carbono, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$ o un anillo de 5 a 6 miembros saturado, parcialmente insaturado o arilo que tiene 0 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre.

Como se utiliza en la presente, el término "sal farmacéuticamente aceptable" se refiere a aquellas sales las cuales están, dentro del alcance del buen juicio médico, son adecuadas para uso en contacto con los tejidos de humanos y animales inferiores sin las formas indebidas de toxicidad, irritación, respuesta alérgica y similares y está conmensurado con la relación razonable entre beneficio/riesgo. Las sales farmacéuticamente aceptables son bien conocidas en el ámbito.

Por ejemplo, S. M. Berge et al., describen sales farmacéuticamente aceptables con detalle en J. Pharmaceutical Sciences, 1977, 66, 1-19, incorporado como referencia en la presente. Las sales farmacéuticamente aceptables de los compuestos de esta invención incluyen aquellos derivados de ácidos y bases inorgánicos y orgánicos adecuadas. Los ejemplos de sales de adición de ácido no tóxicas y farmacéuticamente aceptables son sales de un grupo amino formado con ácidos inorgánicos tales como ácido clorhídrico, ácido bromhídrico, ácido fosfórico, ácido sulfúrico y ácido perclórico o con ácidos orgánicos tales como ácido acético, ácido oxálico, ácido maleico, ácido tartárico, ácido cítrico, ácido succínico o ácido malónico o mediante el uso de otros métodos usados en el ámbito tales como intercambio de iones. Otras sales farmacéuticamente aceptables incluyen adipato, alginato, ascorbato, aspartato, bencensulfonato, benzoato, bisulfato, borato, butirato, canforato, canforsulfonato, citrato, ciclopentanopropionato, digluconato, docecilsulfato, etansulfonato, formiato, fumarato, glucoheptonato, glicerofosfato, gluconato, hemisulfato, heptanoato, hexanoato, yodhidrato, 2-hidroxi-etansulfonato, lactobionato, lactato, laurato, laurilsulfato, malato, maleato, malonato, metansulfonato, 2-naftalensulfonato, nicotinato, nitrato, oleato, oxalato, palmitato, pamoato, pectinato, persulfato, 3-fenilpropionato, fosfato, pivalato, propionato, estearato,

succinato, sulfato, tartrato, tiocianato, p-toluensulfonato, undecanoato, sales de valerato y similares.

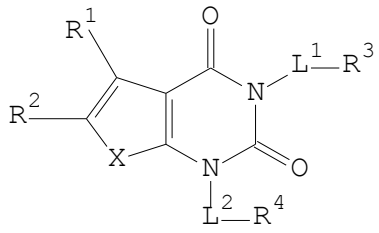
Las sales derivadas de bases apropiadas incluyen sales de metal alcalino, de metal alcalinotérreo, de amonio y N^+(alquilo de 1 a 4 átomos de carbono)$_4$. Las sales representativas alcalinas o alcalinotérreas incluyen sodio, litio, potasio, calcio, magnesio y similares. Las sales farmacéuticamente aceptables adicionales incluyen, cuando es apropiado, amonio no tóxico, amonio cuaternario y cationes de amina formados utilizando contraiones tales como haluro, hidróxido, carboxilato, sulfato, fosfato, nitrato, alquilo inferior sulfonato y arilsulfonato.

A menos que se establezca en otro sentido, las estructuras presentadas en este documento también significa que incluyen todas las formas isoméricas (por ejemplo enantioméricas, diastereoméricas y geométricas) (o conformacionales)) de la estructura: por ejemplo, las configuraciones R y S para cada centro asimétrico, isómeros de enlace doble Z y E e isómeros conformacionales Z y E. Por lo tanto, los isómeros estereoquímicos únicos así como las mezclas enantioméricas diastereoméricas y geométricas (o conformacionales) de los presentes compuestos están dentro del alcance de la invención. A menos que se establezca en otro sentido, todas las formas tautoméricas de los compuestos de la invención están dentro del ámbito de la invención.

Adicionalmente, a menos que se establezca en otro sentido, las estructuras que se presentan en este documento también significa que incluyen compuestos que difieren únicamente en la presencia de uno o más átomos isotópicamente enriquecidos. Por ejemplo, compuestos que tienen las presentes estructuras que incluyen la sustitución de hidrógeno por deuterio o tritio o la sustitución de un carbono por un carbono enriquecido ^{13}C o ^{14}C están dentro del ámbito de esta invención. Estos compuestos son útiles, por ejemplo, como herramientas analíticas, como sondas en análisis biológicos o como agentes terapéuticos, de acuerdo con la presente invención. En algunas modalidades, una porción de cabeza de guerra R^1 o de un compuesto proporcionado comprende uno o más átomos de deuterio.

3. DESCRIPCION DE LAS MODALIDADES EJEMPLARES

En ciertas modalidades, la presente invención proporciona inhibidores de ACC. En algunas modalidades, estos compuestos incluyen a aquellos de fórmula I:



I

o una sal farmacéuticamente aceptable del mismo, en

donde:

X es -O-, -S- o -NR-;

R^1 es hidrógeno o una porción alifática de 1 a 4 átomos de carbono, opcionalmente sustituida con uno o más de halógeno, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o $-SO_2R$;

R^2 es halógeno, -R, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o $-SO_2R$ o Hy, en donde Hy se selecciona de un anillo heterocíclico de 4 a 8 miembros saturado o parcialmente insaturado monocíclico que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

o R^1 y R^2 se toman juntos para formar un anillo opcionalmente sustituido de 4 a 7 miembros parcialmente insaturado carbociclo- o heterociclo-, benzo- o de 5 a 6 miembros heteroarilo-fusionado;

cada R es independientemente hidrógeno, o un grupo

opcionalmente sustituido que se selecciona de un grupo alifático de 1 a 6 átomos de carbono, un anillo de 3 a 8 miembros saturado o parcialmente insaturado monocíclico carbocíclico, fenilo, un anillo carbocíclico aromático bicíclico de 8 a 10 miembros; un anillo heterocíclico monocíclico de 4 a 8 miembros saturado o parcialmente insaturado que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre o un anillo heteroaromático bíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

cada uno de L^1 y L^2 es independientemente un enlace covalente o una cadena de hidrocarburo divalente lineal o ramificada de 1 a 6 miembros opcionalmente sustituida; o un grupo ciclopropilenilo, ciclobutilenilo u oxetanilo;

R^3 es hidrógeno, halógeno, -CN, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-C(O)N(R)S(O)_2R$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, $-C(O)R$, $-C(O)OR$, $-OC(O)R$, $-S(O)R$, $-SO_2R$, $-B(OH)_2$ o un anillo opcionalmente sustituido que se selecciona de fenilo o un heteroarilo de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre; y

R^4 es hidrógeno o un anillo opcionalmente sustituido que se selecciona de un anillo carbocíclico saturado o parcialmente insaturado monocíclico de 3 a 8 miembros, un anillo heterocíclico saturado o parcialmente insaturado monocíclico de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, fenilo, un anillo arilo bicíclico de 8 a 10 miembros, un anillo heteroarilo monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre o un anillo heteroarilo bicíclico de 8 a 10 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre.

En algunas modalidades, si L^2 es un enlace covalente, entonces R^4 no es hidrógeno. En ciertas modalidades el grupo $-L^2-R^4$ no es alquilo cuando R^2 es alquilo no sustituido. En ciertas modalidades el grupo $-L^1-R^3$ tomados juntos no es alquilo no sustituido. En ciertas modalidades R^1 no es el grupo $-CH_2C(O)N(R)V$, en donde V es un arilo o un anillo heteroarilo, cuando $-L^1-R^3$ tomados juntos es alquilo no sustituido.

Como se define de manera general en lo anterior, X es -O-, -S- o -NR-. En ciertas modalidades X es -O-. En ciertas modalidades, X es -S-. En ciertas modalidades X es -NR-. En ciertas modalidades, X es -NH-.

Como se define generalmente en lo anterior, R^1 es

hidrógeno o alifático de 1 a 4 átomos de carbono, opcionalmente sustituido con uno o más de halógeno, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2-$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R_2)$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o $-SO_2R$. En ciertas modalidades, R^1 es hidrógeno. En ciertas modalidades R^1 es alifático de 1 a 4 átomos de carbono. En ciertas modalidades R^1 es metilo. En ciertas modalidades R^1 es trifluorometilo.

Como se define generalmente en lo anterior, R^2 es halógeno, R, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2-$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R_2)$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o $-SO_2R$ o Hy, en donde Hy se selecciona de un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre o un anillo heteroaromático bíciclico de 8 a 10 miembros que tiene 1 a 5 heteroaromáticos que se seleccionan independientemente de nitrógeno, oxígeno o azufre. En ciertas modalidades, R^2 es halógeno. En ciertas modalidades, R^2 es metilo. En ciertas modalidades, R^2 es trifluorometilo. En ciertas modalidades, R^2 es flúor. En ciertas modalidades, R^2 es cloro. En ciertas modalidades, R^2 es bromo. En ciertas

modalidades, R^2 es yodo. En ciertas modalidades, R^2 es -C(O)OR o -C)O)N(R)$_2$. En ciertas modalidades, R^2 es Hy.

Como se define de manera general en lo anterior, Hy se selecciona de un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, o un anillo heteroaromático bíciclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre. En ciertas modalidades, Hy es un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre. En ciertas modalidades, Hy es un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre. En ciertas modalidades, Hy es un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre. En ciertas modalidades, Hy es oxazolilo.

En ciertas modalidades, R^1 y R^2 se toman juntos para formar un anillo carbocíclico parcialmente insaturado de 4 a 7

miembros opcionalmente sustituido. En ciertas modalidades, R^1 y R^2 se toman juntos para formar un anillo opcionalmente sustituido, de 4 a 7 miembros, parcialmente insaturado, carbociclo- o heterociclo-, benzo- o heteroarilo- de 5 a 6 miembros fusionado.

Como se define de manera general en lo anterior, R^3 es hidrógeno, halógeno, -CN, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-C(O)N(R)S(O)_2R$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, $-C(O)R$, $-C(O)OR$, $-OC(O)R$, $-S(O)R$, $-SO_2R$, $-B(OH)_2$ o un anillo opcionalmente sustituido que se selecciona de fenilo o un heteroarilo de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre. En ciertas modalidades, R^3 es -CN, -OR, $-C(O)OR$, $-C(O)N(R)_2$, $-SO_2R$, o un anillo opcionalmente sustituido que se selecciona de fenilo o un heteroarilo de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre. En algunas modalidades, R^3 es -OR. En algunas modalidades, R^3 es $-C(O)OR$. En algunas modalidades, R^3 es fenilo o tetrazolilo.

Como se define de manera general en lo anterior, cada R es independientemente hidrógeno o un grupo opcionalmente sustituido que se selecciona de un grupo alifático de 1 a 6 átomos de carbono, un anillo carbocíclico monocíclico saturado o parcialmente insaturado de 3 a 8

miembros, fenilo, un anillo carbocíclico aromático bicíclico de 8 a 10 miembros; un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre o un anillo heteroaromático bíciclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre.

En ciertas modalidades, cada R es independientemente hidrógeno o un grupo opcionalmente sustituido que se selecciona de un grupo alifático de 1 a 6 átomos de carbono, un anillo carbocíclico monocíclico insaturado o parcialmente insaturado de 3 a 8 miembros. En algunas modalidades, cada R es independientemente hidrógeno o un grupo alifático de 1 a 6 átomos de carbono opcionalmente sustituido.

Como se define de manera general en lo anterior, cada uno de L^1 y L^2 es independientemente un enlace covalente o una cadena de hidrocarburo divalente lineal o ramificada de 1 a 6 miembros, opcionalmente sustituida, o un grupo ciclopropilenilo, ciclobutilenilo u oxetanilo. En ciertas modalidades, L^1 es una cadena de hidrocarburo divalente lineal o ramificada de 1 a 3 átomos de carbono. En ciertas modalidades, L^1 es una cadena de hidrocarburo de 2 átomos de

carbono bivalente lineal o ramificada. En ciertas modalidades, L^1 es una cadena de hidrocarburo de 3 átomos de carbono divalente lineal o ramificada. En ciertas modalidades, L^1 es un grupo ciclopropilenilo, ciclobutilenilo u oxetanilo.

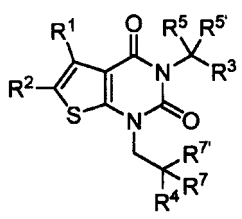
En algunas modalidades, L^2 es una cadena de hidrocarburo lineal o ramificada de 1 a 3 átomos de carbono opcionalmente sustituida. En algunas modalidades, L^2 es una cadena de hidrocarburo lineal de 2 átomos de carbono opcionalmente sustituida. En algunas modalidades, L^2 es una cadena de hidrocarburo lineal o ramificada de 3 átomos de carbono opcionalmente sustituida.

Como se define de manera general en lo anterior, R^4 es hidrógeno o un anillo opcionalmente sustituido que se selecciona de un anillo carbocíclico saturado o parcialmente insaturado monocíclico de 3 a 8 miembros. Un anillo heterocíclico saturado o parcialmente insaturado monocíclico de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, fenilo, un anillo arilo bicíclico de 8 a 10 miembros, un anillo heteroarilo monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, o un anillo heteroarilo bicíclico de 8 a 10 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre.

En ciertas modalidades, R^4 es hidrógeno. En ciertas

modalidades, R^4 es un anillo saturado o parcialmente insaturado monocíclico de 5 a 6 miembros opcionalmente sustituido. En ciertas modalidades, R^4 es un anillo heterocíclico saturado o parcialmente insaturado monocíclico de 5 a 6 miembros opcionalmente sustituido que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre. En ciertas modalidades, R^4 es fenilo opcionalmente sustituido. En ciertas modalidades, R^4 es un anillo arilo bicíclico de 10 miembros opcionalmente sustituido. En ciertas modalidades, R^4 es un anillo heteroarilo monocíclico de 5 a 6 miembros opcionalmente sustituido que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre. En ciertas modalidades, R^4 es un anillo heteroarilo bicíclico de 8 a 10 miembros opcionalmente sustituido que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre.

En ciertas modalidades, la presente invención proporciona un compuesto de fórmula II:



II

o una sal farmacéuticamente aceptable del mismo, en

donde:

R^1 es hidrógeno o un grupo alifático de 1 a 4 átomos de carbono, opcionalmente sustituido con uno o más de halógeno, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -C(O)OR, -S(O)R o $-SO_2R$;

R^2 es halógeno, -R, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o $-SO_2R$ o Hy, en donde Hy se selecciona de un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre; o R^1 y R^2 se toman juntos para formar un anillo opcionalmente sustituido de 4 a 7 miembros parcialmente insaturado carbociclo- o heterociclo-, benzo- o de 5 a 6 miembros heteroarilo-fusionado;

cada R es independientemente hidrógeno, o un grupo opcionalmente sustituido que se selecciona de un grupo alifático de 1 a 6 átomos de carbono, un anillo carbocíclico

monocíclico saturado o parcialmente insaturado de 3 a 8 miembros, fenilo, un anillo carbocíclico aromático bicíclico de 8 a 10 miembros; un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

R^3 es hidrógeno, halógeno, -CN, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, $-C(O)R$, $-C(O)OR$, $-OC(O)R$, $-S(O)R$, $-SO_2R$, $-B(OH)_2$ o un anillo opcionalmente sustituido que se selecciona de fenilo o un heteroarilo de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

R^4 es un anillo fenilo o naftilo opcionalmente sustituido;

cada uno de R^5 y $R^{5'}$ es independientemente -R, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, $-C(O)R$, $-C(O)OR$, $-OC(O)R$, $-S(O)R$ o $-SO_2R$; o R^5 y $R^{5'}$ se toman juntos para formar un grupo ciclopropilenilo, ciclobutilenilo u

oxetanilo; y

Cada uno de R^7 y $R^{7'}$ es independientemente hidrógeno, -R, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o $-SO_2R$; o R^7 y $R^{7'}$ se toman juntos para formar un anillo carbocíclico monocíclico saturado o parcialmente insaturado de 3 a 8 miembros, o un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre.

Como se define de manera general en lo anterior, cada uno de R^5 y $R^{5'}$ es independientemente -R, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o $-SO_2R$; o R^5 y $R^{5'}$ se toman juntos para formar un grupo ciclopropilenilo, ciclobutilenilo u oxetanilo.

En algunas modalidades, cada uno de R^5 y $R^{5'}$ es -R en donde -R no es hidrógeno. En algunas modalidades, cada uno de R^5 y $R^{5'}$ es metilo. En algunas modalidades, R^5 y $R^{5'}$ se toman juntos para formar un grupo ciclopropilenilo, ciclobutilenilo u oxetanilo. En algunas modalidades, R^5 y $R^{5'}$ se toman juntos para formar un grupo ciclobutilenilo.

Como se define generalmente en lo anterior, cada uno de R^7 y $R^{7'}$ es independientemente hidrógeno, -R, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$,

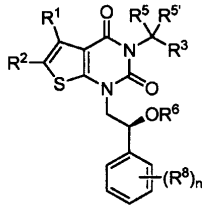
$-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, $-C(O)R$, $-C(O)OR$, $-OC(O)R$, $-S(O)R$ o $-SO_2R$; o R^7 y $R^{7'}$ se toman juntos para formar un anillo carbocíclico monocíclico saturado o parcialmente insaturado de 3 a 8 miembros, o un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre.

En algunas modalidades, uno de R^7 y $R^{7'}$ es independientemente hidrógeno y el otro es -OR. En algunas modalidades, uno de R^7 y $R^{7'}$ es hidrógeno y el otro es isopropoxi. En algunas modalidades, R^7 y $R^{7'}$ se toman juntos para formar un anillo carbocíclico monocíclico saturado o parcialmente insaturado de 3 a 6 miembros. En algunas modalidades, R^7 y $R^{7'}$ se toman juntos para formar un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 6 miembros que tienen 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre. En algunas modalidades, uno de R^7 y $R^{7'}$ es hidrógeno y el otro es -OR, en donde R en este caso es un anillo heterocíclico saturado de 4 a 7 miembros que contiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno y azufre. En algunas modalidades, uno de R^7 y $R^{7'}$ es hidrógeno y el otro es -OR, en donde R en esta instancia es oxetano, tetrahidrofurano o tetrahidropirano.

En ciertas modalidades, la presente invención

proporciona un compuesto de fórmula II, en donde cada variable es como se describe en las modalidades para la fórmula I, supra, o se describen modalidades en la presente, de manera única o en combinación.

En ciertas modalidades, la presente invención proporciona un compuesto de fórmula III:



III

o una sal farmacéuticamente aceptable del mismo, en donde:

R^1 es hidrógeno o un grupo alifático de 1 a 4 átomos de carbono, opcionalmente sustituido con uno o más de halógeno, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -C(O)OR, -S(O)R o $-SO_2R$;

R^2 es halógeno, -R, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o $-SO_2R$; o R^1 y R^2 se toman juntos para formar un anillo opcionalmente sustituido de 4 a 7 miembros parcialmente insaturado carbociclo- o heterociclo- o benzo- o de 5 a 6 miembros heteroarilo-fusionado;

cada R es independientemente hidrógeno, o un grupo

opcionalmente sustituido que se selecciona de un grupo alifático de 1 a 6 átomos de carbono, un anillo carbocíclico monocíclico saturado o parcialmente insaturado de 3 a 8 miembros, fenilo, un anillo carbocíclico aromático bicíclico de 8 a 10 miembros; un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

R^3 es hidrógeno, halógeno, -CN, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $SO_2N(R)_2$, $-C(O)R$, $-C(O)OR$, $-OC(O)R$, $-S(O)R$, $-SO_2R$, $-B(OH)_2$ o un anillo opcionalmente sustituido que se selecciona de fenilo o un heteroarilo de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

cada uno de R^5 y $R^{5'}$ es independientemente -R, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, $-C(O)R$, $-C(O)OR$, $-OC(O)R$, $-S(O)R$ o $-SO_2R$; o R^5 y $R^{5'}$ se toman juntos para formar un grupo ciclopropilenilo, ciclobutilenilo u

oxetanilo;

R^6 es -R, $-C(O)N(R)_2$ o -C(O)R;

cada R^8 se selecciona independientemente de halógeno, -R, -OR, -SR, $-N(R)_2$ o deuterio; y

n es 0 a 5.

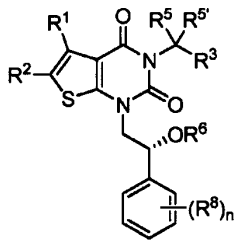
En ciertas modalidades, la presente invención proporciona un compuesto de fórmula III, en donde cada variable es como se describe en las modalidades para la fórmula I o II, *supra*.

En ciertas modalidades, R^6 es hidrógeno. En ciertas modalidades, R^6 es isopropilo.

Como se define de manera general en lo anterior, cada uno en ciertas modalidades, cada R^8 se selecciona independientemente de halógeno, -R, -OR, -SR, $-N(R)_2$ o deuterio. En ciertas modalidades, cada R^8 es halógeno.

Como se define de manera general en lo anterior, n es 0 a 5. En ciertas modalidades, n es 0. En algunas modalidades, n es 1 a 2.

En ciertas modalidades, la presente invención proporciona un compuesto de fórmula IV:



IV

o una sal farmacéuticamente aceptable del mismo, en donde:

R^1 es hidrógeno o un grupo alifático de 1 a 4 átomos de carbono, opcionalmente sustituido con uno o más de halógeno, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2RN(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -C(O)OR, -S(O)R o $-SO_2R$;

R^2 es halógeno, -R, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o $-SO_2R$; o R^1 y R^2 se toman juntos para formar un anillo opcionalmente sustituido de 4 a 7 miembros parcialmente insaturado carbociclo- o heterociclo-, benzo- o de 5 a 6 miembros heteroarilo-fusionado;

cada R es independientemente hidrógeno, o un grupo opcionalmente sustituido que se selecciona de un grupo alifático de 1 a 6 átomos de carbono, un anillo carbocíclico monocíclico saturado o parcialmente insaturado de 3 a 8 miembros, fenilo, un anillo carbocíclico aromático bicíclico de 8 a 10 miembros; un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o

azufre o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

R^3 es hidrógeno, halógeno, -CN, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $SO_2N(R_2)$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, $-SO_2R$, $-B(OH)_2$ o un anillo opcionalmente sustituido que se selecciona de fenilo o un heteroarilo de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

cada uno de R^5 y $R^{5'}$ es independientemente -R, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o $-SO_2R$; o R^5 y $R^{5'}$ se toman juntos para formar un grupo ciclopropilenilo, ciclobutilenilo u oxetanilo; y

R^6 es -R, $-C(O)N(R)_2$ o -C(O)R;

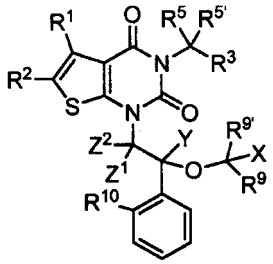
cada R^8 se selecciona independientemente de halógeno, -R, -OR, -SR, $-N(R)_2$ o deuterio; y

n es 0 a 5.

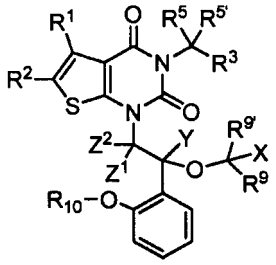
En ciertas modalidades, la presente invención proporciona un compuesto de fórmula IV, en donde cada variable es como se describe en las modalidades para la fórmula I o II, *supra*.

En ciertas modalidades, la presente invención

proporciona un compuesto de fórmula V-i o V-ii:



V-i



V-ii,

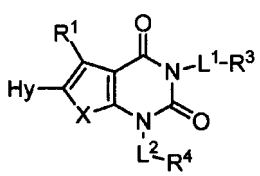
o una sal farmacéuticamente aceptable del mismo, en donde R^2, R^3, R^5, $R^{5'}$ son como se describen en modalidades para la fórmula I, *supra*; y

cada uno de R^1, R^9 y $R^{9'}$ es independientemente CH_3 o CD_3;

cada uno de X, Y, Z^1 y Z^2 es independientemente H o D; y

R^{10} es CH_3, CD_3, CH_2CH_3, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, CF_2H, CH_2CD_3, CD_2CH_3 o CD_2CD_3.

En ciertas modalidades, la presente invención proporciona un compuesto de fórmula I, en donde R^2 es Hy, por lo que se forma un compuesto de fórmula VI:

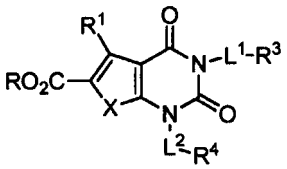


VI

o una sal farmacéuticamente aceptable del mismo, en donde cada uno de X, L^1, L^2, R^1, R^3, R^4 y Hy se definen en lo

anterior y se describen en modalidades en la presente, de manera sola o en combinación.

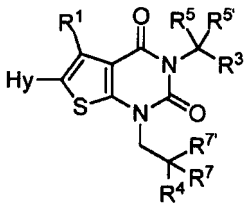
En ciertas modalidades, la presente invención proporciona un compuesto de fórmula I en donde R^2 es C(O)OR, por lo que se forma un compuesto de fórmula VII:



VII

o una sal farmacéuticamente aceptable del mismo, en donde cada uno de X, L^1, L^2, R, R^1, R^3 y R^4 y es como se define en lo anterior y como se describen en modalidades en la presente, de manera sola y en combinación.

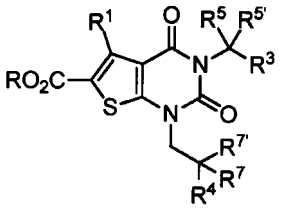
En ciertas modalidades, la presente invención proporciona un compuesto de fórmula II en donde R^2 es Hy por lo que se forma un compuesto de fórmula VIII:



VIII

o una sal farmacéuticamente aceptable del mismo, en donde cada uno de R^1, R^3, R^4, R^5, $R^{5'}$, R^7, $R^{7'}$ y Hy es como se define en lo anterior y como se describen en modalidades en la presente, ambos, de manera sola y en combinación.

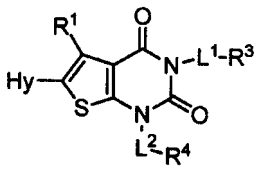
En ciertas modalidades, la presente invención proporciona un compuesto de fórmula II en donde R^2 es -C(O)OR, por lo que se forma un compuesto de fórmula IX:



IX

o una sal farmacéuticamente aceptable del mismo, en donde cada uno de R^1, R^3, R^4, R^5, $R^{5'}$, R^7, $R^{7'}$ es como se define en lo anterior y como se describen en modalidades en la presente, tanto de manera sola como en combinación.

En ciertas modalidades, la presente invención proporciona un compuesto de fórmula VI en donde X es S, por lo que se forma un compuesto de fórmula X:

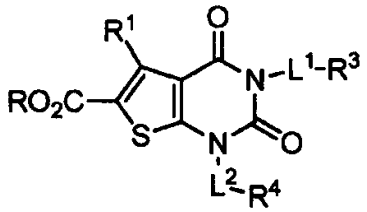


X

o una sal farmacéuticamente aceptable del mismo, en donde cada uno de L^1, L^2, R^1. R^3, R^4 y Hy es como se define en lo anterior y como se describen en modalidades en la presente, tanto de manera sola como en combinación.

En ciertas modalidades, la presente invención proporciona un compuesto de fórmula VII en donde X es S, por

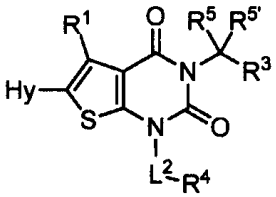
lo que se forma un compuesto de fórmula XI:



XI

o una sal farmacéuticamente aceptable del mismo, en donde cada uno de L^1, L^2, R, R^1, R^3, R^4 se definen en lo anterior y se describen en modalidades en la presente, de manera sola como en combinación.

En ciertas modalidades, la presente invención proporciona un compuesto de fórmula X en donde L^1 es $-C(R^5)(R^{5'})-$, por lo que se forma un compuesto de fórmula XII:

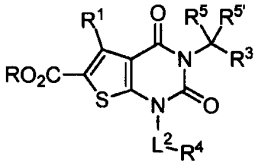


XII

o una sal farmacéuticamente aceptable del mismo, en donde cada uno de L^2, R^1, R^3, R^4, R^5, $R^{5'}$ y HY se definen en lo anterior y se describen en modalidades en la presente, de manera sola y en combinación.

En ciertas modalidades, la presente invención proporciona un compuesto de fórmula XI en donde L^1 es $-C(R^5)(R^{5'})-$, por lo que se forma un compuesto de fórmula

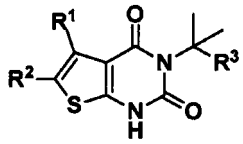
XIII:



XIII

o una sal farmacéuticamente aceptable del mismo, en donde cada uno de L^2, R, R^1, R^3, R^4, R^5, $R^{5'}$, y R^4 es como se define en lo anterior y como se describe en modalidades en la presente, de manera sola y en combinación.

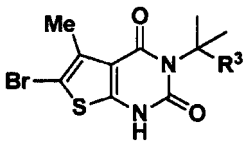
En ciertas modalidades, la presente invención proporciona un compuesto de fórmula XIV de la fórmula



XIV

o una sal farmacéuticamente aceptable del mismo, en donde cada uno de R^1, R^2 y R^3 se define en lo anterior y se describe en modalidades en la presente, de manera sola o en combinación.

En ciertas modalidades, la presente invención proporciona un compuesto de fórmula XIV en donde R^1 es metilo y R^2 es bromo, por lo que se forma un compuesto de fórmula XV:

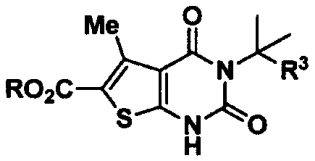


XV

o una sal farmacéuticamente aceptable del mismo, en

donde R^3 se define en lo anterior y se describe en modalidades en la presente, de manera sola y en combinación.

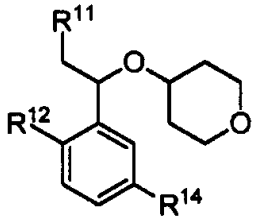
En ciertas modalidades, la presente invención proporciona un compuesto de fórmula XIV en donde R^1 es metilo y R^2 es -C(O)OR, por lo que se forma un compuesto de fórmula XVI:



XVI

o una sal farmacéuticamente aceptable del mismo, en donde R^3 se define en lo anterior y se describe en modalidades en la presente, de manera sola y en combinación.

En ciertas modalidades, la presente invención proporciona un compuesto de fórmula XVII de la fórmula:



XVII

en donde:

R^{11} se selecciona del grupo que consiste de -OH,

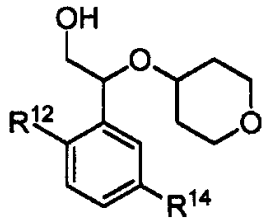
halógeno y $-OS(O)_2R$

R^{12} es $-R^{13}$ o $-OR^{13}$;

R^{13} es un grupo alifático de 1 a 4 átomos de carbono lineal o ramificado; y

R^{14} es hidrógeno o halógeno.

En ciertas modalidades, la presente invención proporciona un compuesto de fórmula XVII, en donde R^{11} es -OH, por lo que se forma un compuesto de fórmula XVIII:



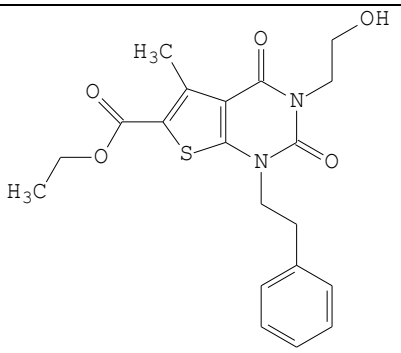
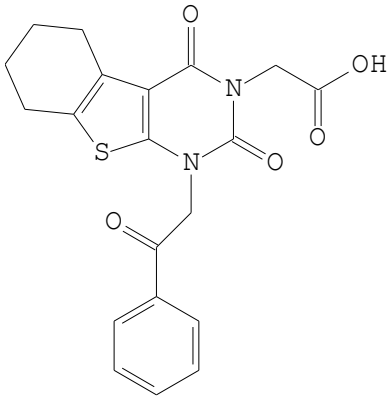
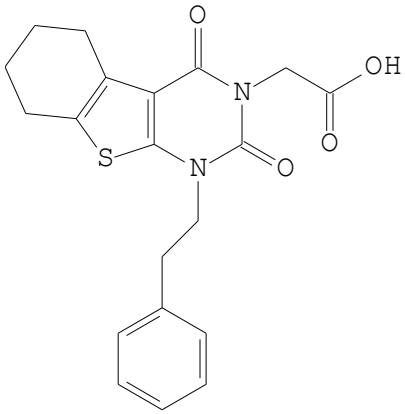
XVIII

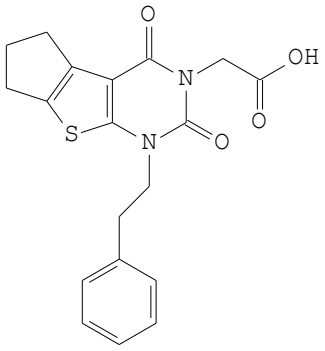
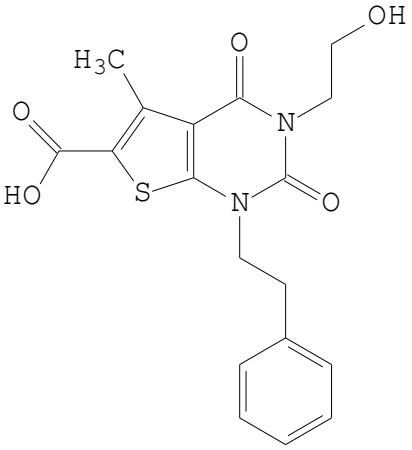
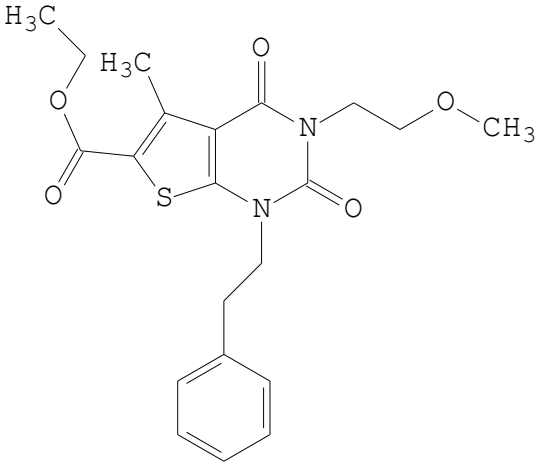
en donde cada uno de R^{12}, R^{13} y R^{14} se definen en lo anterior para la fórmula XVII y se describen en modalidades en la presente, de manera sola y en combinación.

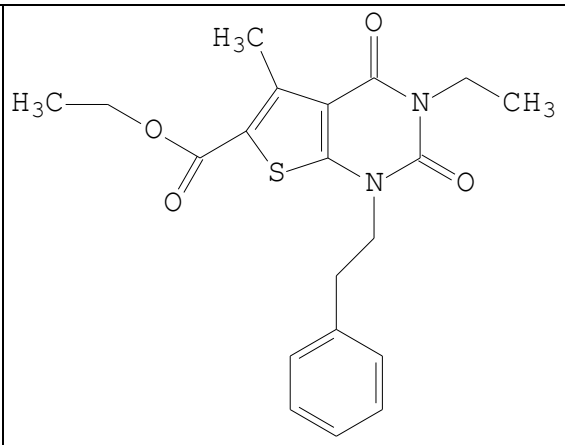
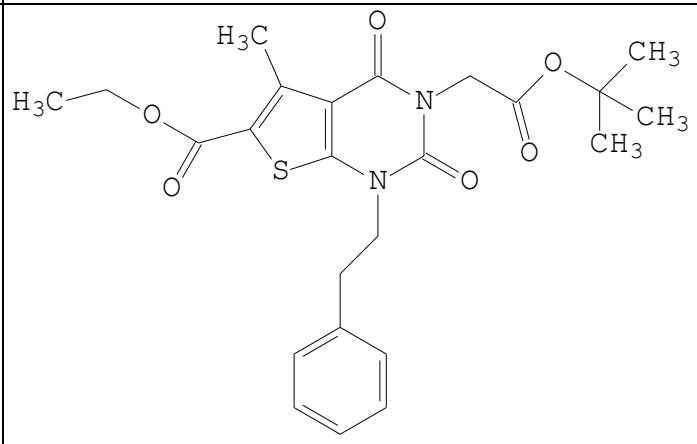
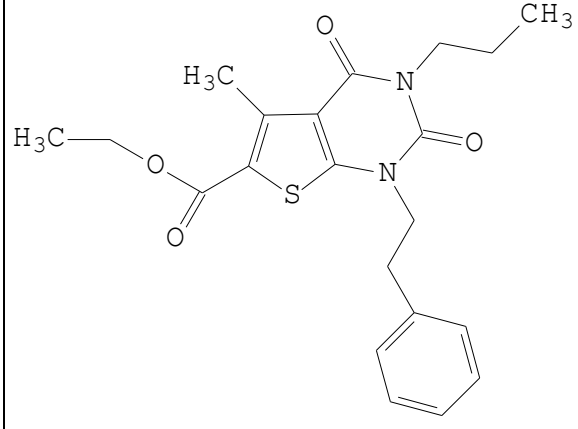
En ciertas modalidades, la presente invención proporciona un compuesto de fórmula XVIII, en donde R^{12} se selecciona del grupo que consiste de metilo, etilo, metoxi y etoxi.

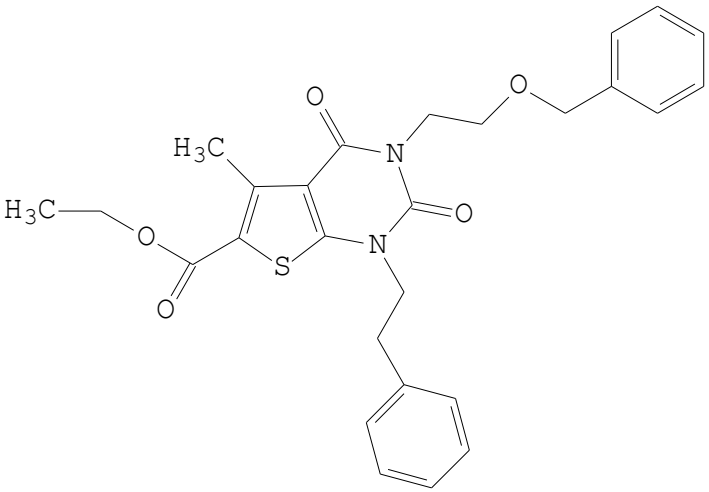
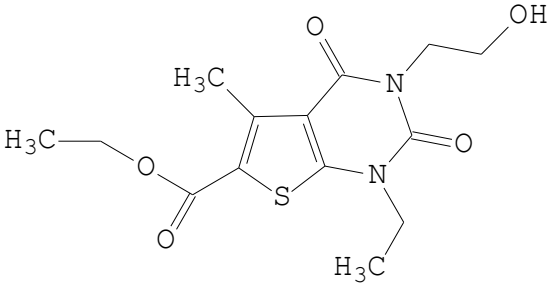
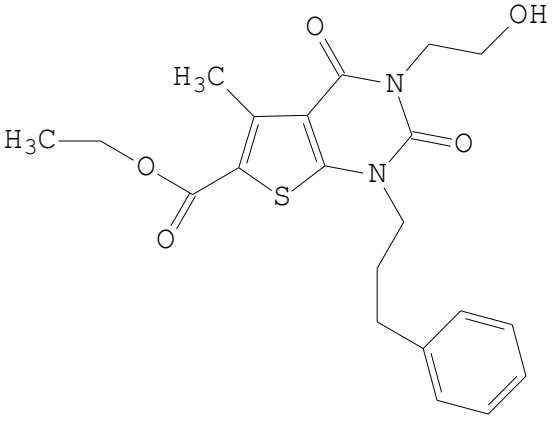
Los compuestos ejemplares de fórmula I se establecen en la tabla 1 a continuación:

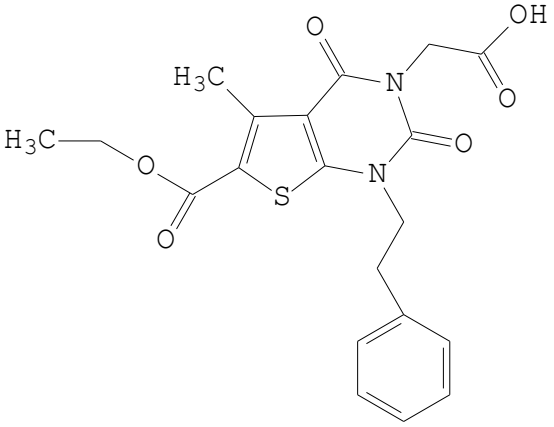
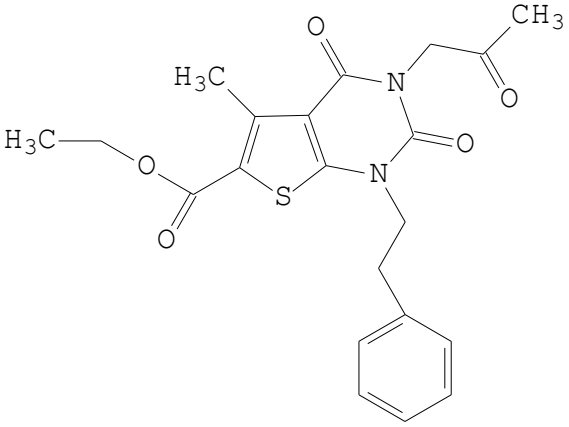
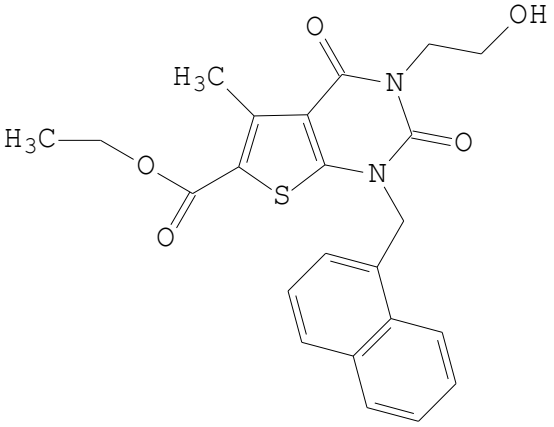
TABLA 1. COMPUESTOS EJEMPLARES DE FÓRMULA I

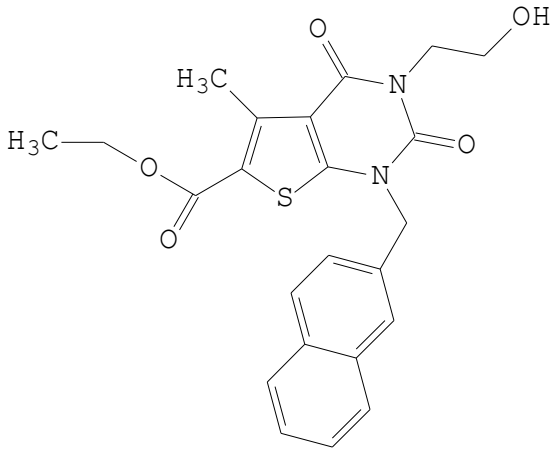
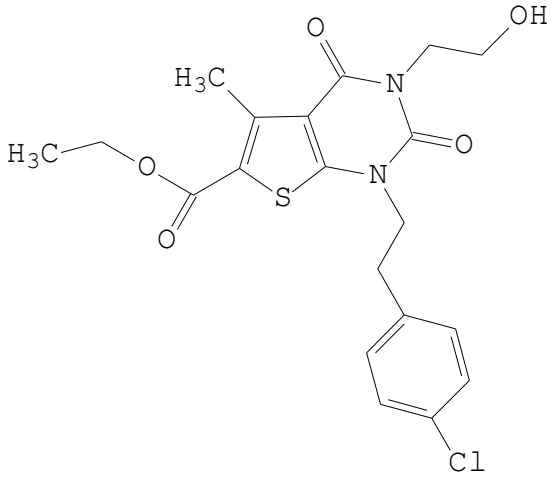
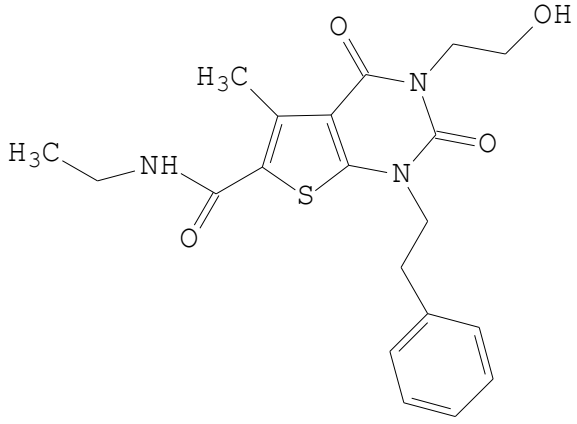
# de compues-to	Estructura del compuesto	m/z
I-1		403 (M+1)
I-2		399 (M+1)
I-3		385 (M+1)

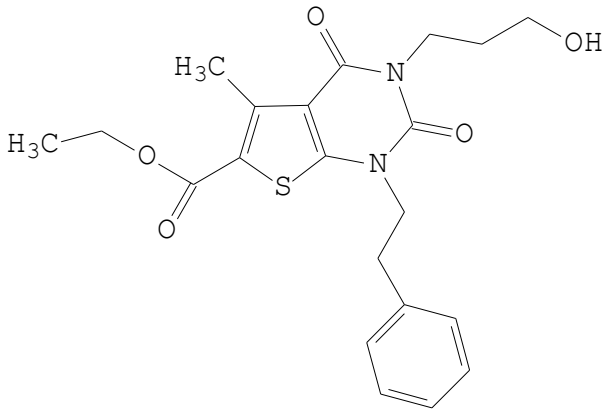
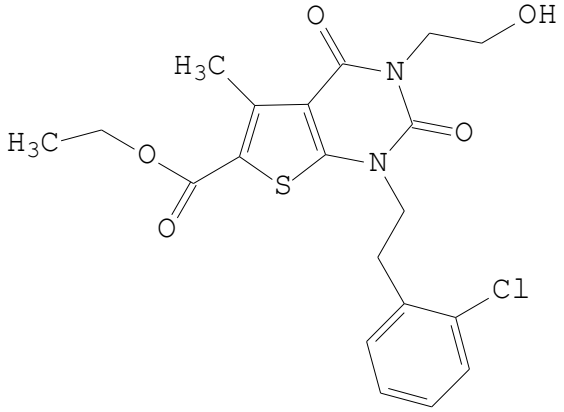
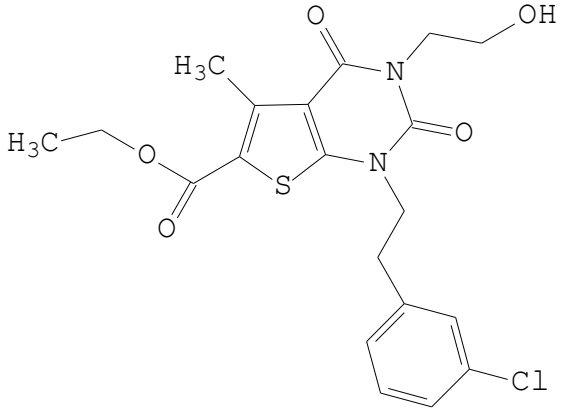
I-4		371 (M+1)
I-5		375 (M+1)
I-6		417 (M+1)

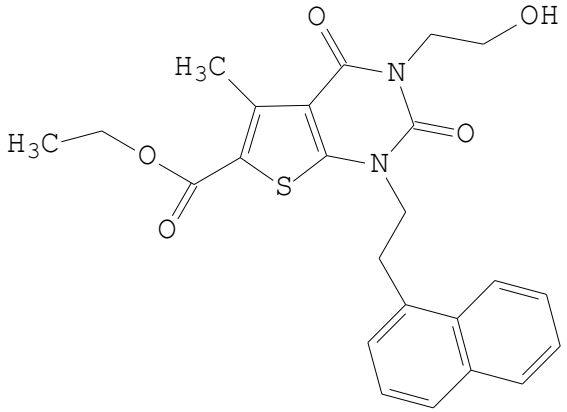
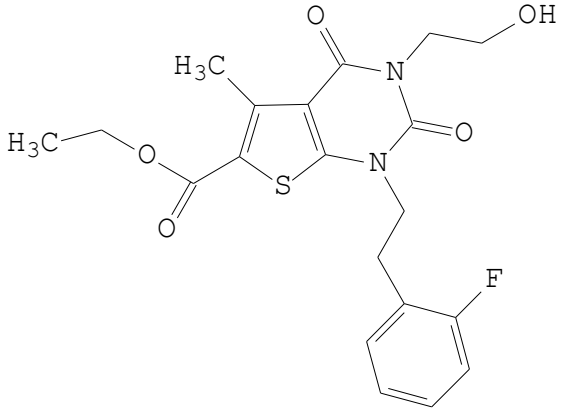
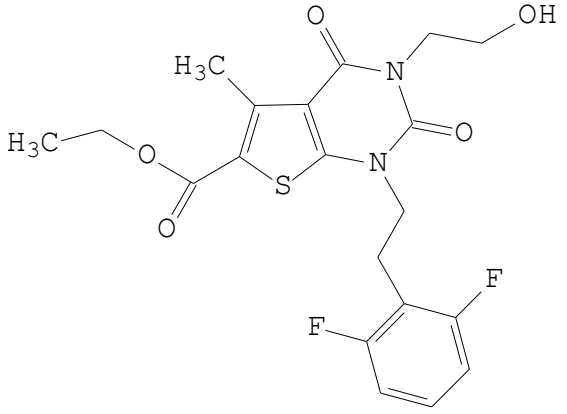
I-7		387 (M+1)
I-8		495 (M+Na)
I-9		401 (M+1)

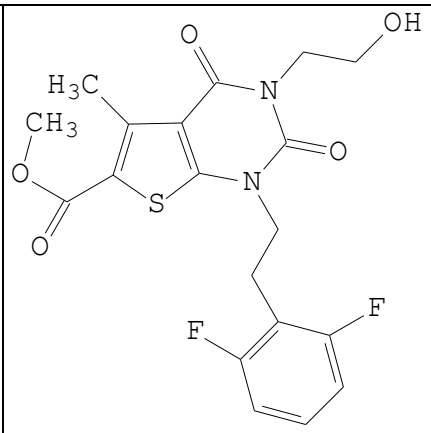
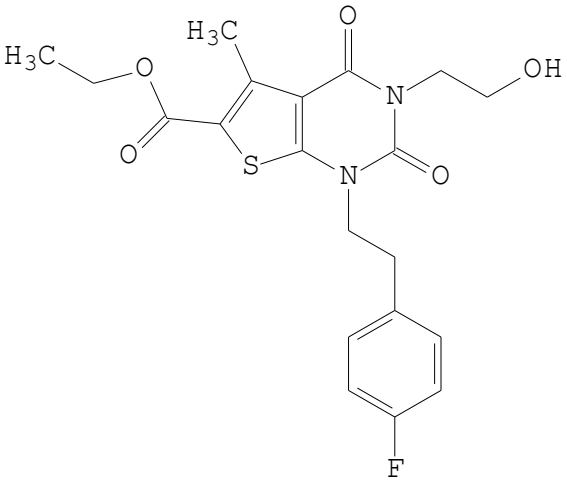
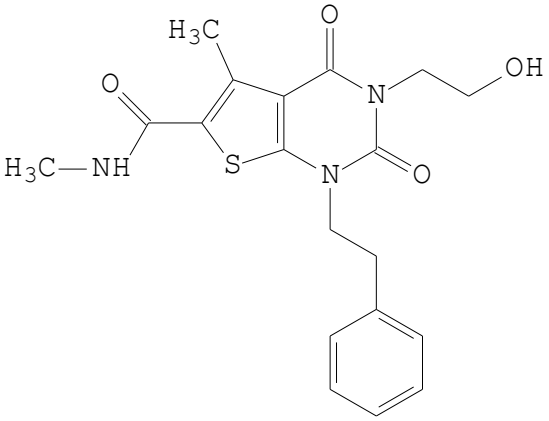
I-10		493 (M+1)
I-11		327 (M+1)
I-12		417 (M+1)

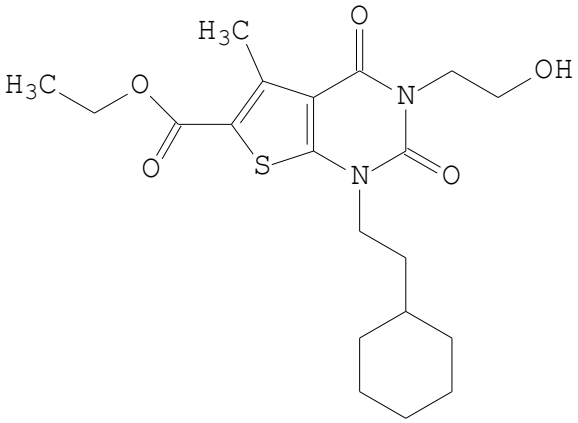
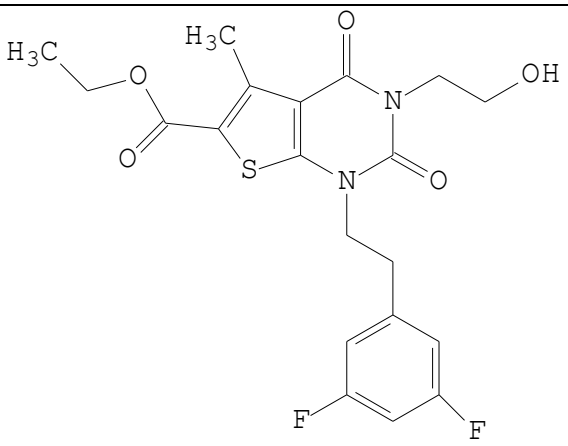
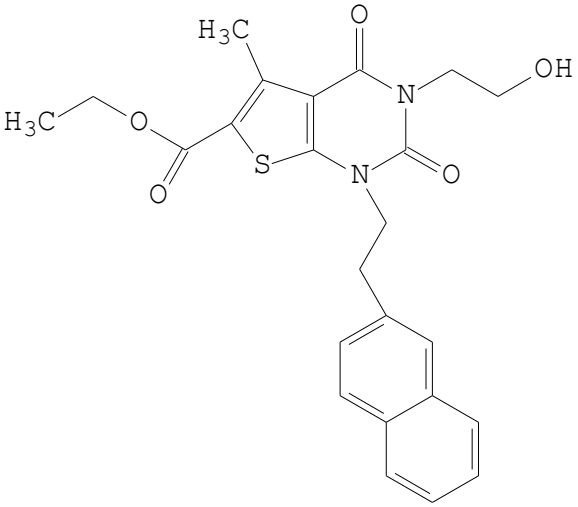
I-13		417 (M+1)
I-14		416 (M+1)
I-15		439 (M+1)

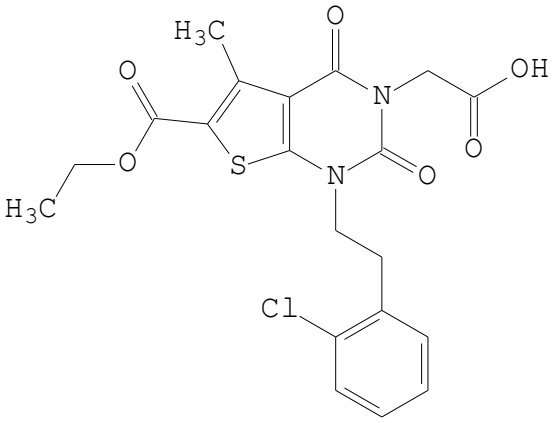
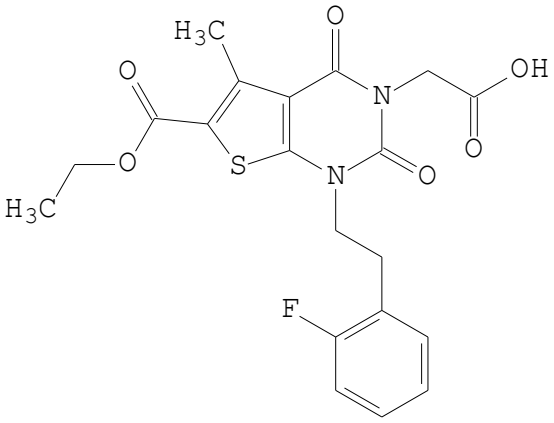
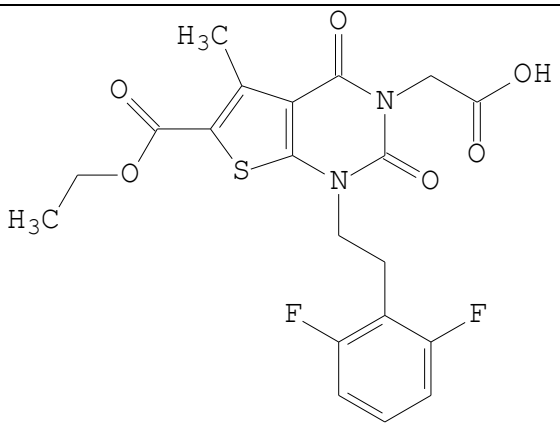
I-16		439 (M+1)
I-17		437 (M+1)
I-18		402 (M+1)

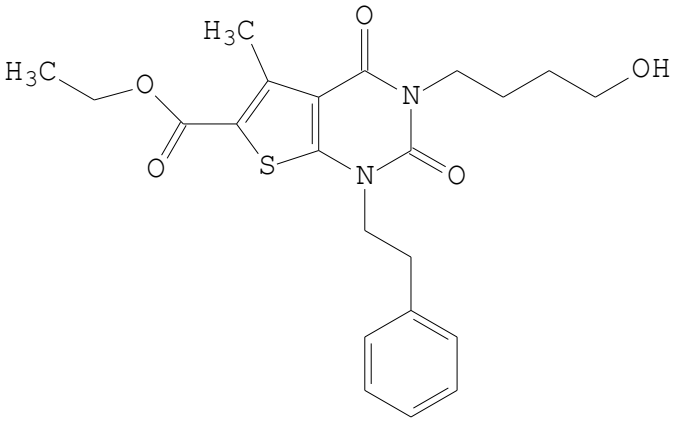
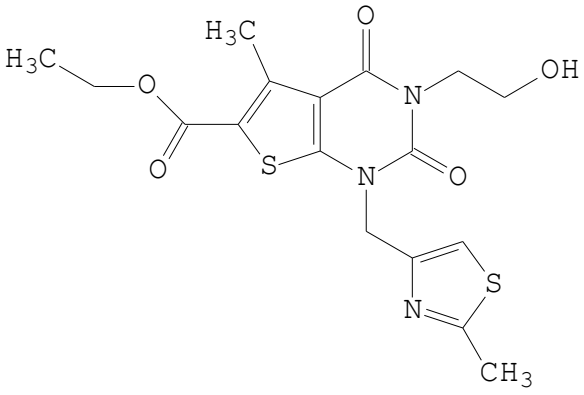
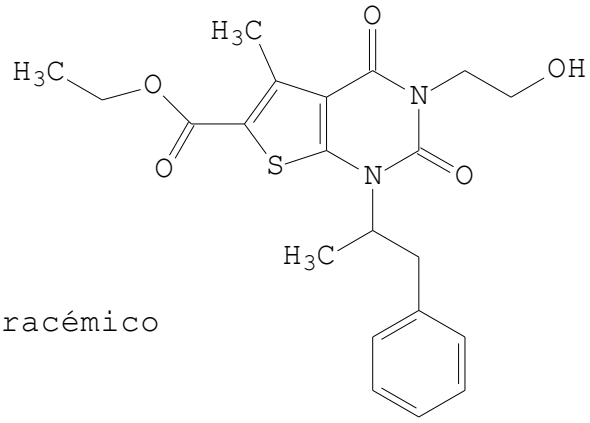
I-19		417 (M+1)
I-20		437 (M+1)
I-21		437 (M+1)

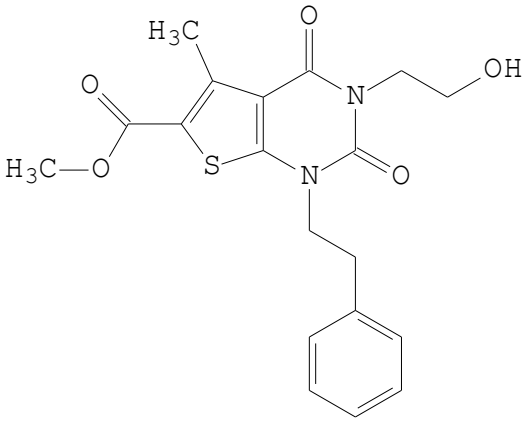
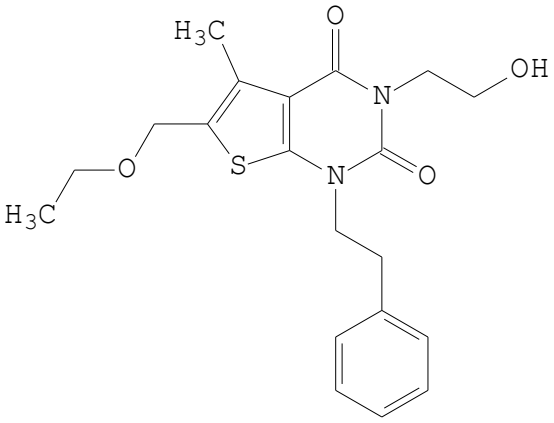
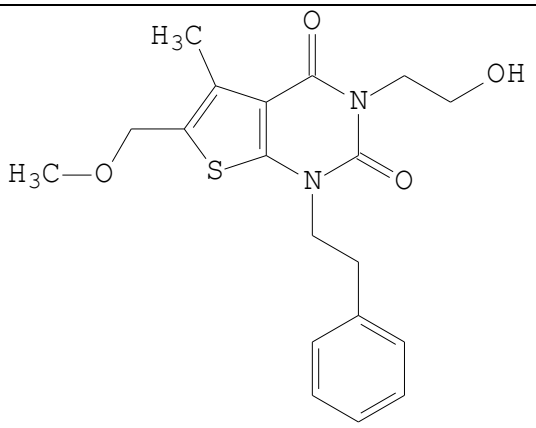
I-22		453 (M+1)
I-23		421 (M+1)
I-24		439 (M+1)

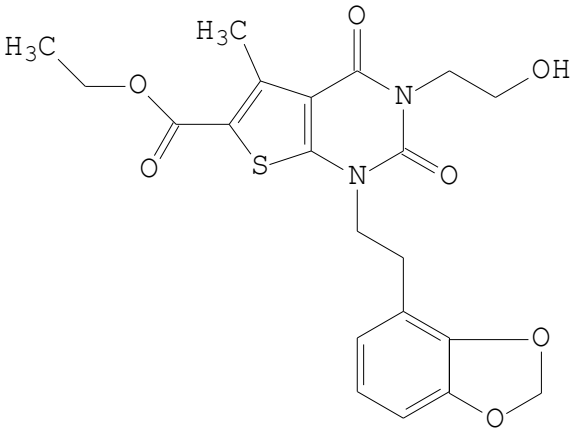
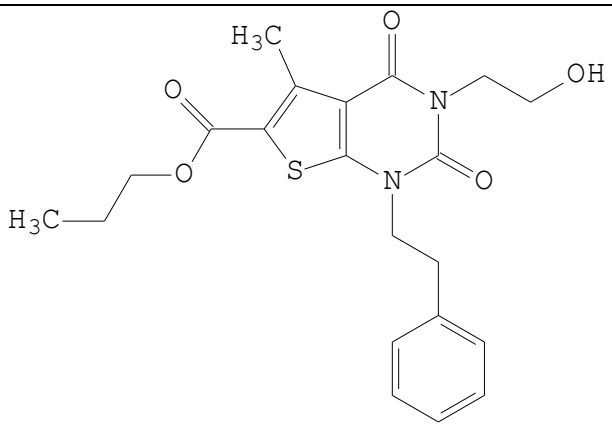
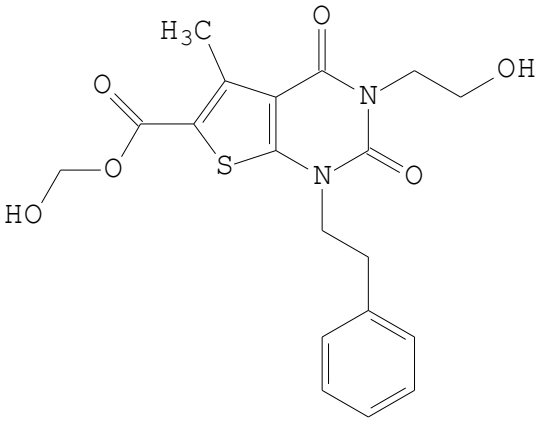
I-25		425 (M+1)
I-26		421 (M+1)
I-27		388 (M+1)

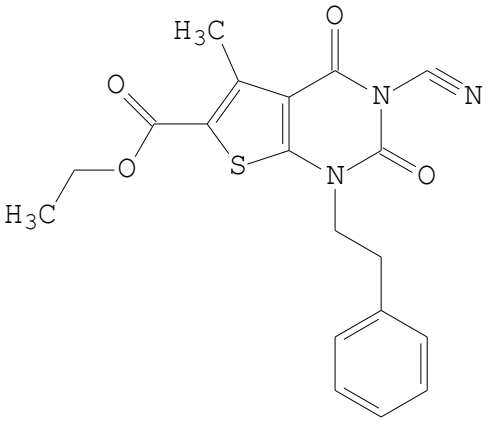
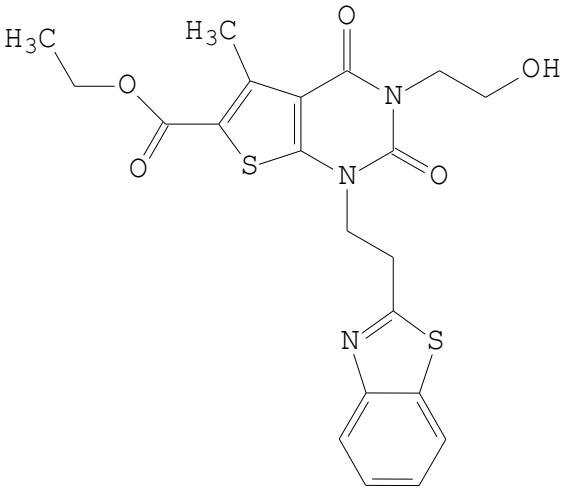
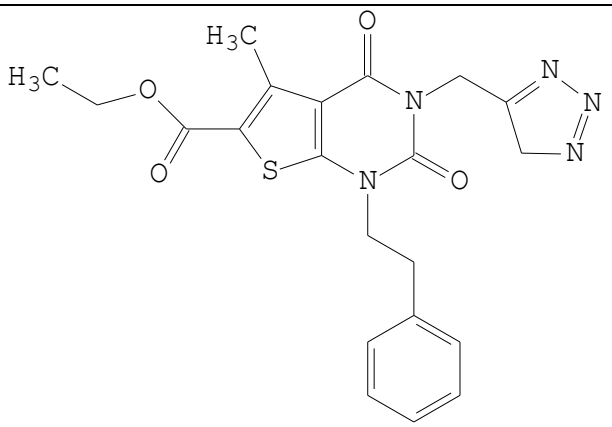
I-28		409 (M+1)
I-29		439 (M+1)
I-30		453 (M+1)

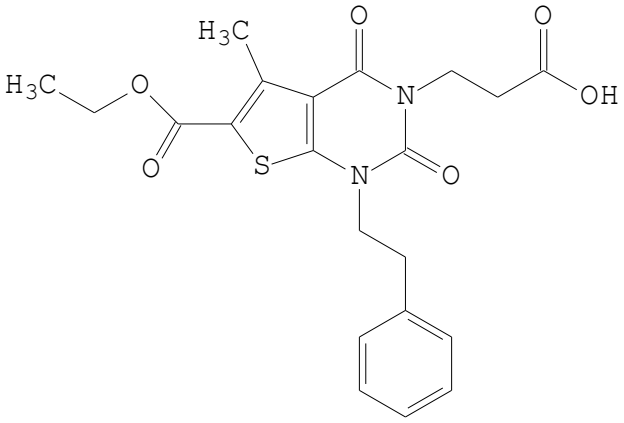
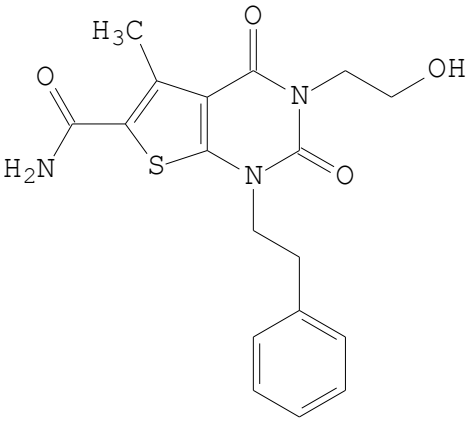
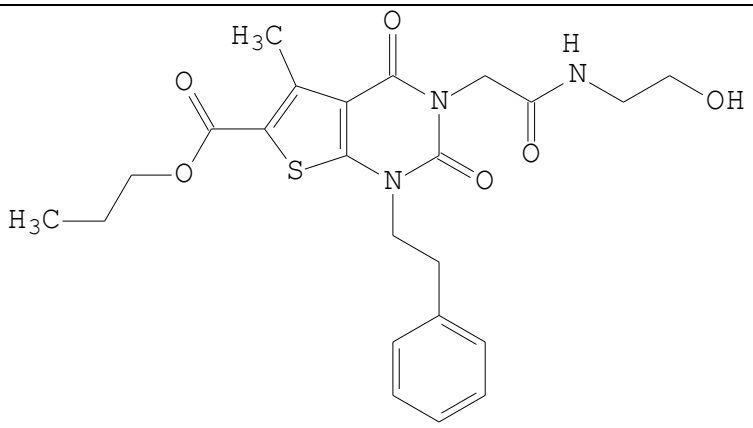
I-31		451 (M+1)
I-32		435 (M+1)
I-33		453 (M+1)

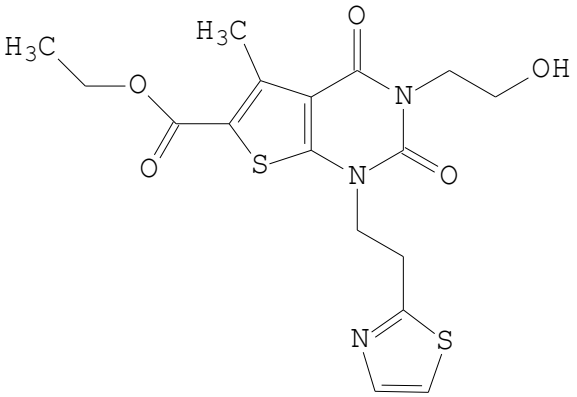
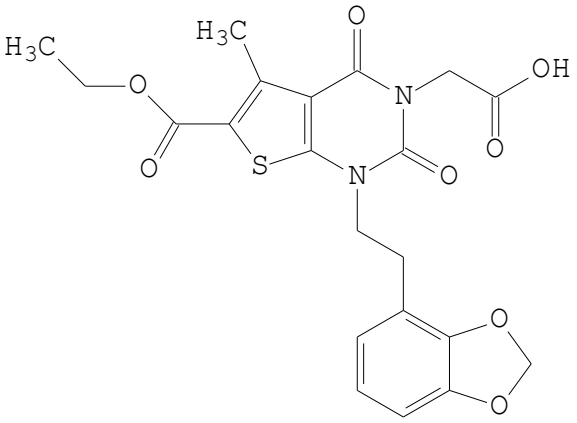
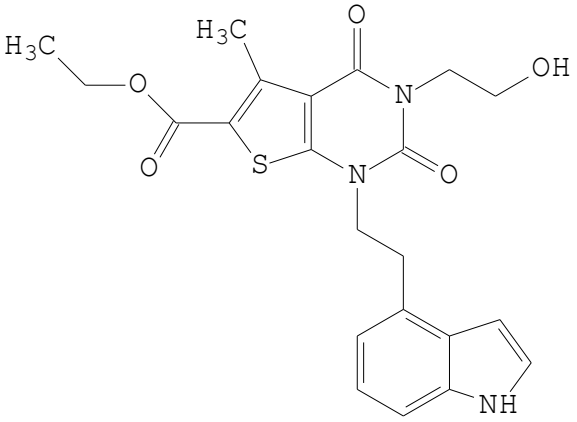
I-34		431 (M+1)
I-35		410 (M+1)
I-36	 racémico	417 (M+1)

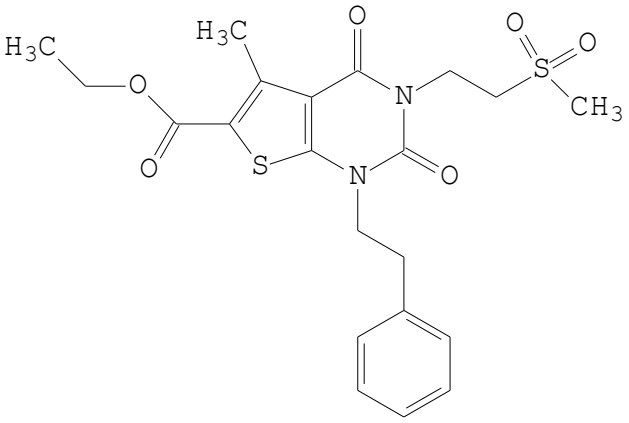
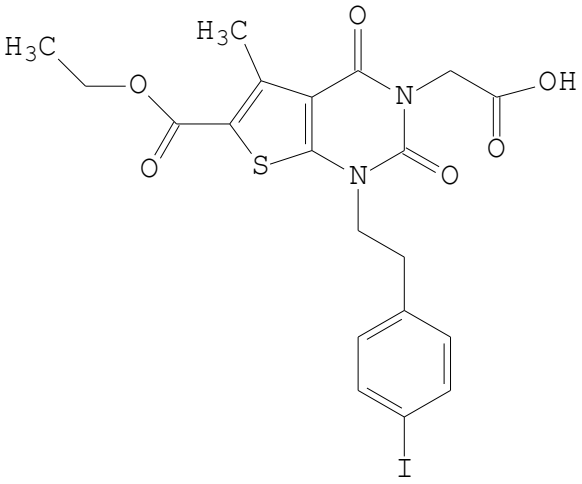
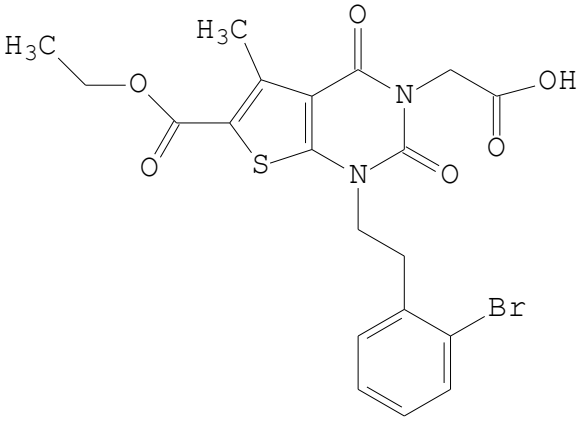
I-37		389 (M+1)
I-38		389 (M+1)
I-39		375 (M+1)

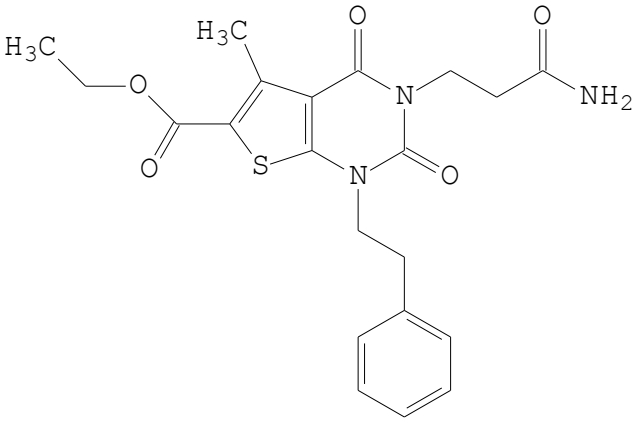
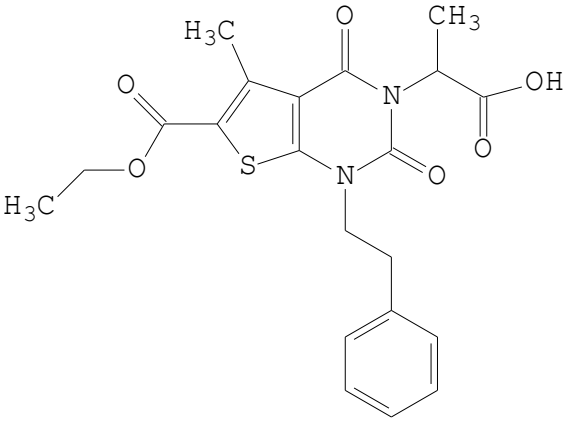
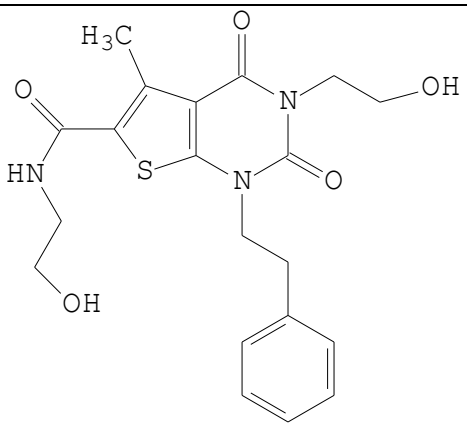
I-40		433 (M+1)
I-41		417 (M+1)(
I-42		419 (M+1)

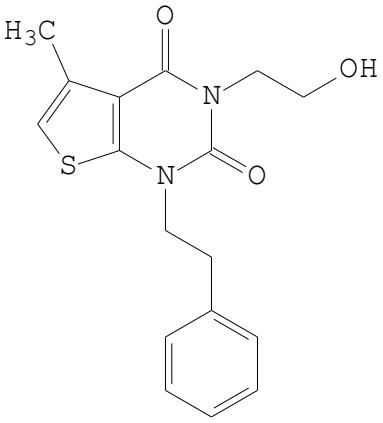
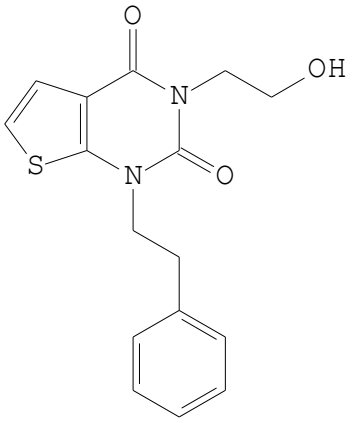
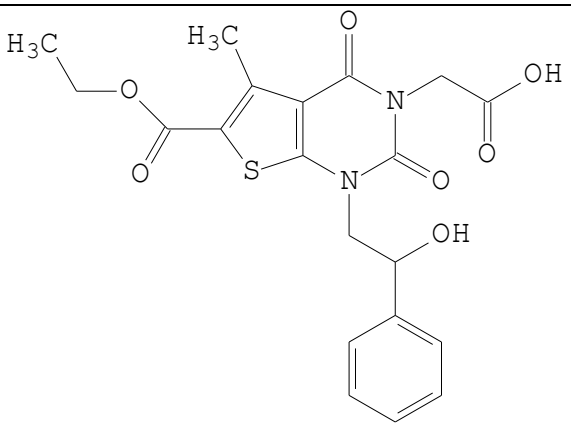
I-43		398 (M+1)
I-44		460 (M+1)
I-45		441 (M+1)

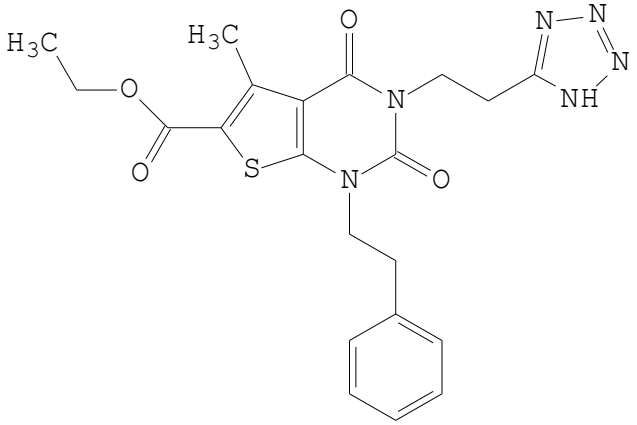
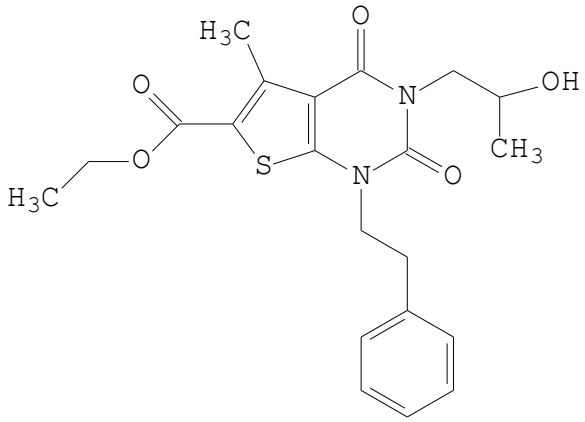
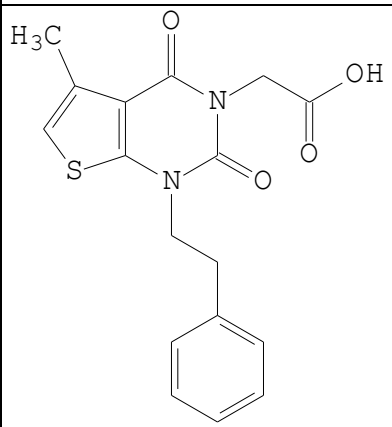
I-46		431 (M+1)
I-47		374 (M+1)
I-48		460 (M+1)

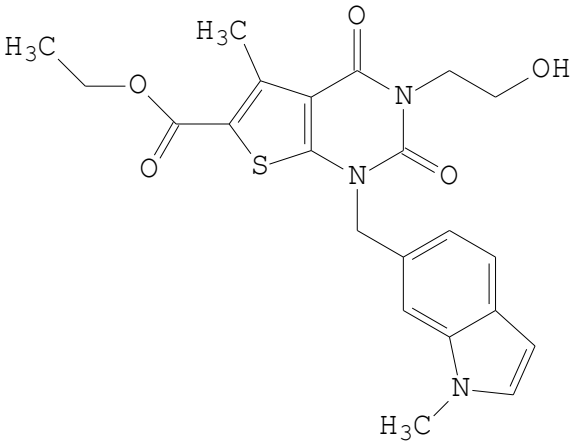
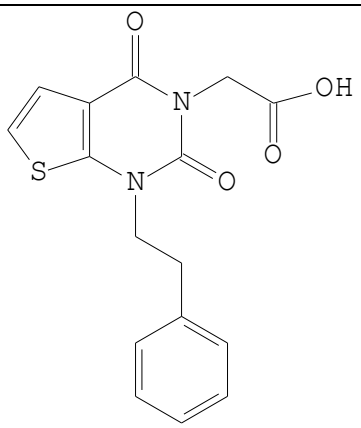
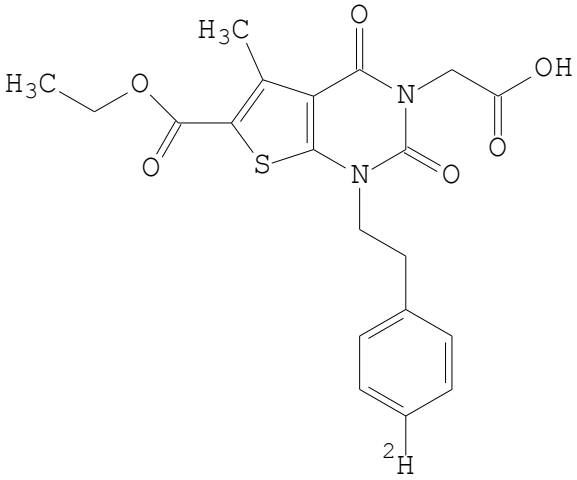
I-49		410 (M+1)
I-50		447 (M+1)
I-51		428 (M+1)

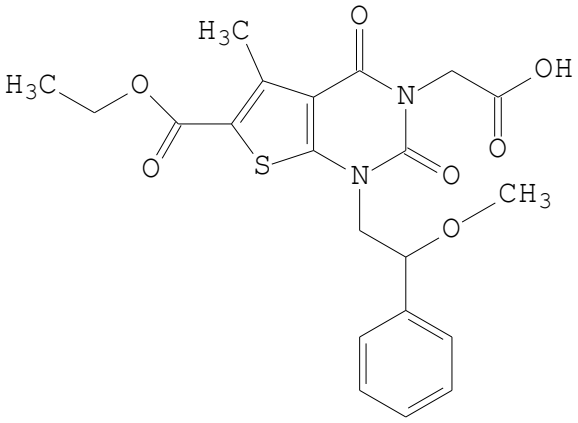
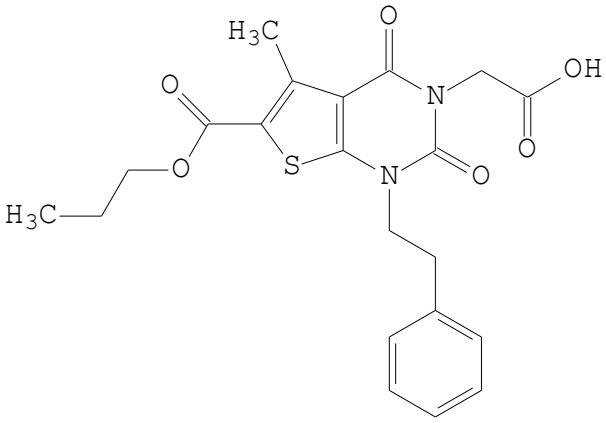
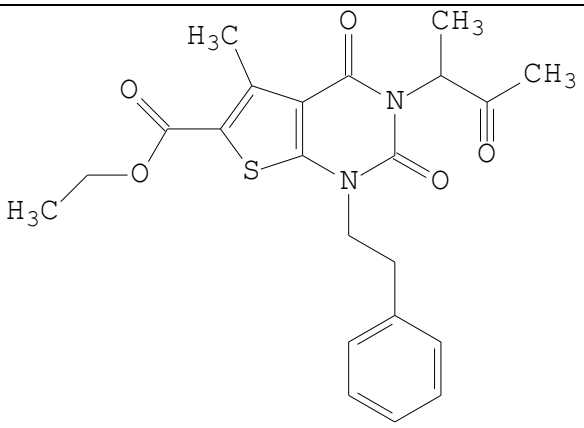
I-52		465 (M+1)
I-53		543 (M+1)
I-54		495 (M+1)

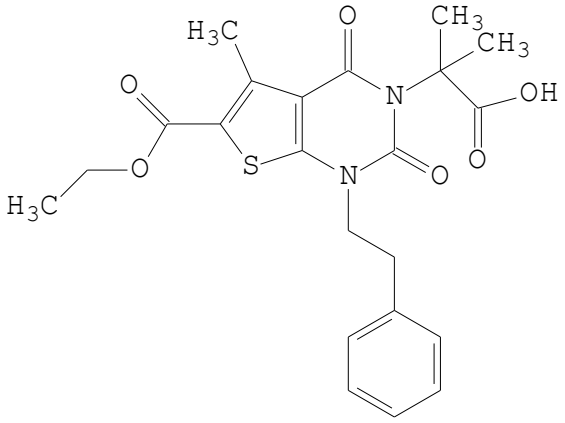
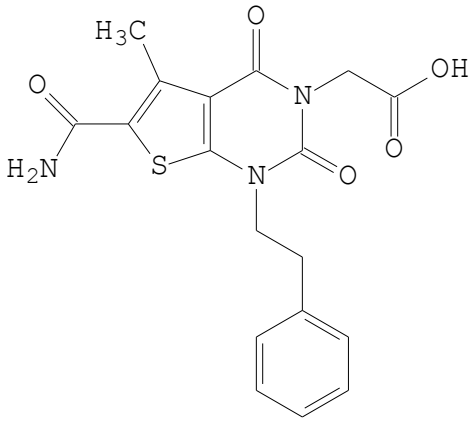
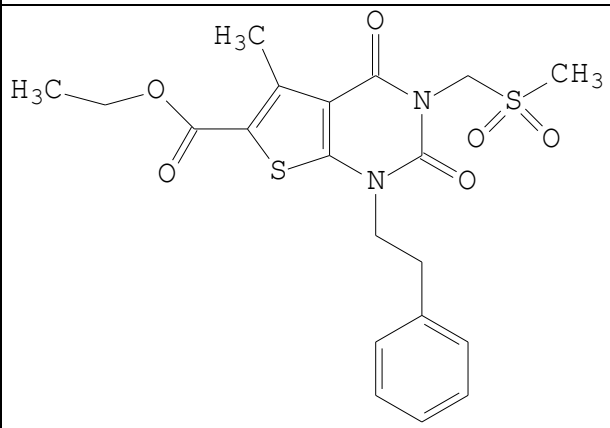
I-55		430 (M+1)
I-56		431 (M+1)
I-57		418 (M+1)

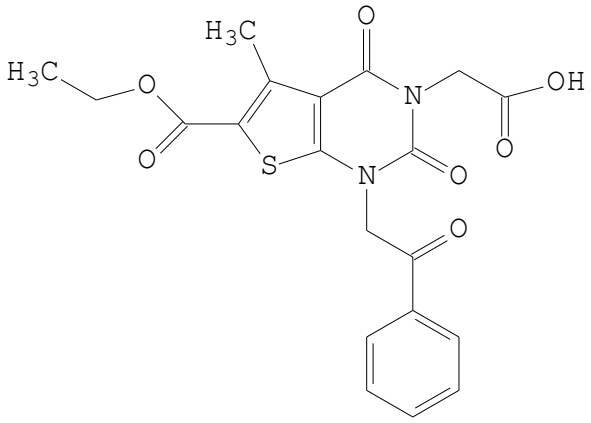
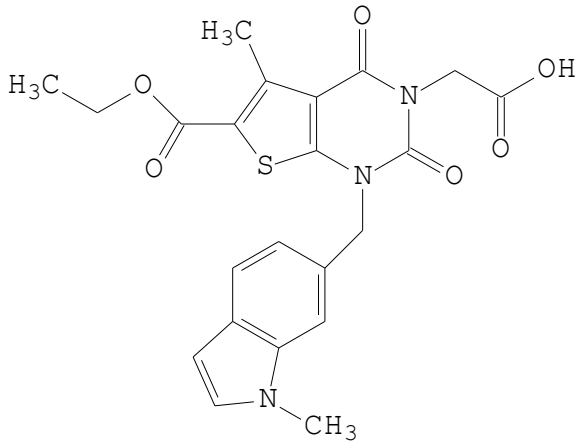
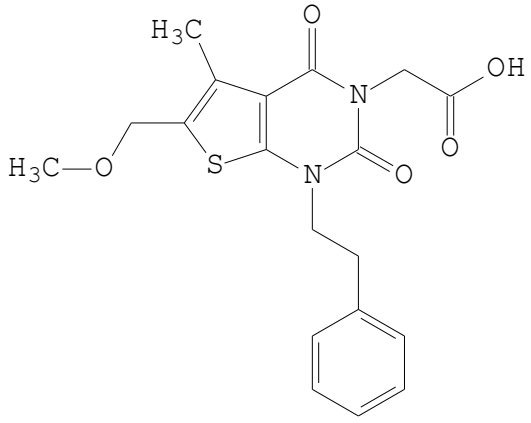
I-58		331 (M+1)
I-59		317 (M+1)
I-60		433 (M+1)

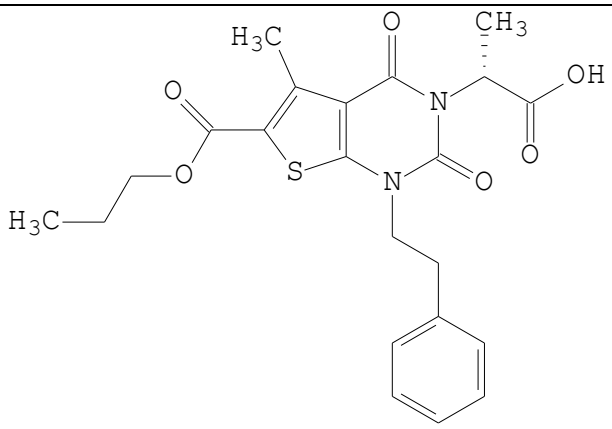
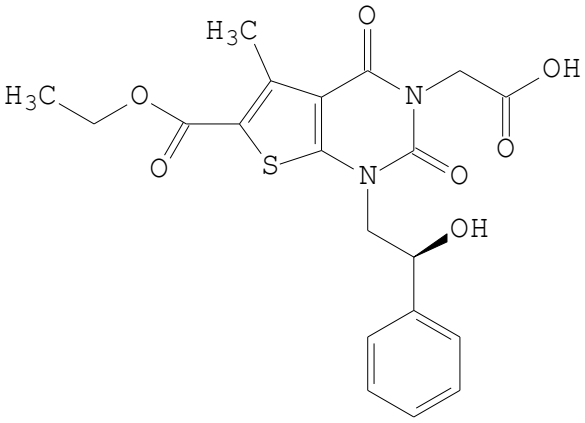
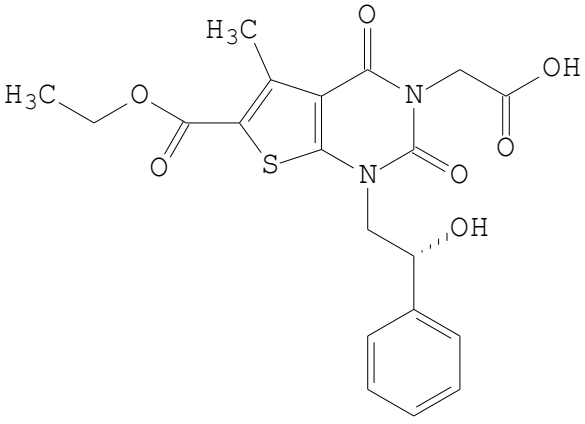
I-61		455 (M+1)
I-62		417 (M+1)
I-63		345 (M+1)

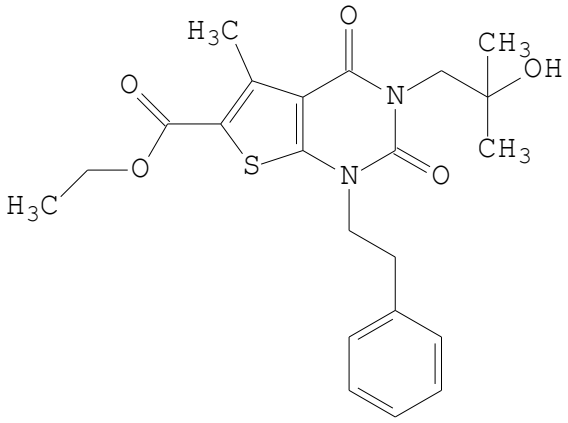
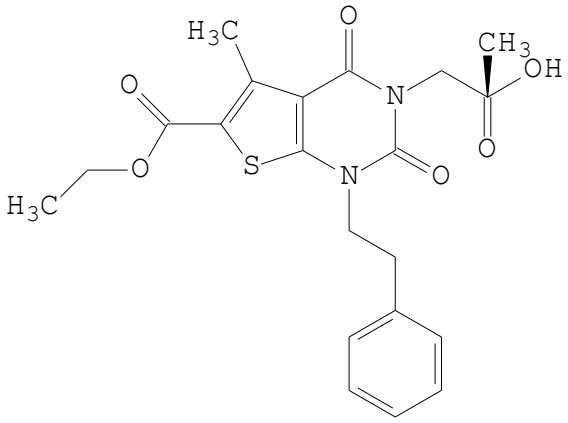
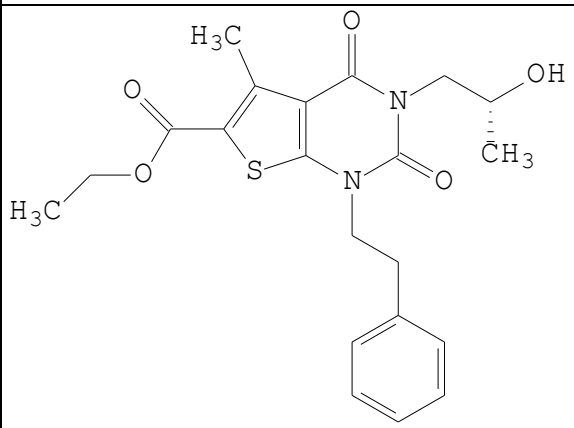
I-64		442 (M+1)
I-65		331 (M+1)
I-66		418 (M+1)

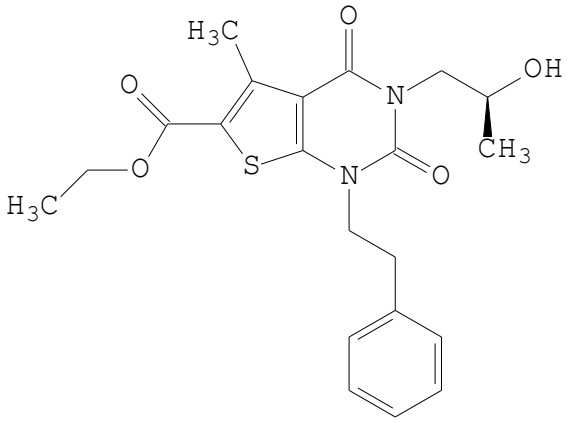
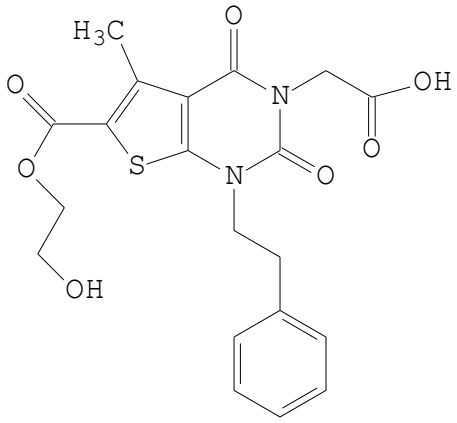
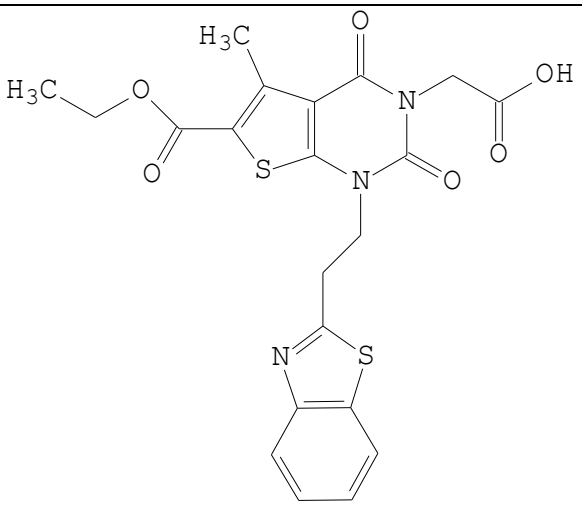
I-67		447 (M+1)
I-68		431 (M+1)
I-69		430 (M+1)

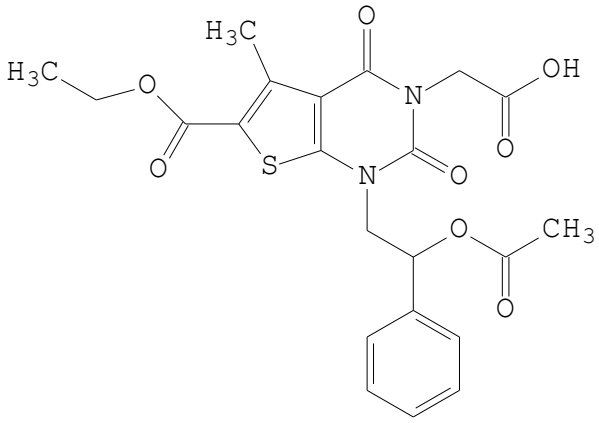
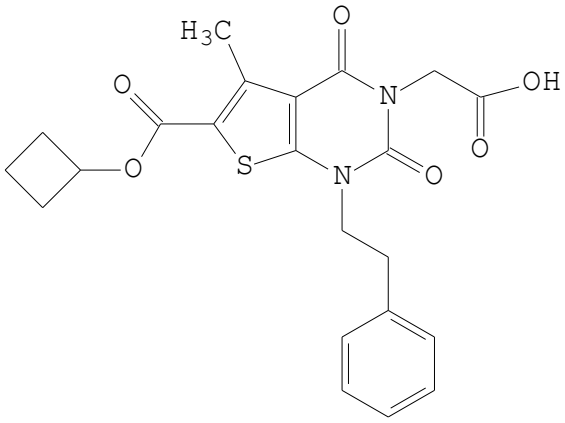
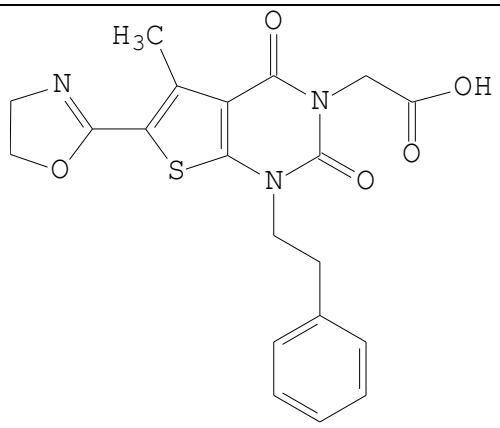
I-70		445 (M+1)
I-71		388 (M+1)
I-72		473 (M+Na)

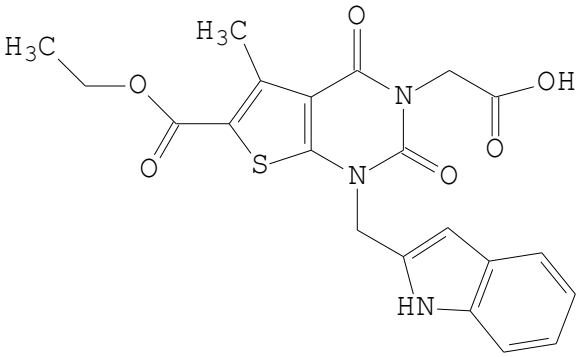
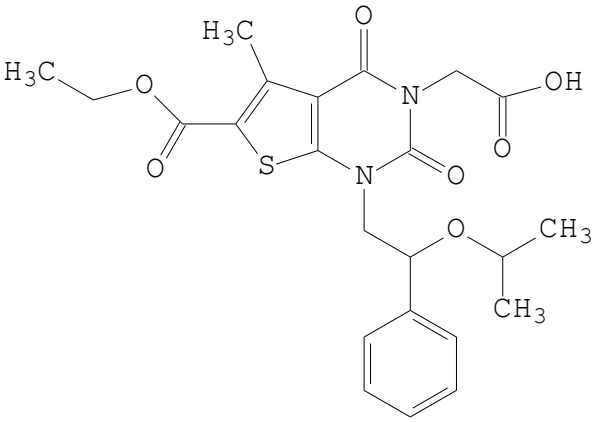
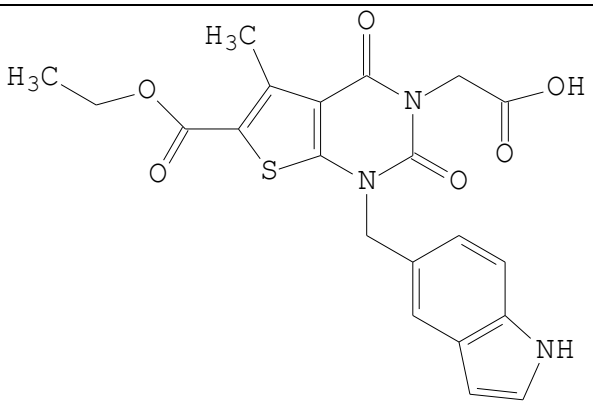
I-73		431 (M+1)
I-74		456 (M+1)
I-75		389 (M+1)

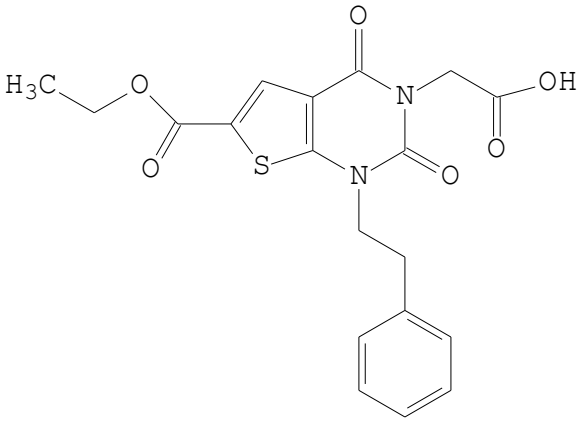
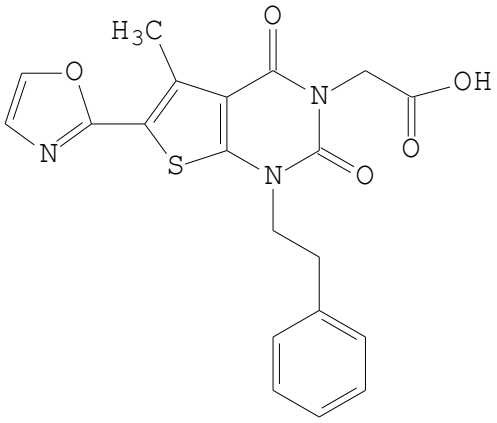
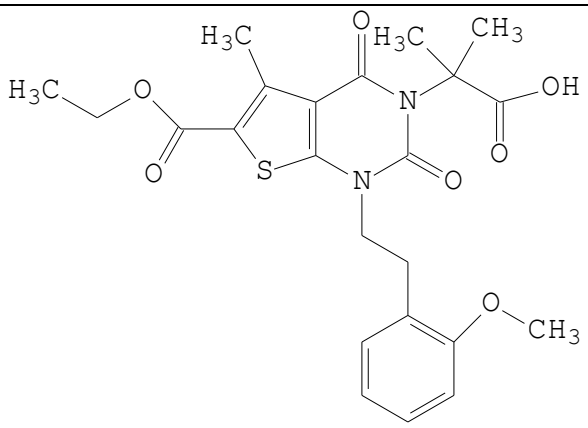
I-76		431 (M+1)
I-77		433 (M+1)
I-78		433 (M+1)

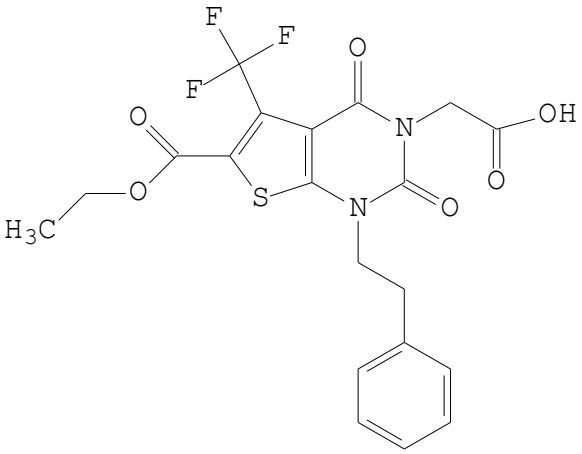
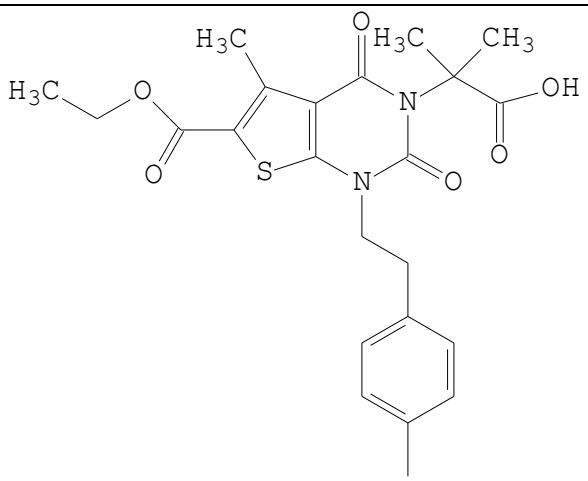
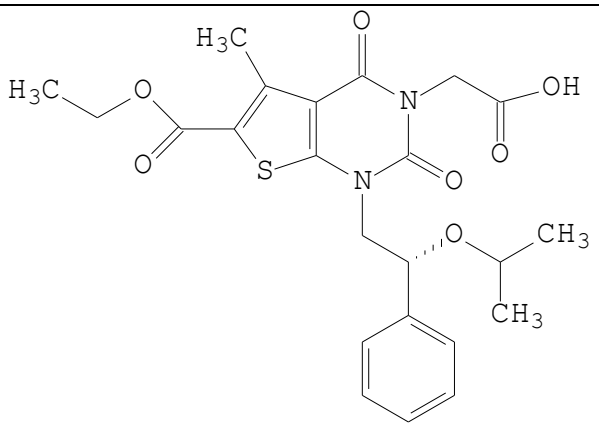
I-79		453 (M+Na)
I-80		431 (M+1)
I-81		417 (M+1)

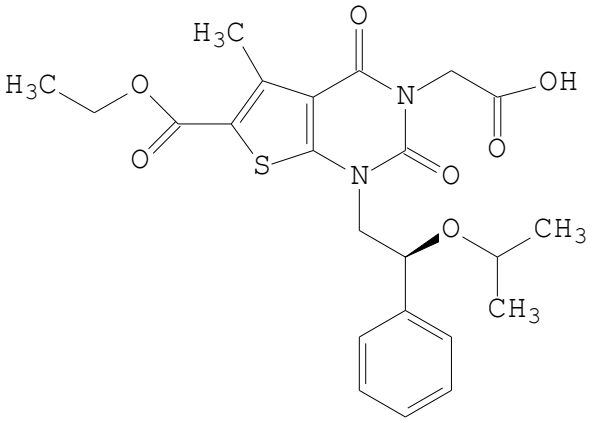
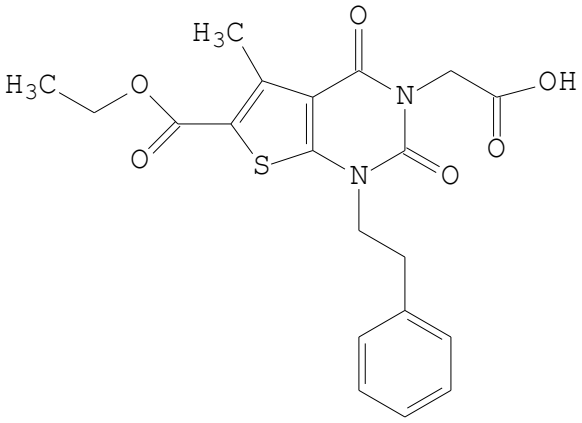
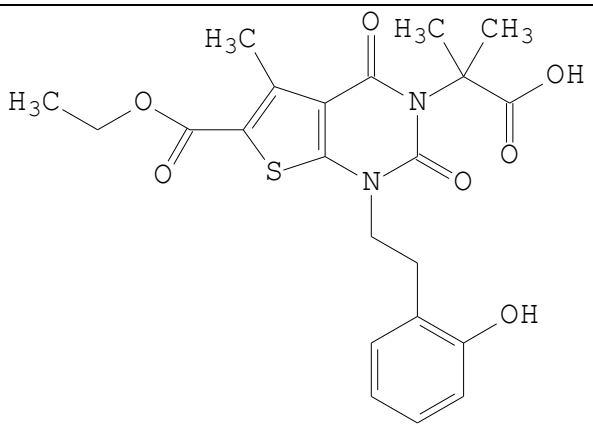
I-82		417 (M+1)
I-83		433 (M+1)
I-84		474 (M+1)

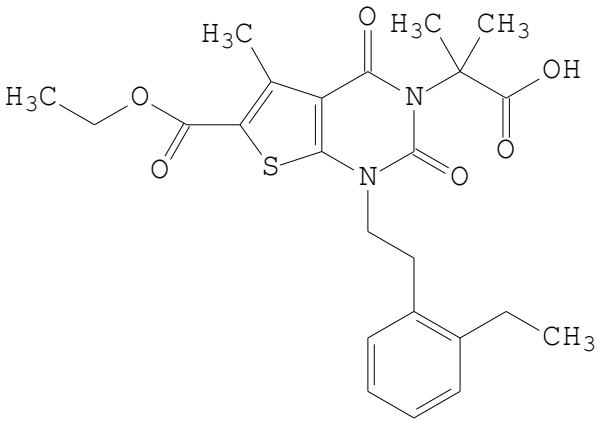
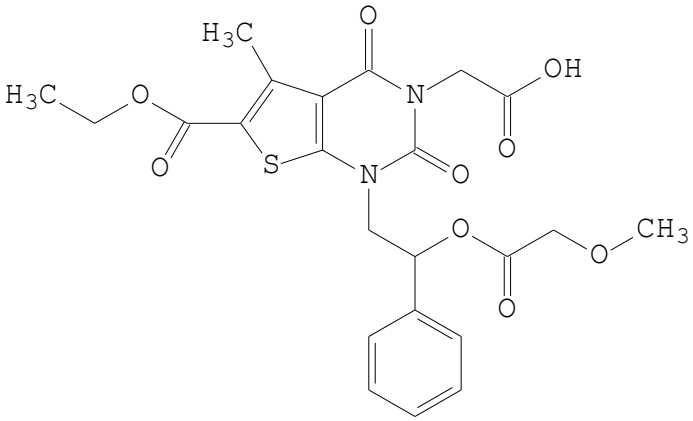
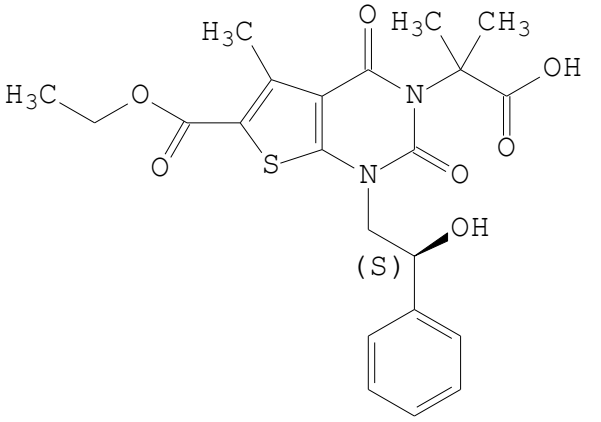
I-85		475 (M+1)
I-86		443 (M+1)
I-87		414 (M+1)

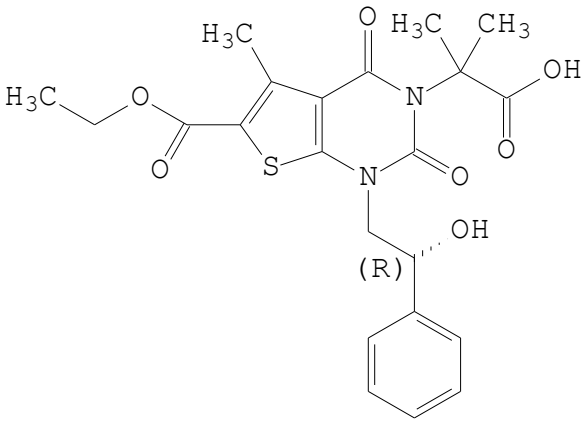
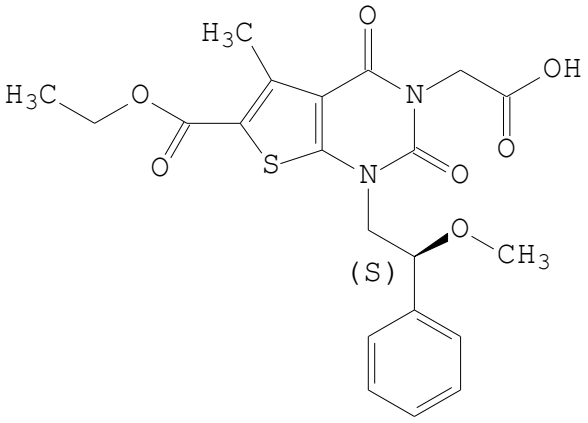
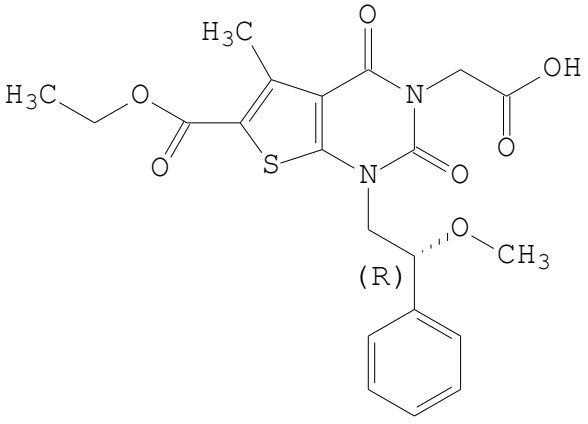
I-88		442 (M+1)
I-89		475 (M+1)
I-90		442 (M+1)

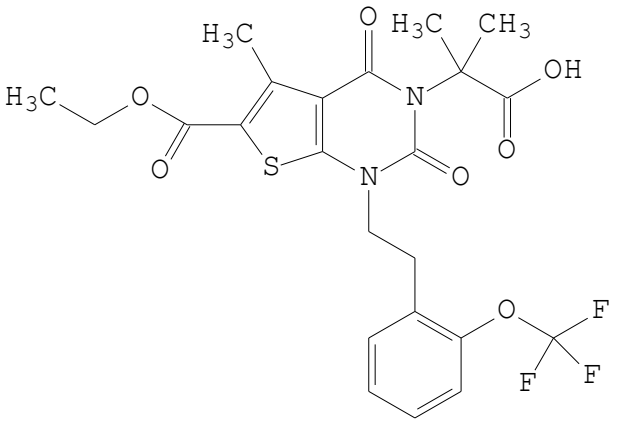
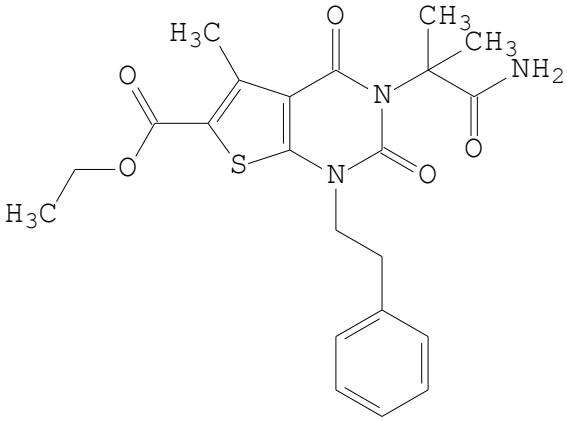
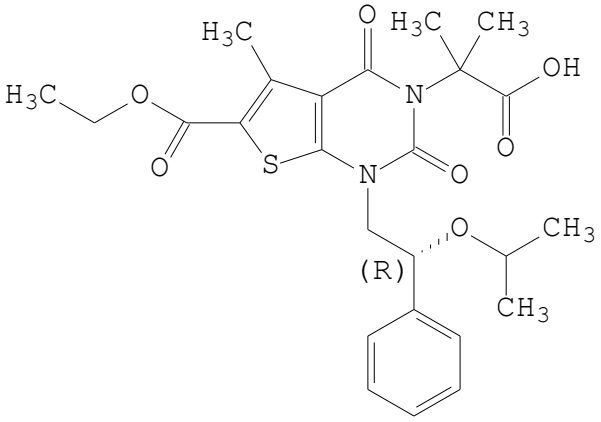
I-91		403 (M+1)
I-92		412 (M+1)
I-93		475 (M+1)

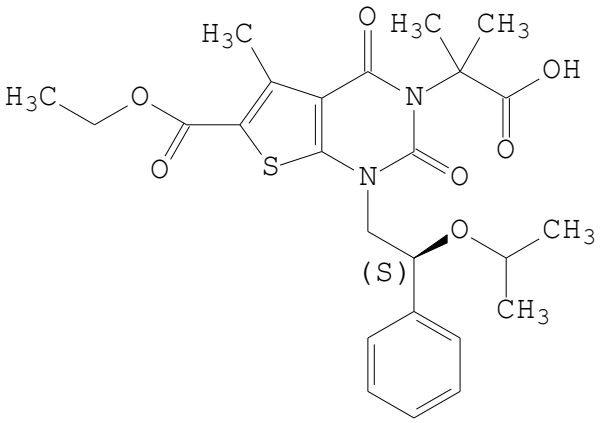
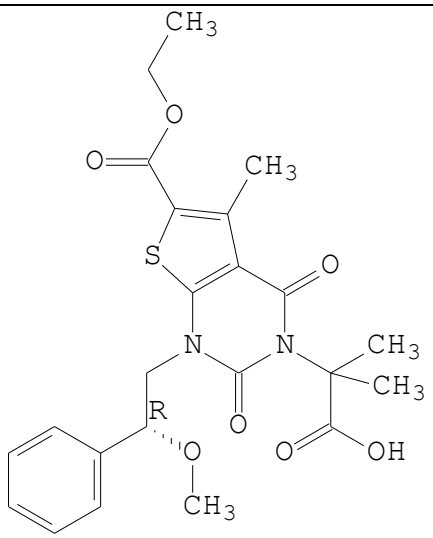
I-94		471 (M+1)
I-95		571 (M+1)
I-96		475 (M+1)

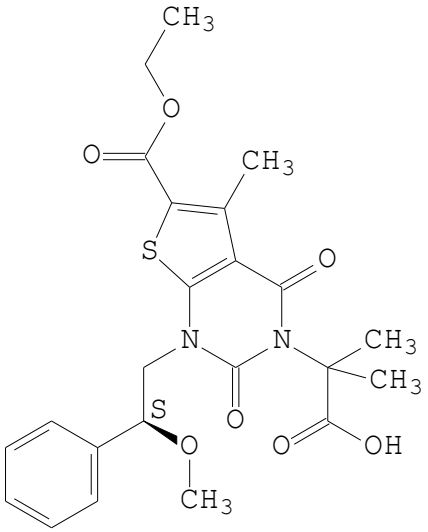
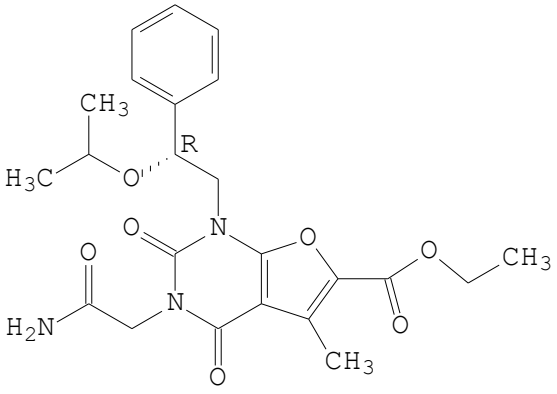
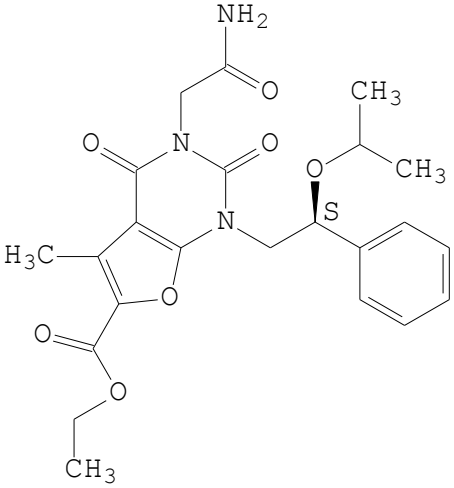
I-97		475 (M+1)
I-98		400 (M+1)
I-99		461 (M+1)

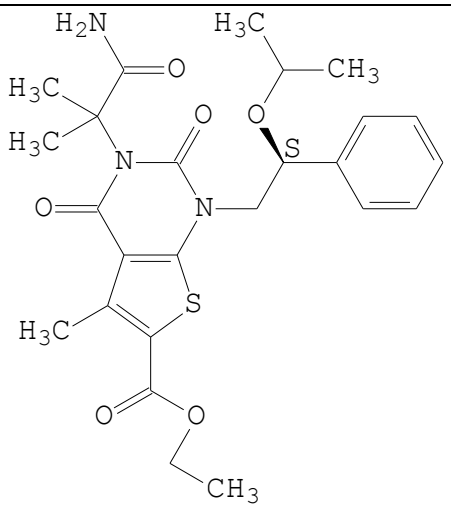
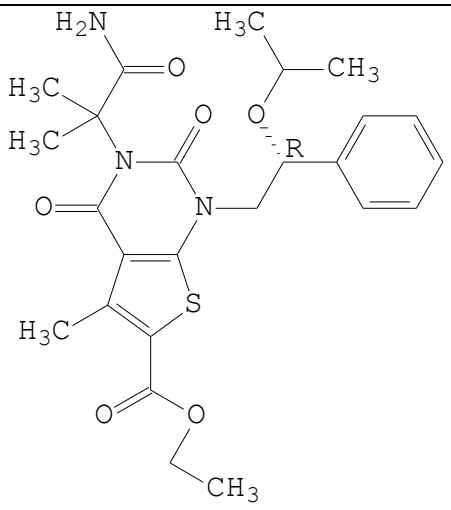
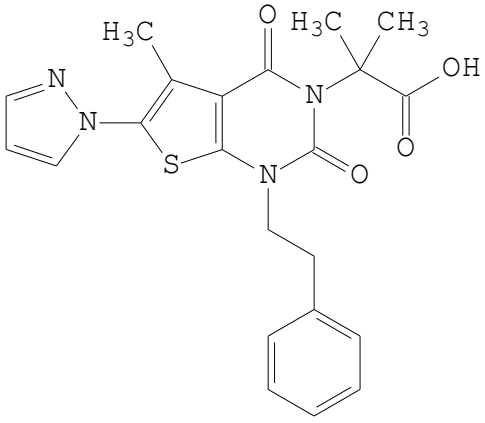
I-100		473 (M+1)
I-101		527 (M+Na)
I-102		461 (M+1)

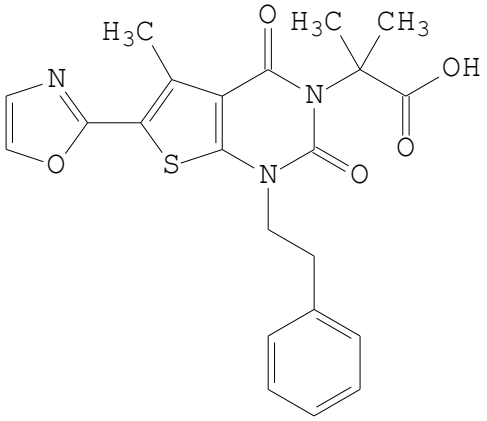
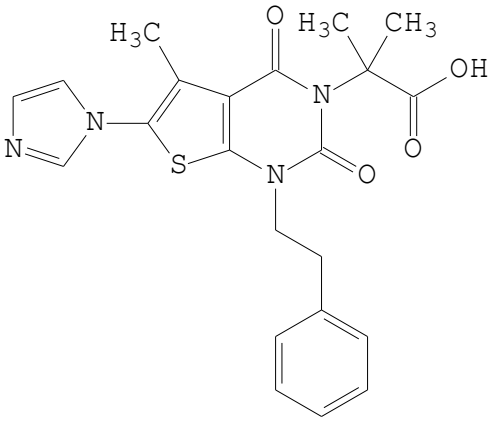
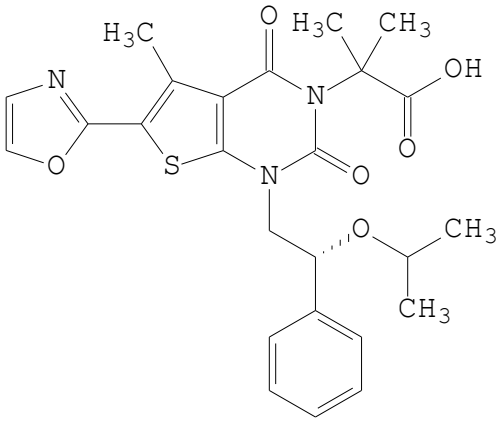
I-103		461 (M+1)
I-104		447 (M+1)
I-105		447 (M+1)

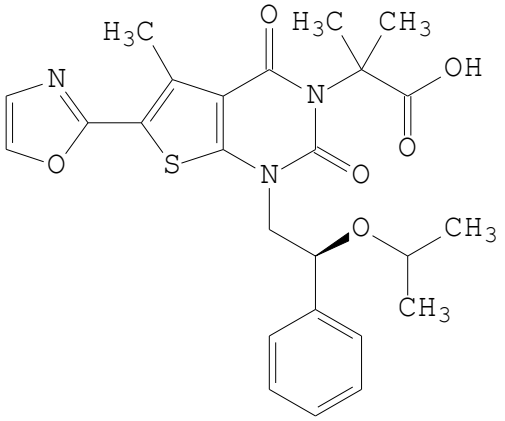
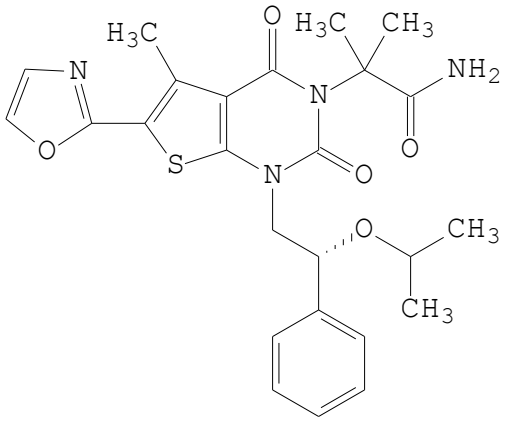
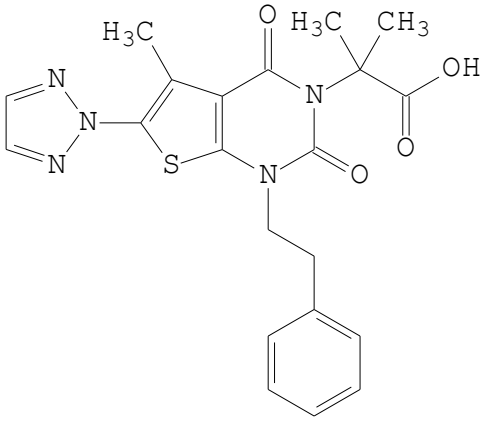
I-106		529 (M+1)
I-107		466 (M+Na)
I-108		503 (M+1)

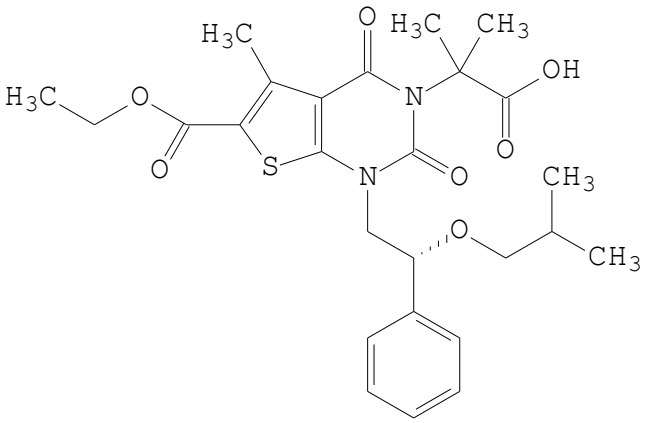
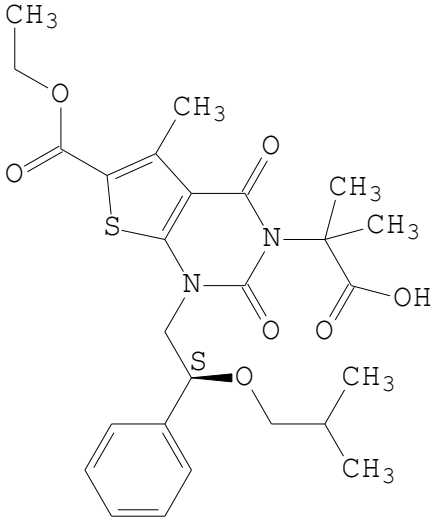
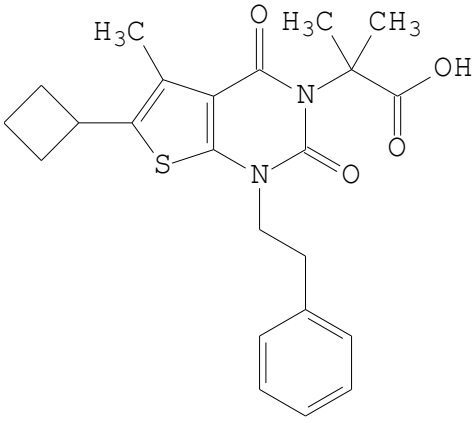
I-109		503 (M+1)
I-110		475 (M+1)

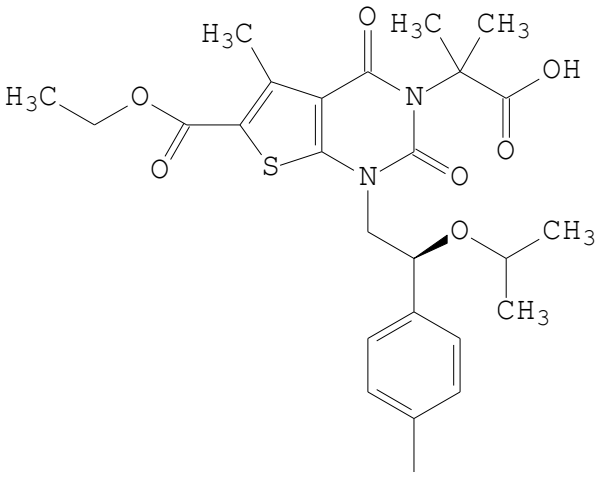
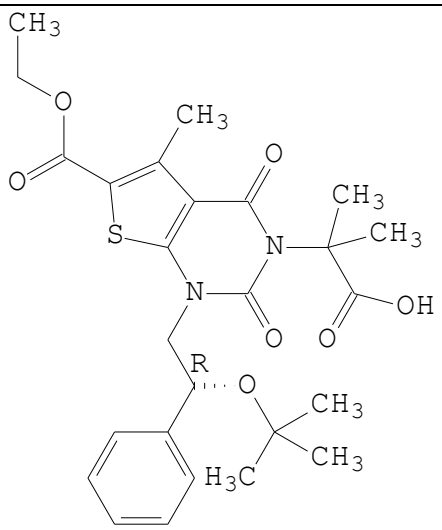
I-111		475 (M+1)
I-112		474 (M+1)
I-113		474 (M+1)

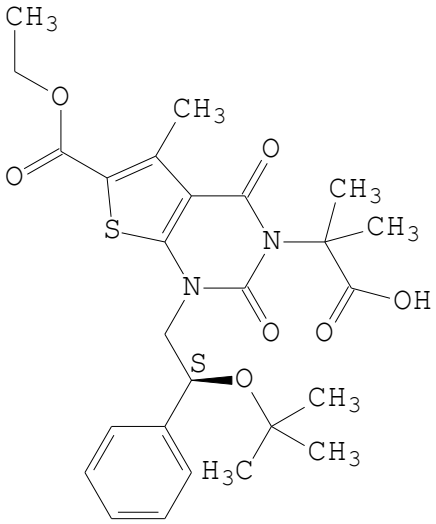
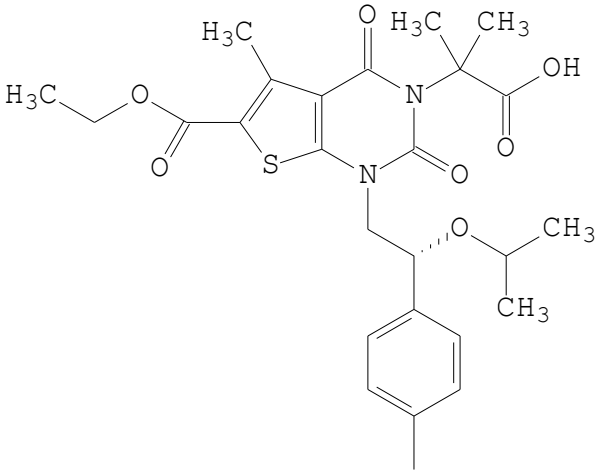
I-114		524 (M+Na)
I-115		524 (M+Na)
I-116		439 (M+1)

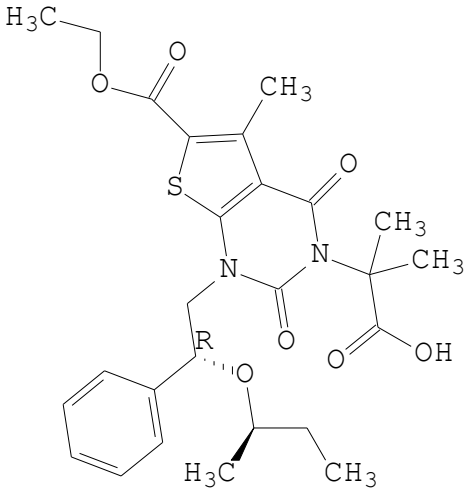
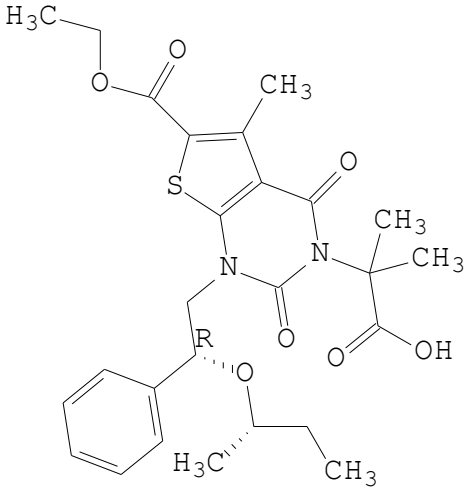
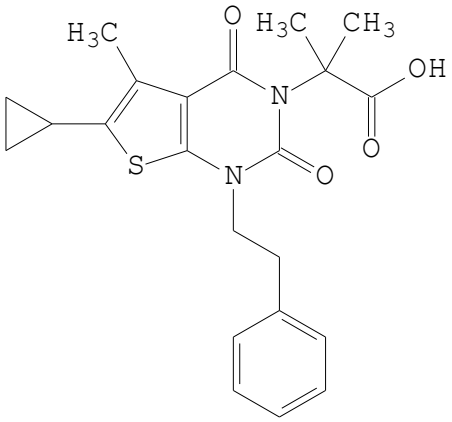
I-117		440 (M+1)
I-118		439 (M+1)
I-119		498 (M+1)

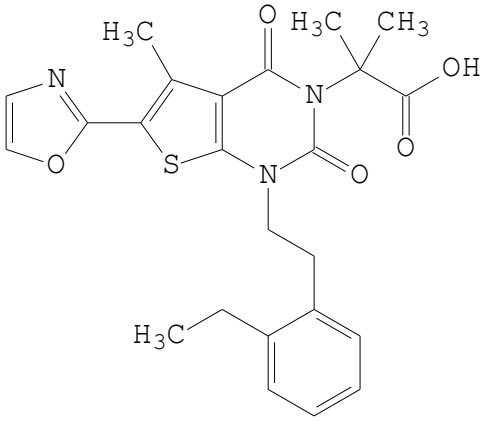
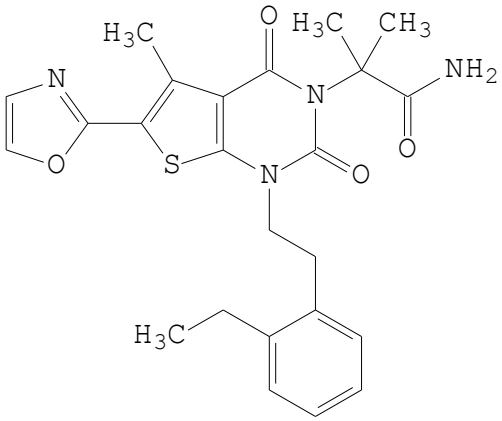
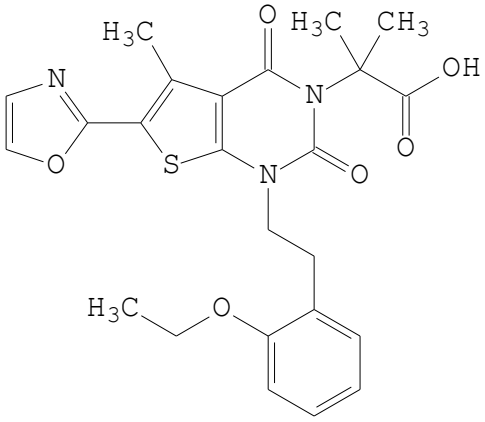
I-120		498 (M+1)
I-121		480 (M-NH2)
I-122		440 (M+1)

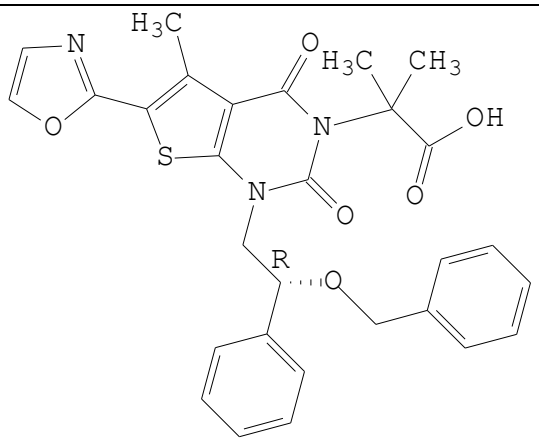
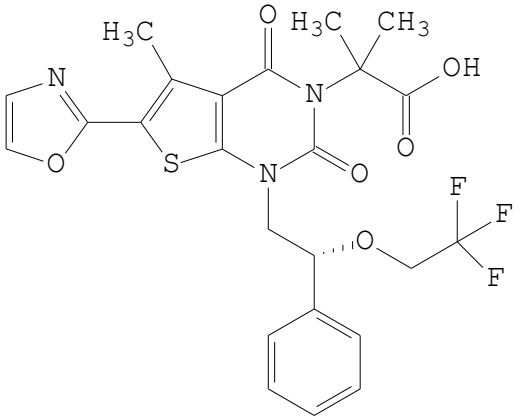
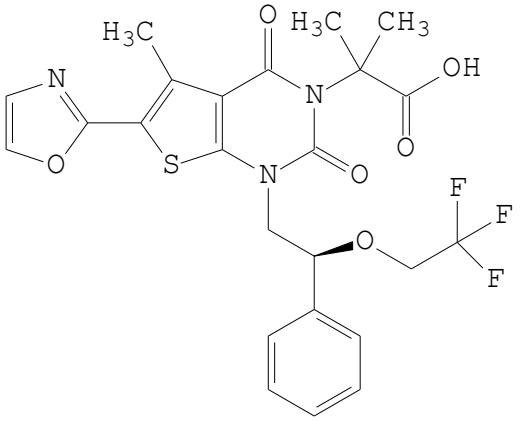
I-123		517 (M+1)
I-124		517 (M+1)
I-125		427 (M+1)

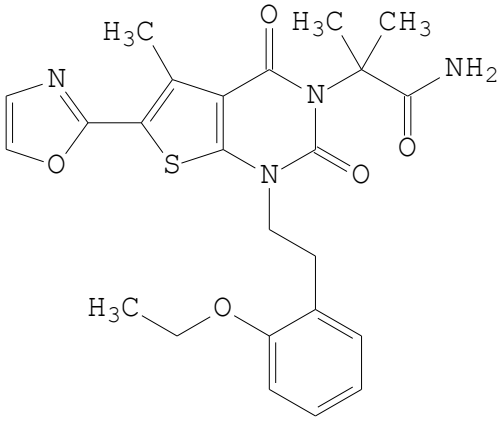
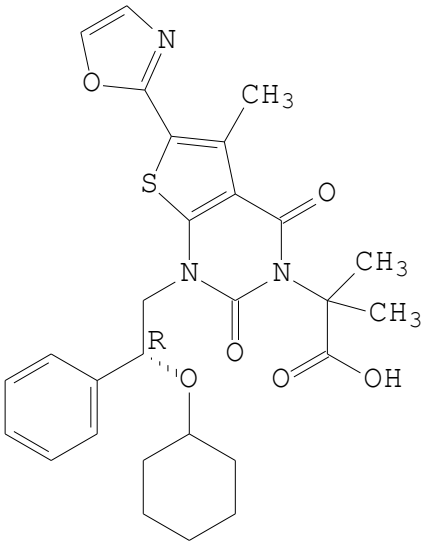
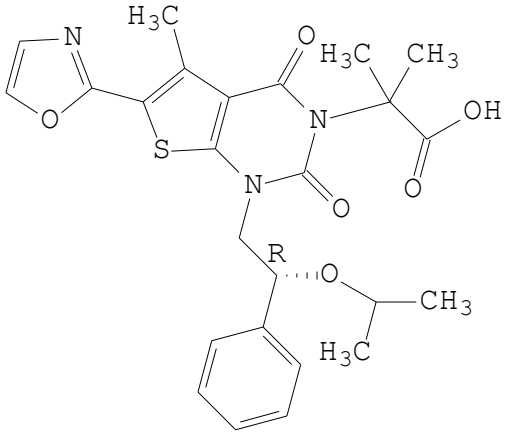
I-126		629 (M+1)
I-127		443 (M-C_4H_9O)

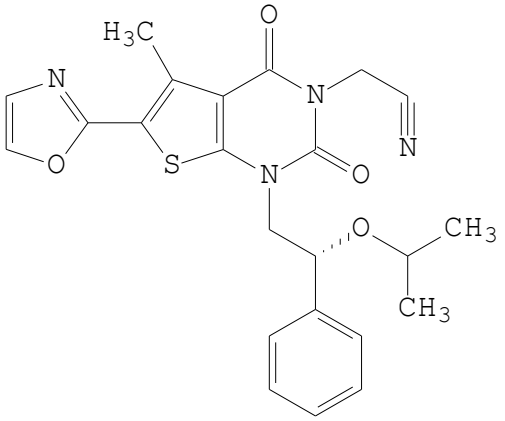
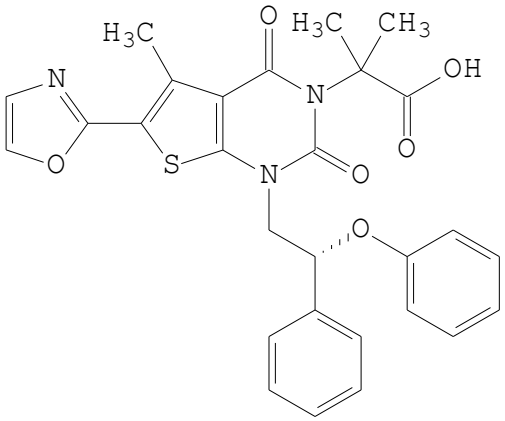
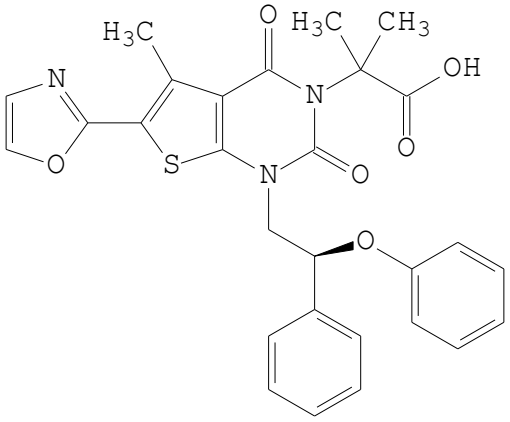
I-128		445 (M-C_4H_9O)
I-129		629 (M+1)

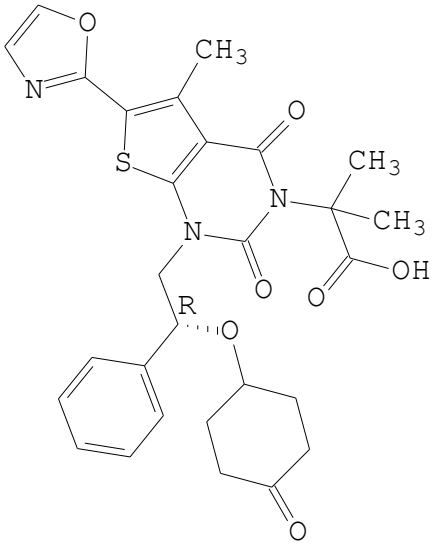
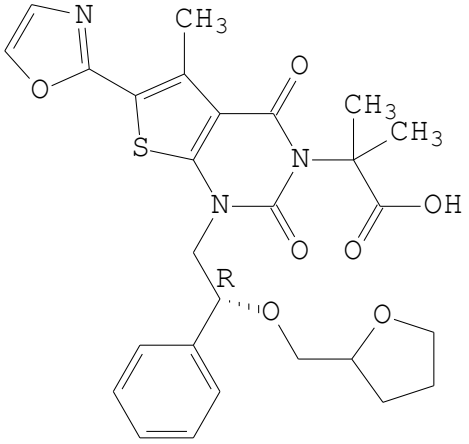
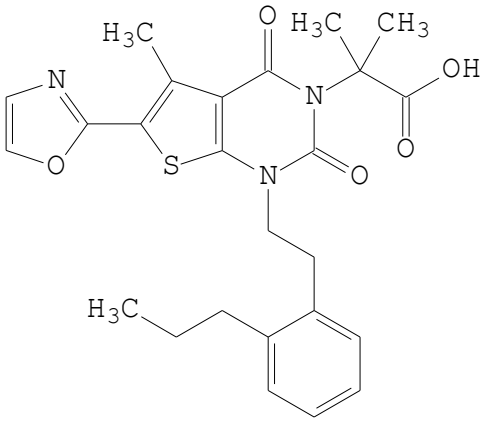
I-130		517 (M+1)
I-131		517 (M+1)
I-132		413 (M+1)

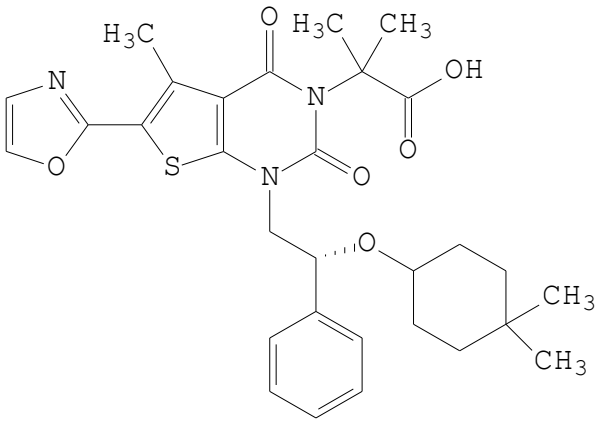
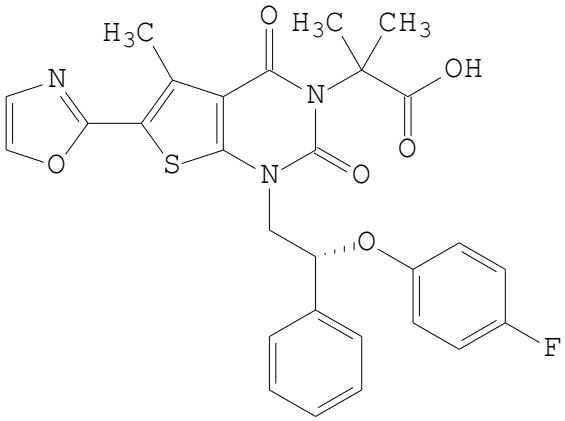
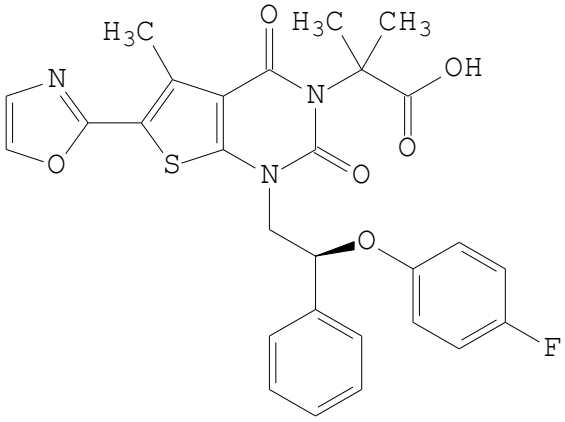
I-133		468 (M+1)
I-134		450 (M-NH2)
I-135		484 (M+1)

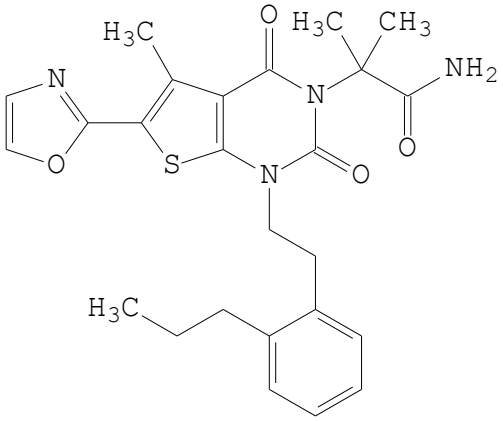
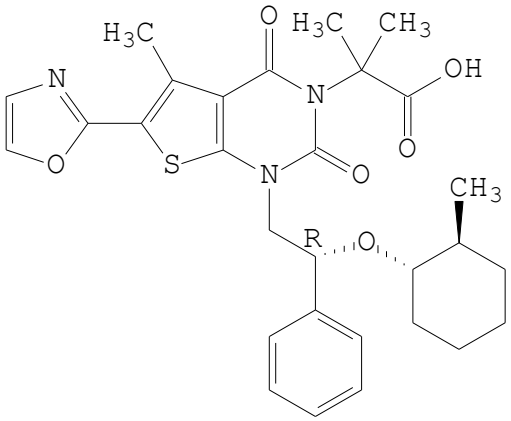
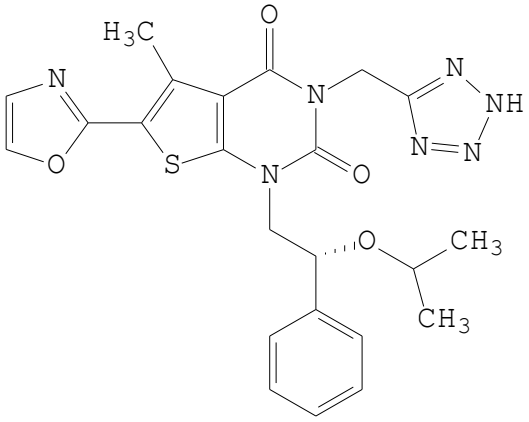
I-136		546 (M+1)
I-137		538 (M+1)
I-138		538 (M+1)

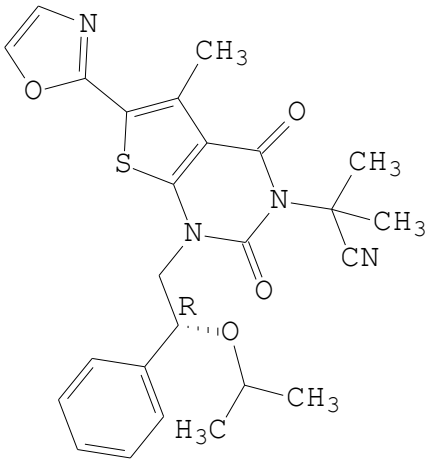
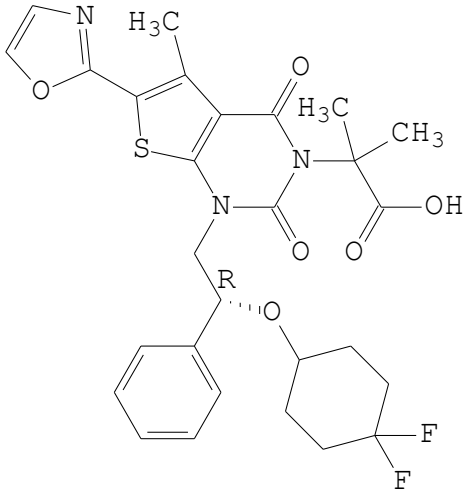
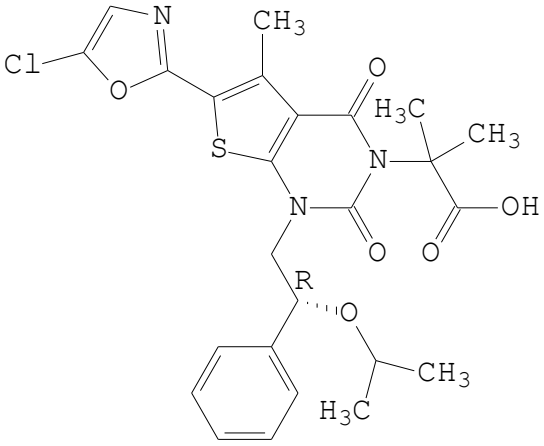
I-139		505 (M+Na)
I-140		538 (M+1)
I-141		514 (M+1)

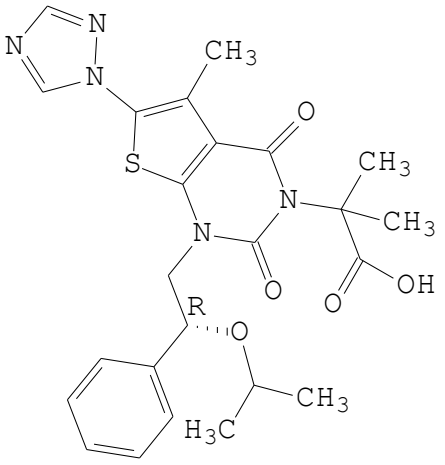
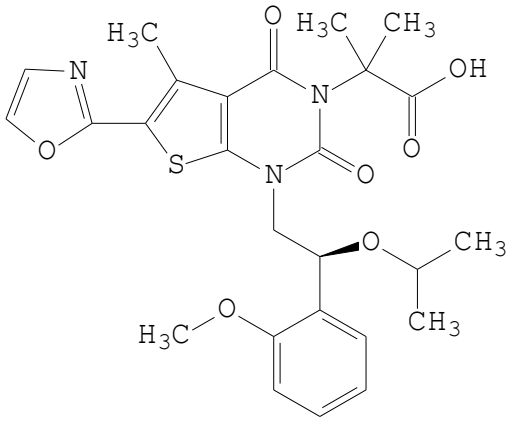
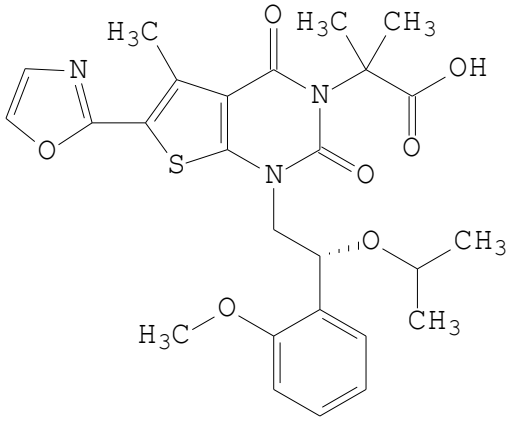
I-142		451 (M+1)
I-143		532 (M+1)
I-144		532 (M+1)

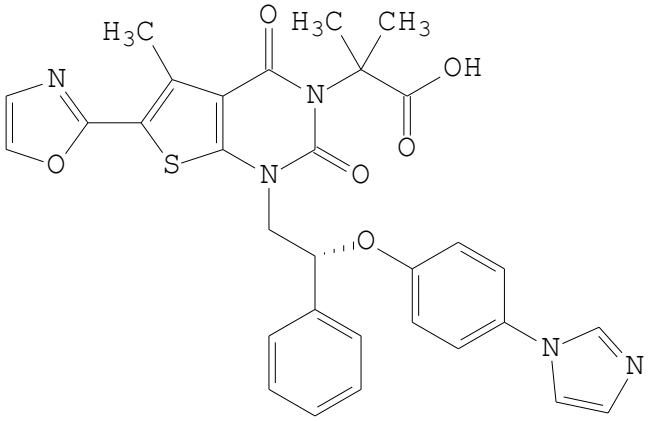
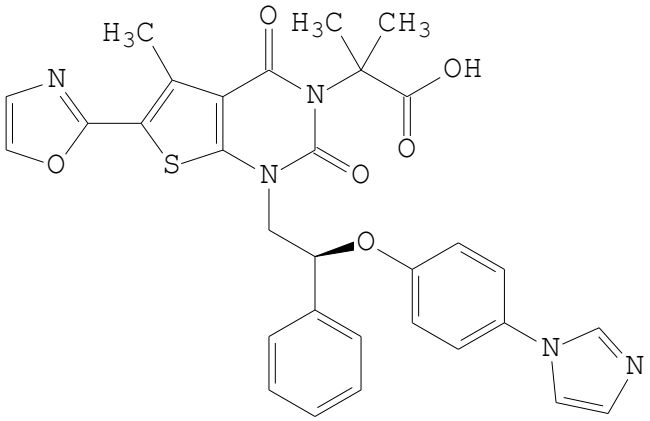
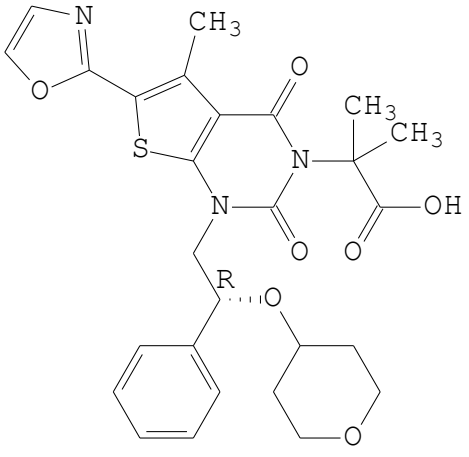
I-145		552 (M+1)
I-146		562 (M+Na)
I-147		482 (M+1)

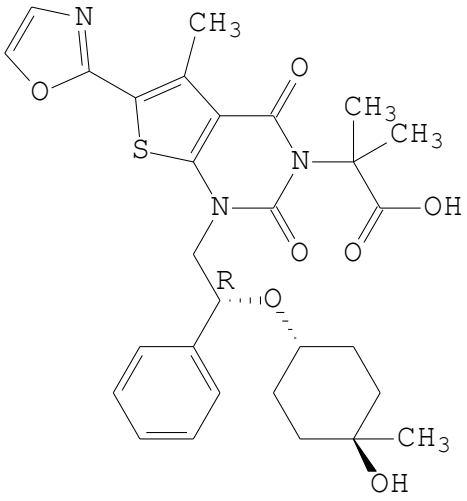
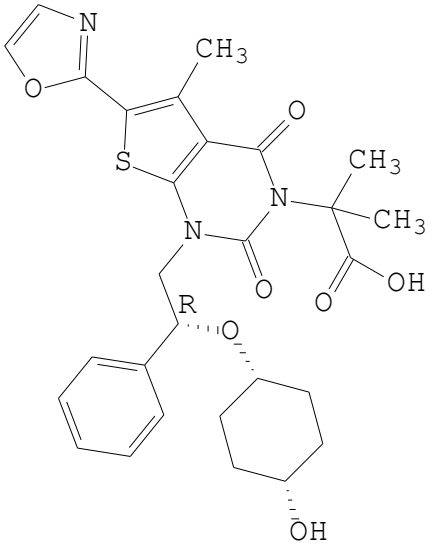
I-148		566 (M+1)
I-149		550 (M+1)
I-150		550 (M+1)

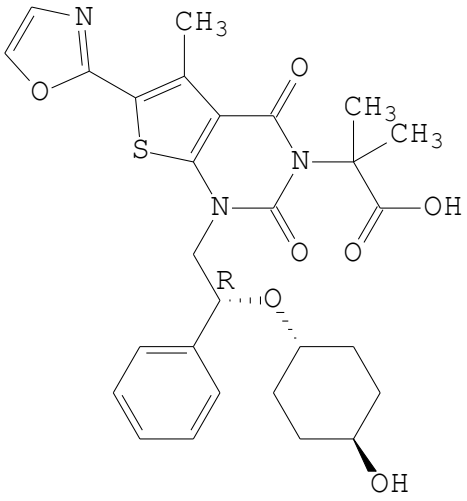
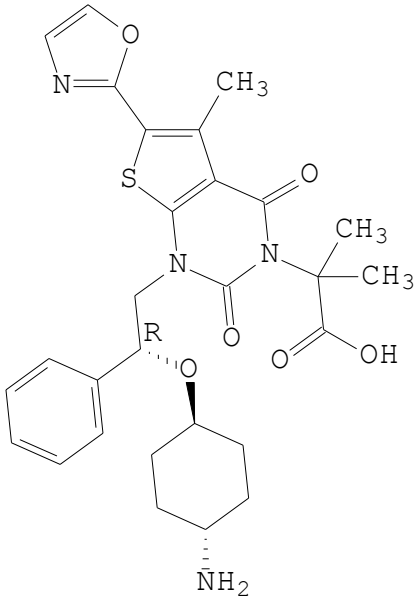
I-151		464 (M-NH2)
I-152		552 (M+1)
I-153		494 (M+1)

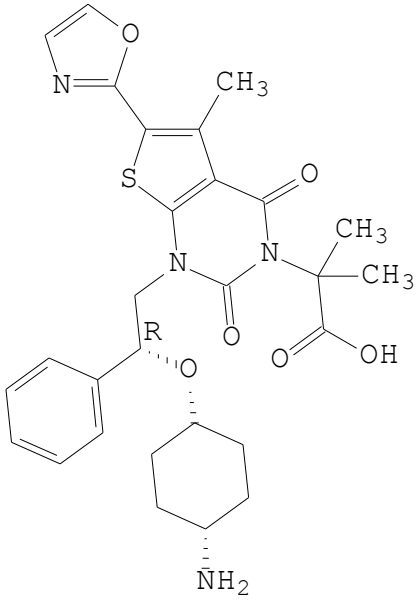
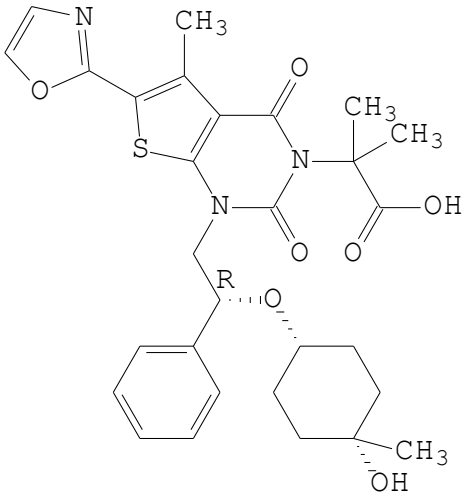
I-154		479 (M+1)
I-155		574 (M+1)
I-156		532 (M+1)

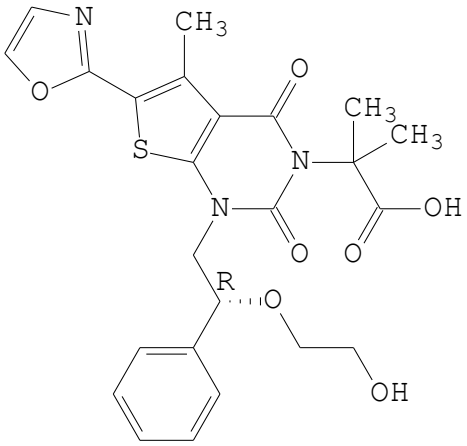
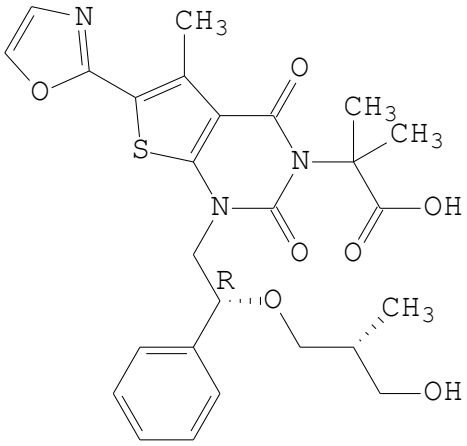
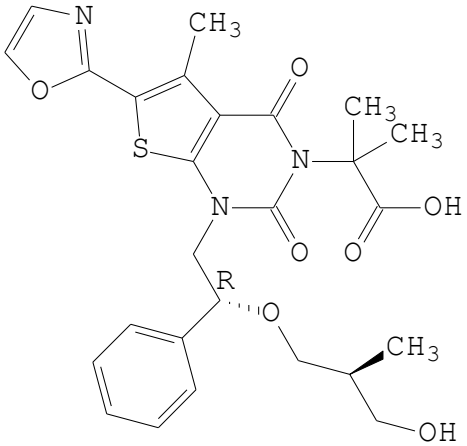
I-157		498 (M+1)
I-158		528 (M+1)
I-159		528 (M+1)

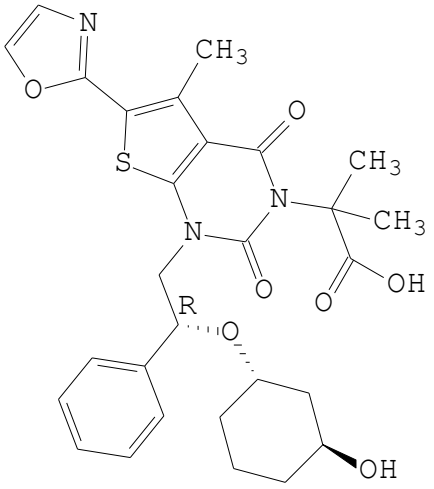
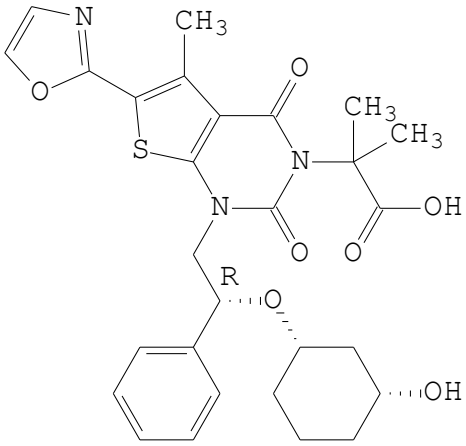
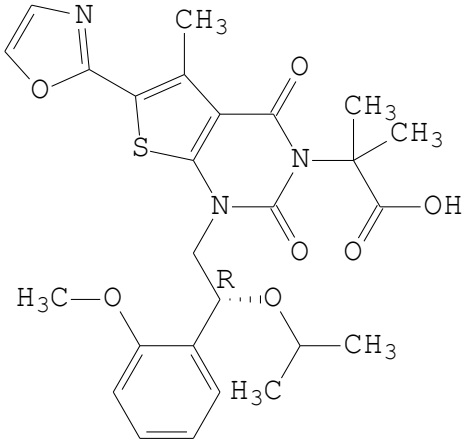
I-160		598 (M+1)
I-161		598 (M+1)
I-162		540 (M+1)

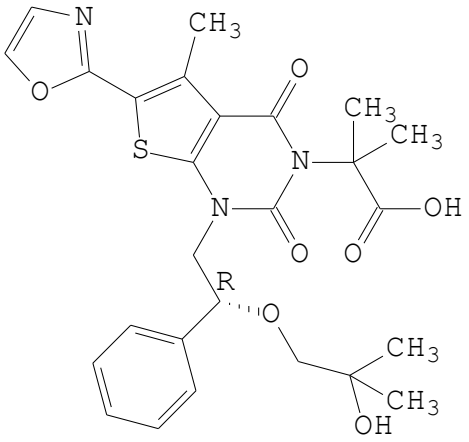
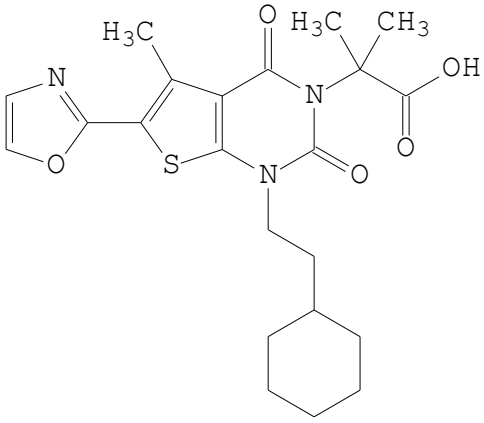
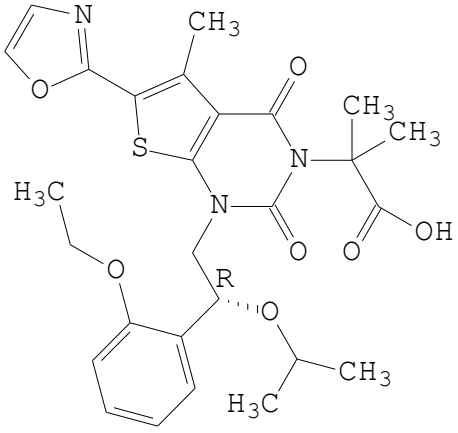
I-163		568 (M+1)
I-164		554 (M+1)

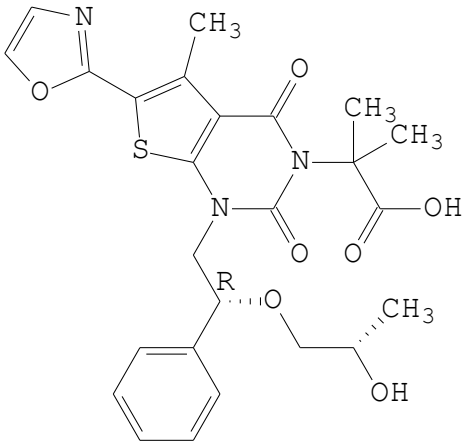
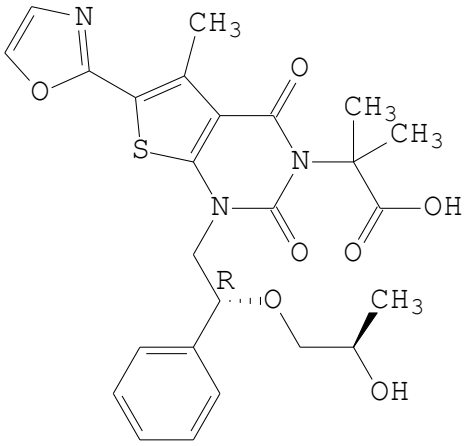
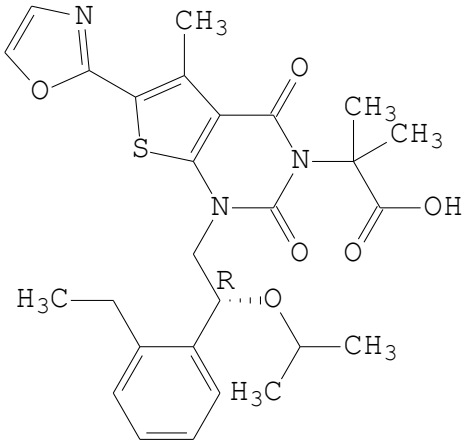
I-165		554 (M+1)
I-166		553 (M+1)

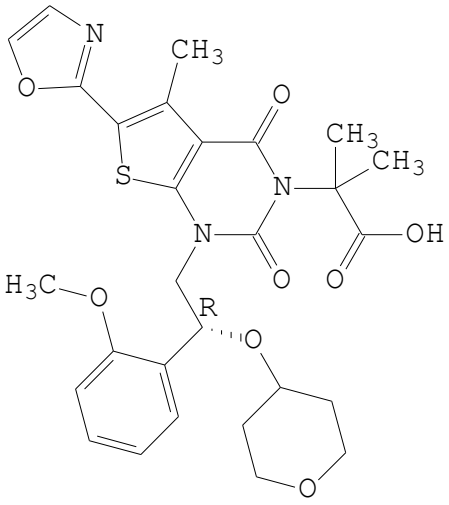
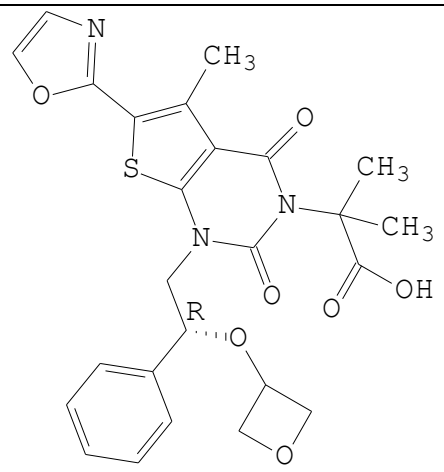
I-167		553 (M+1)
I-168		568 (M+1)

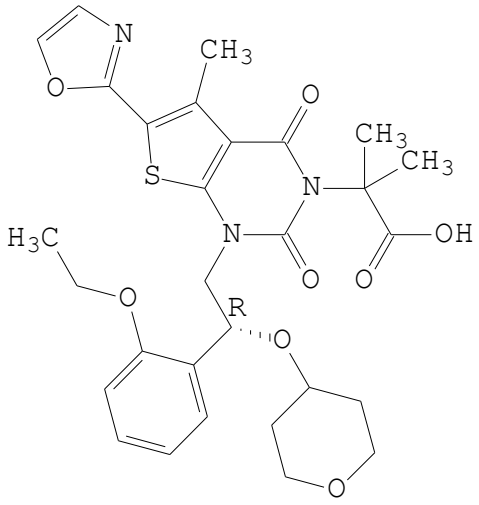
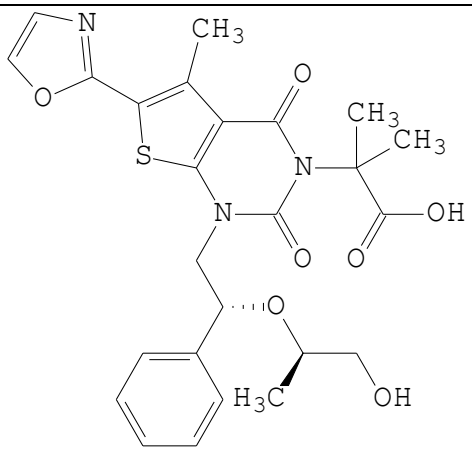
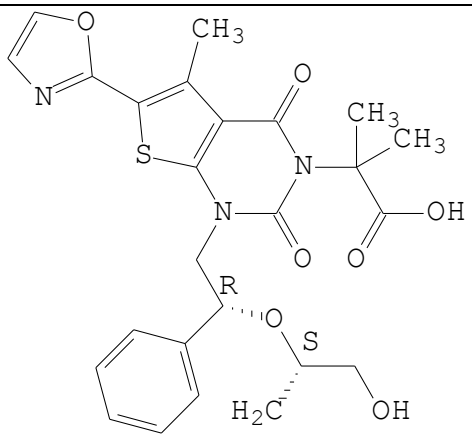
I-169		500 (M+1)
I-170		528 (M+1)
I-171		528 (M+1)

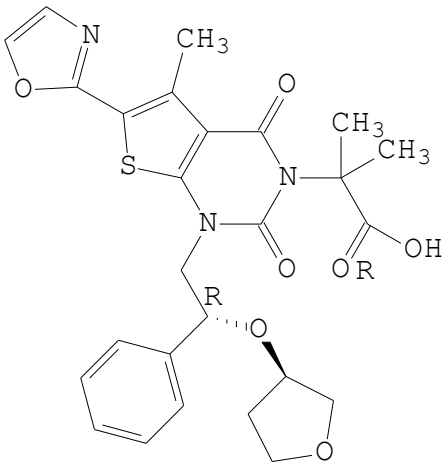
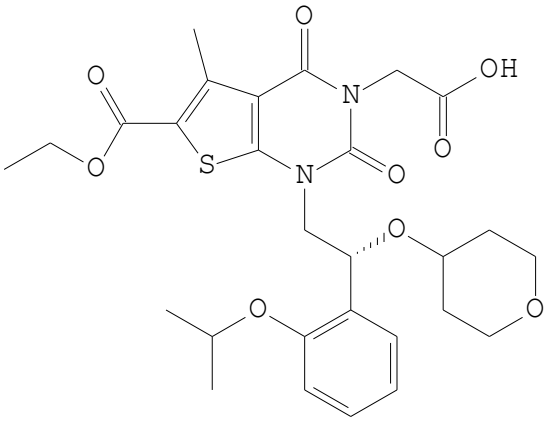
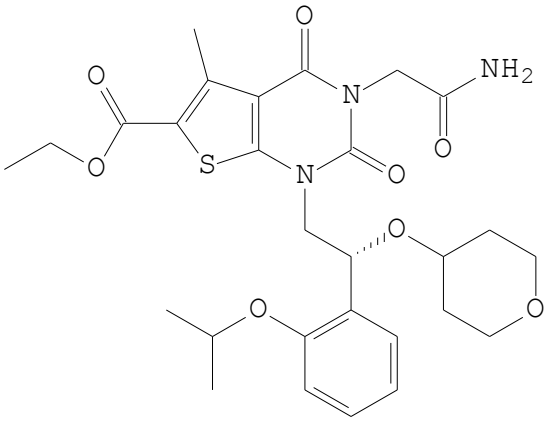
I-172		554 (M+1)
I-173		554 (M+1)
I-174		510 ($M-NH_2$)

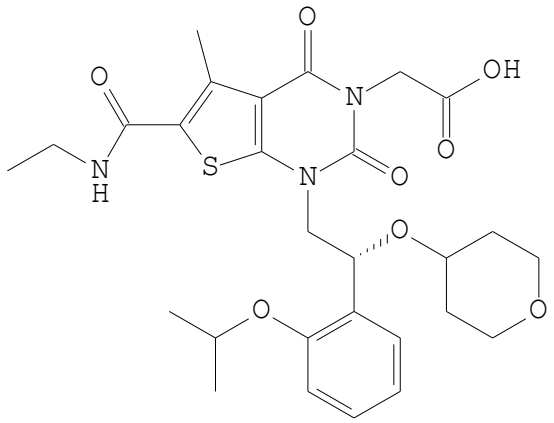
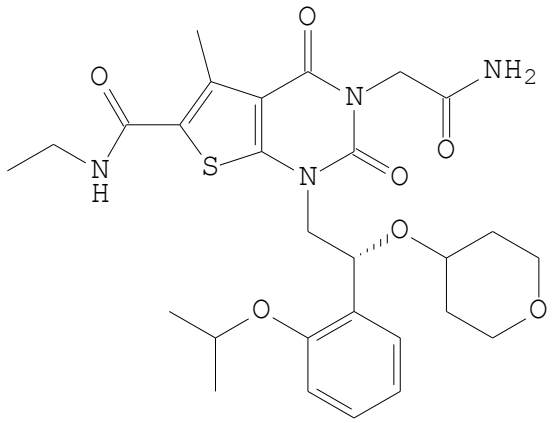
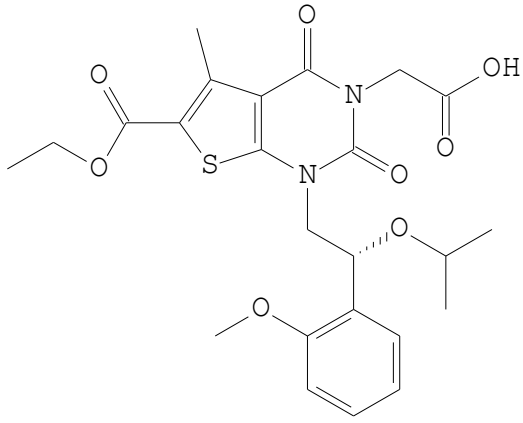
I-175		528 (M+1)
I-176		446 (M+1)
I-177		542 (M+1)

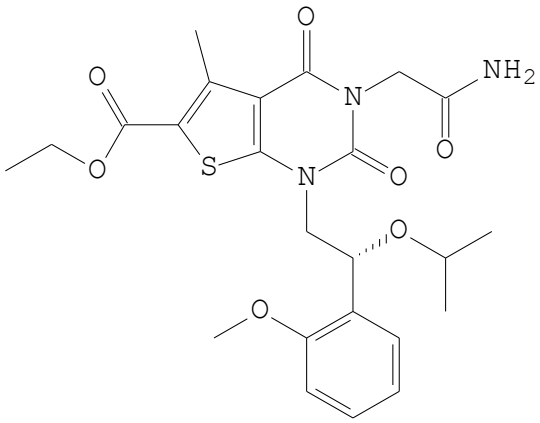
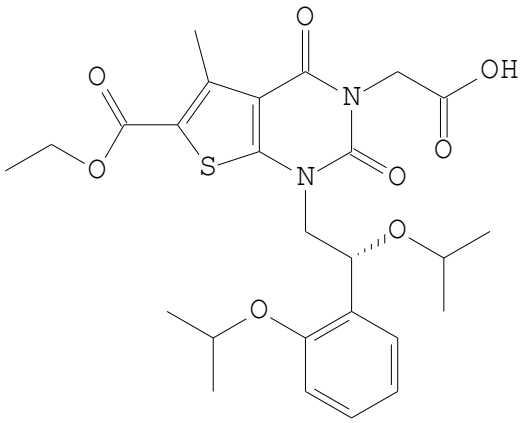
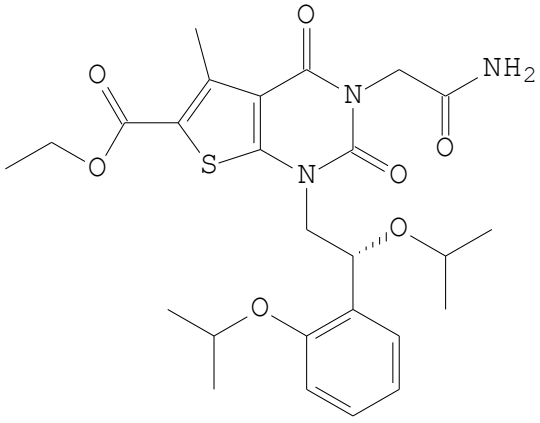
I-178		514 (M+1)
I-179		514 (M+1)
I-180		526 (M+1)

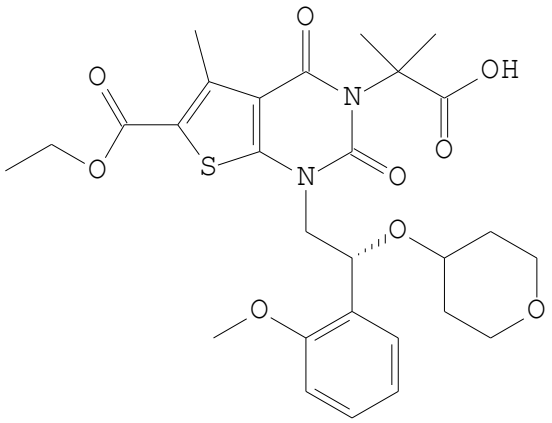
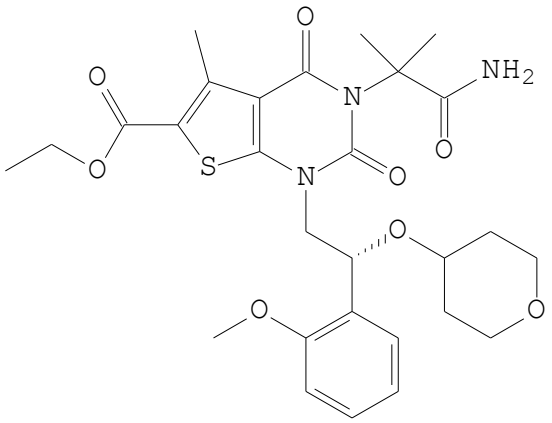
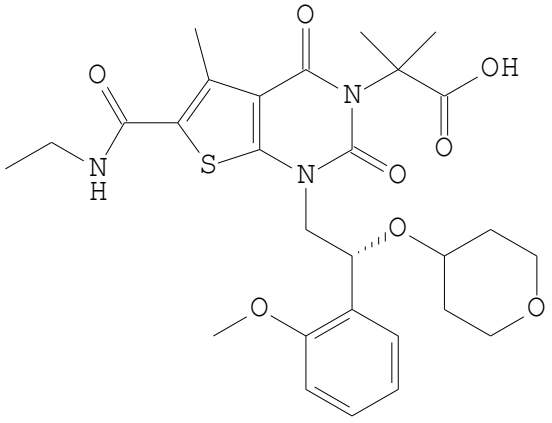
I-181		570 (M+1)
I-182		512 (M+1)

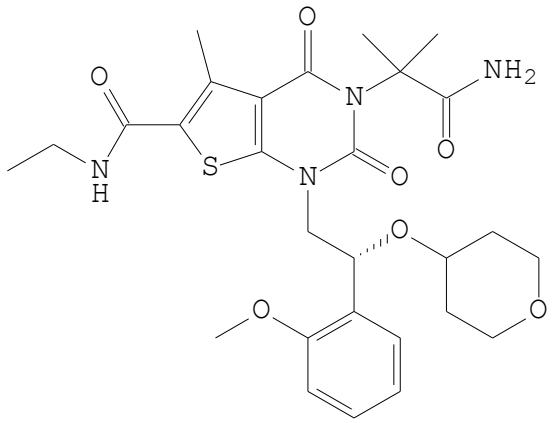
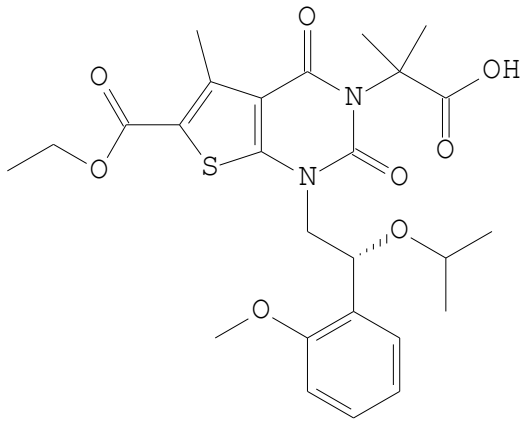
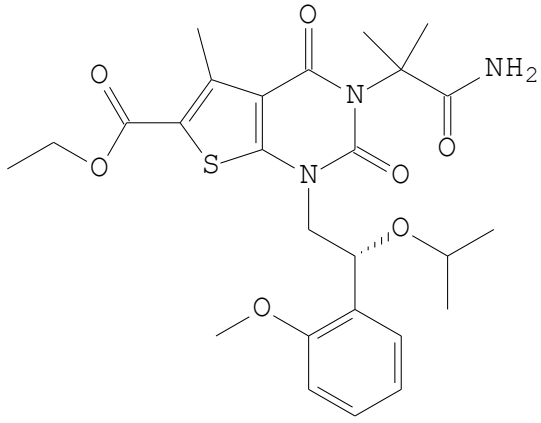
I-183		606 (M+Na)
I-184		514 (M+1)
I-185		514 (M+1)

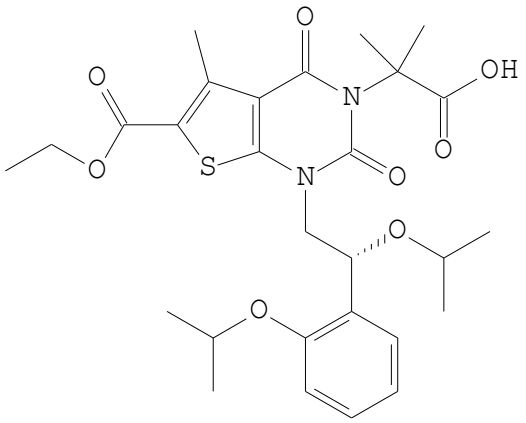
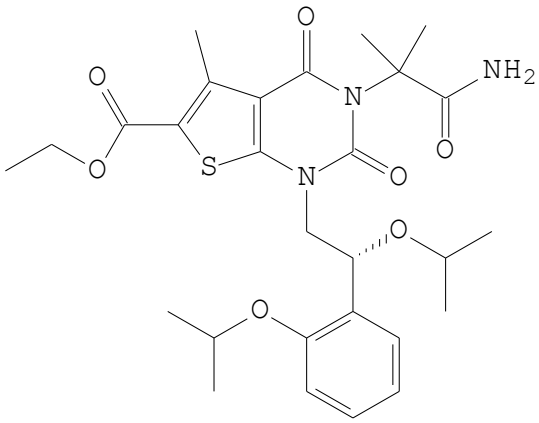
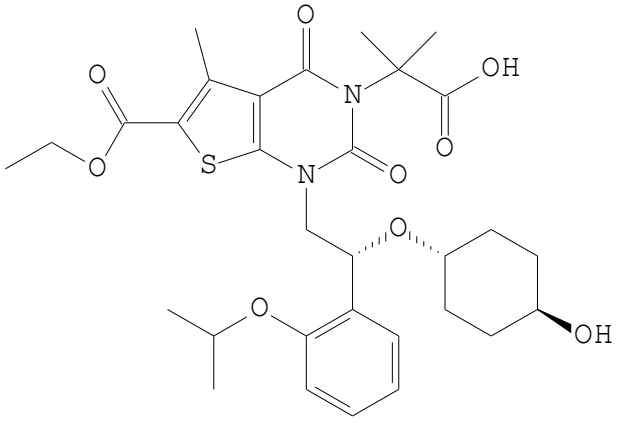
I-186		526 (M+1)
I-187		
I-188		

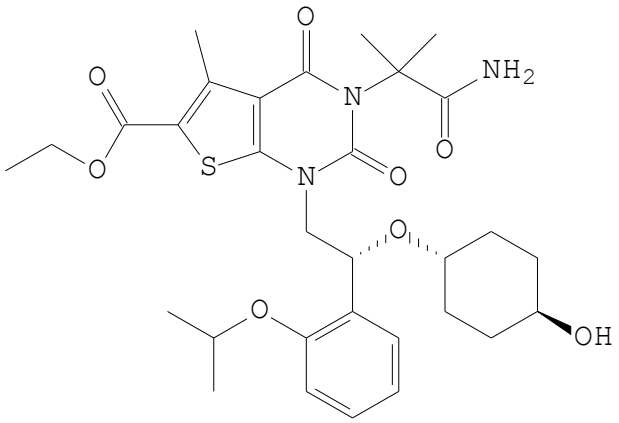
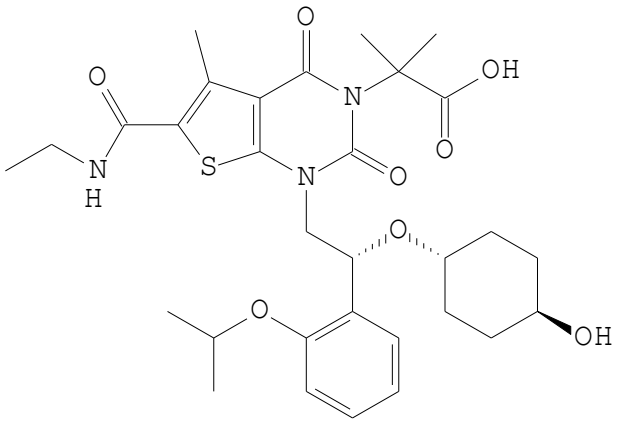
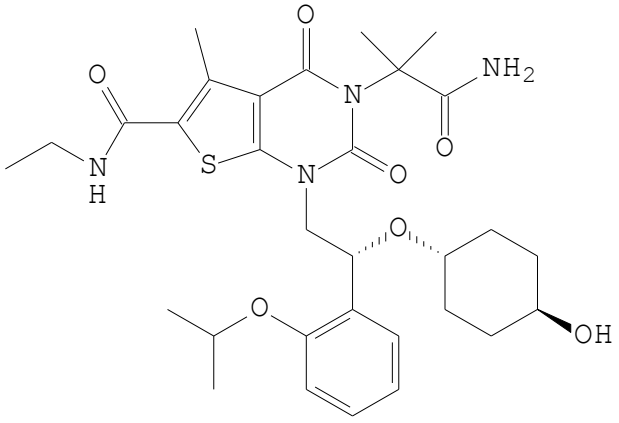
I-189		
I-190		
I-191		

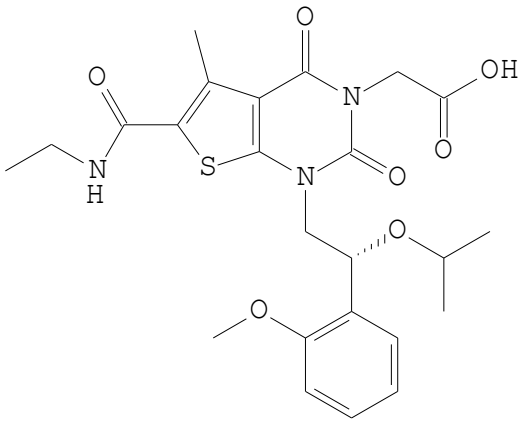
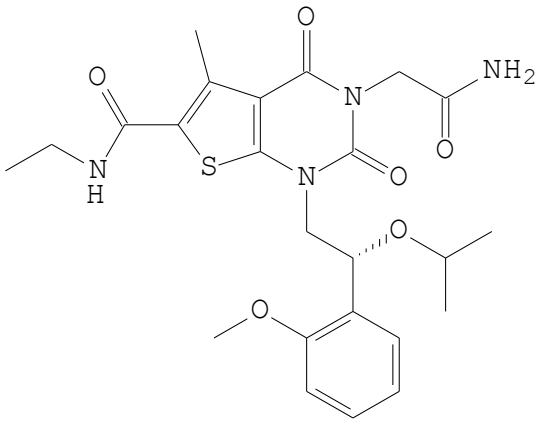
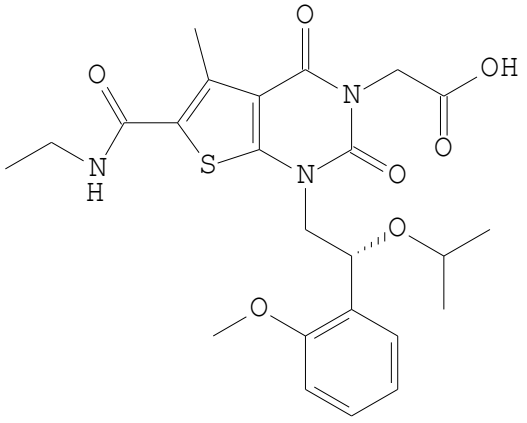
I-192		
I-193		
I-194		

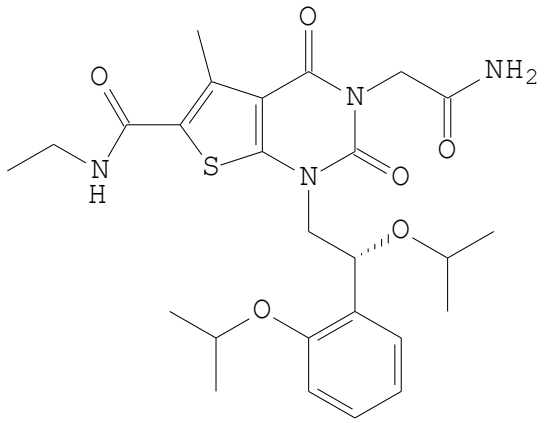
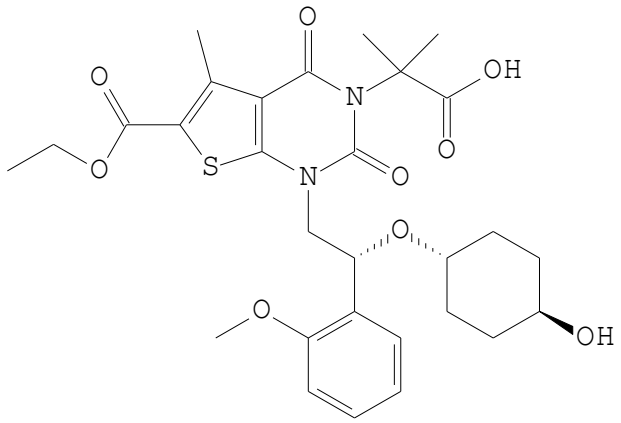
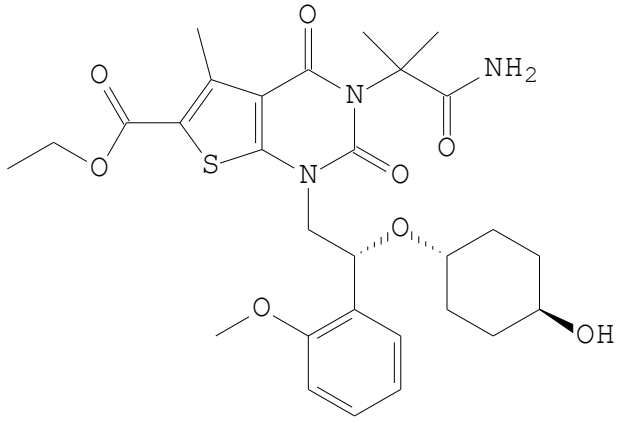
I-195		
I-196		
I-197		

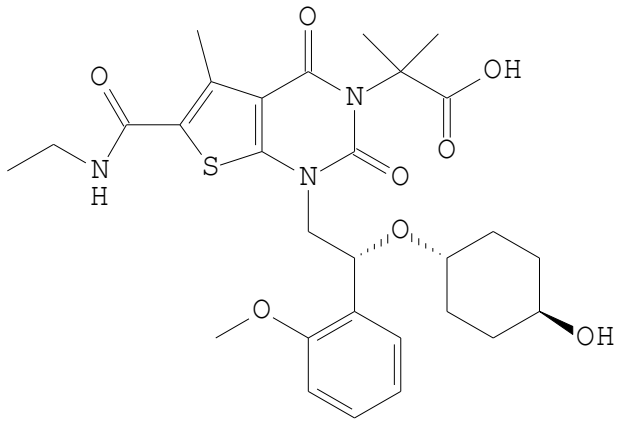
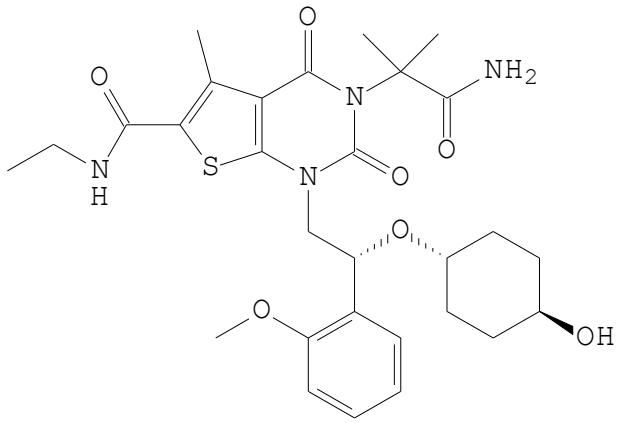
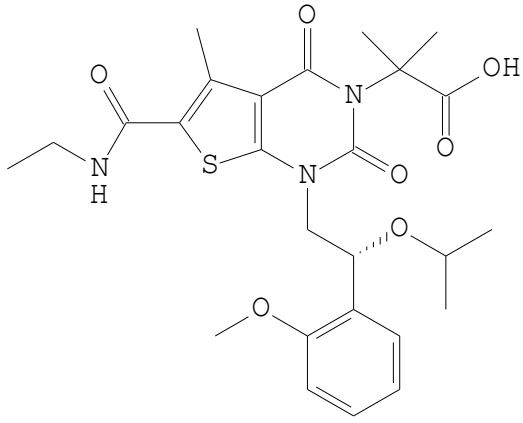
I-198		
I-199		
I-200		

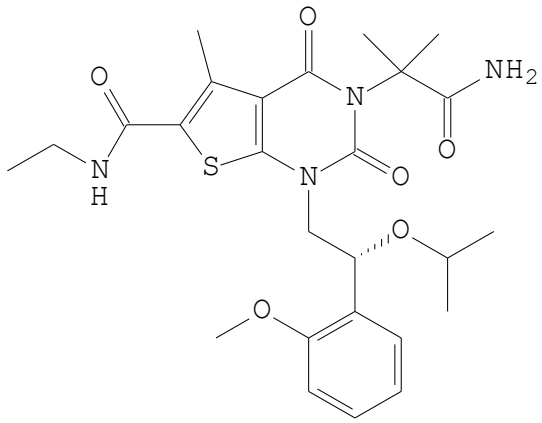
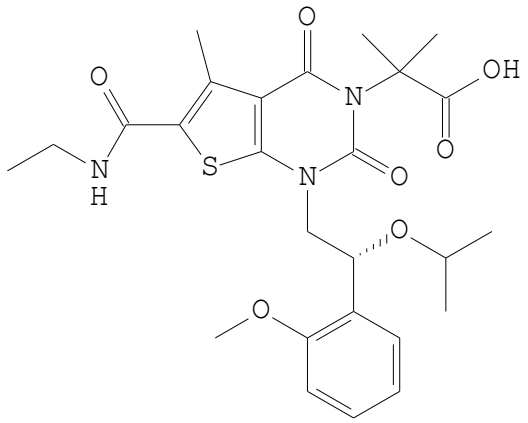
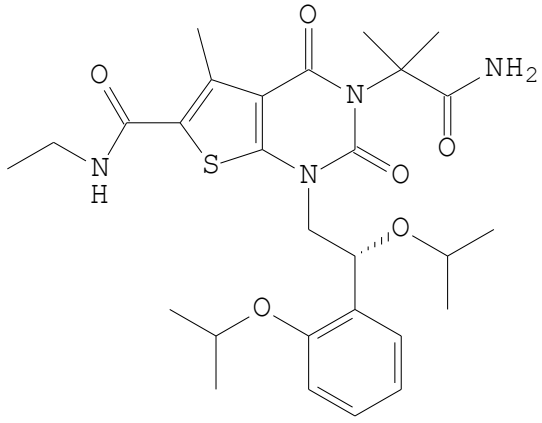
I-201		
I-202		
I-203		

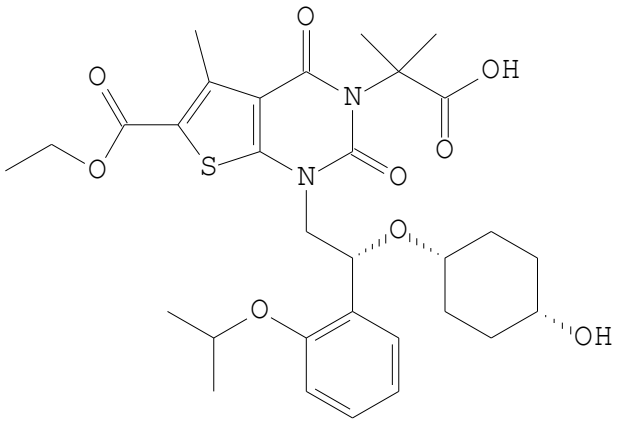
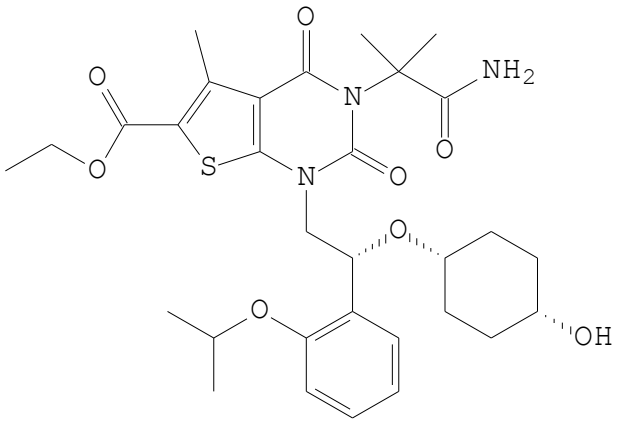
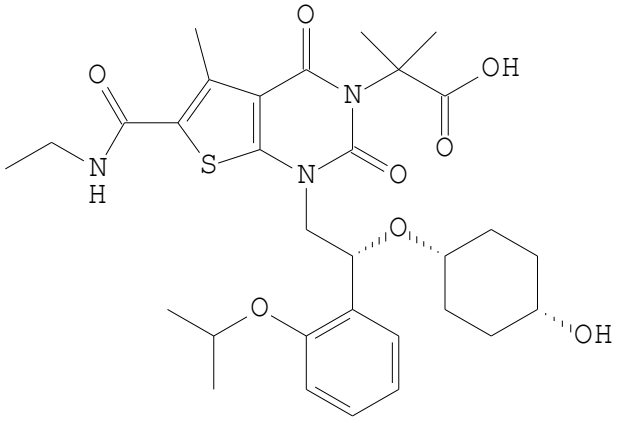
I-204		
I-205		
I-206		

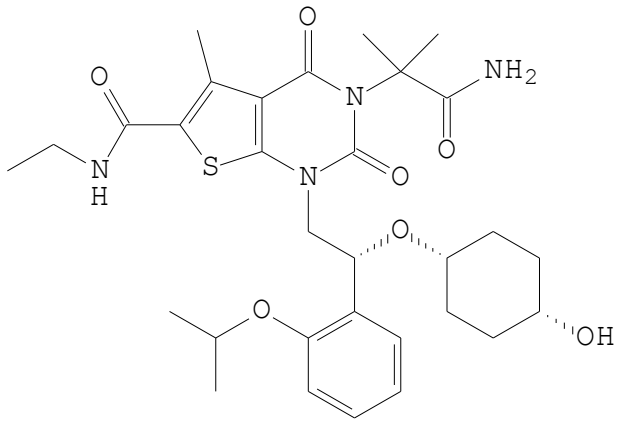
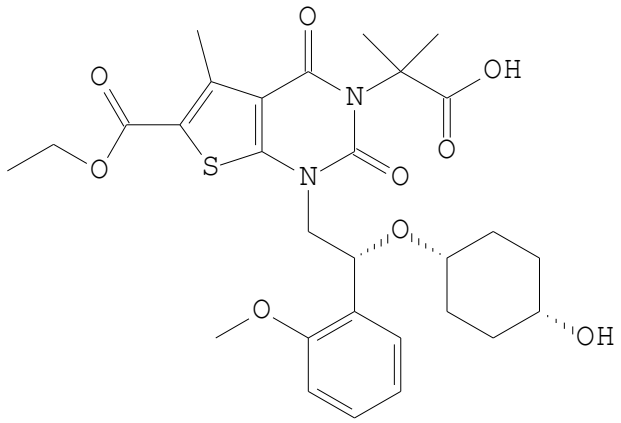
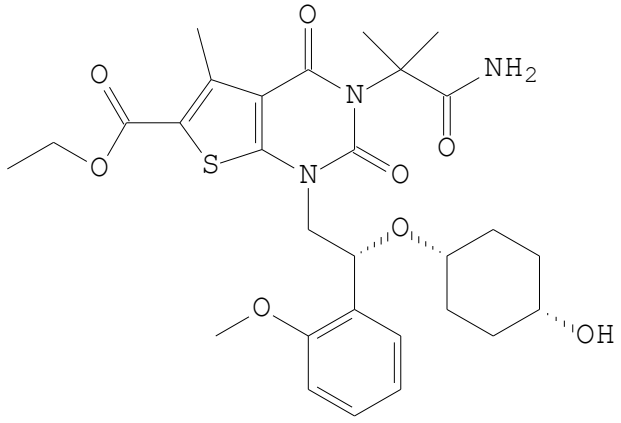
I-207		
I-208		
I-209		

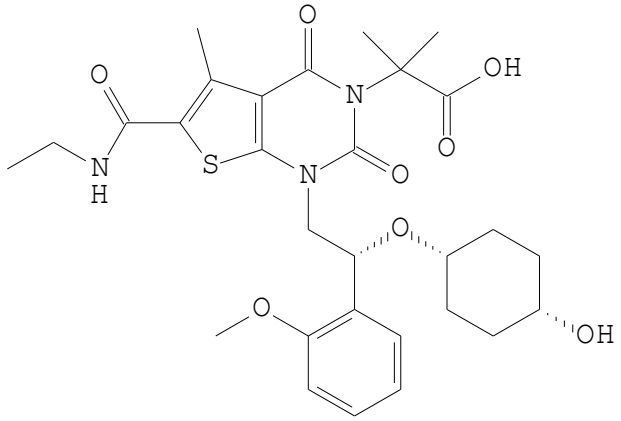
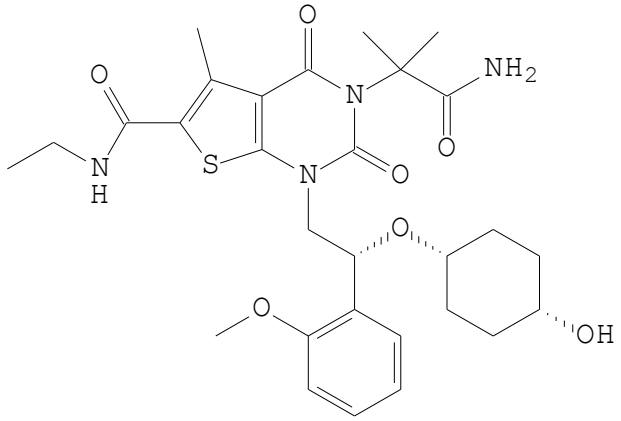
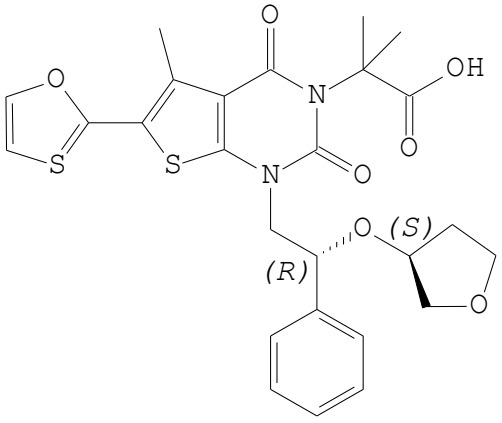
I-210		
I-211		
I-212		

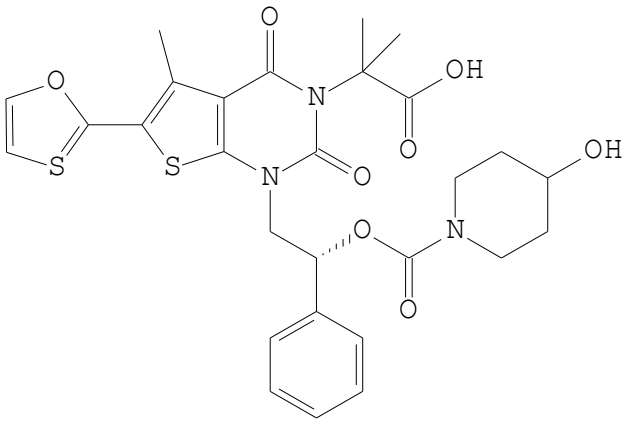
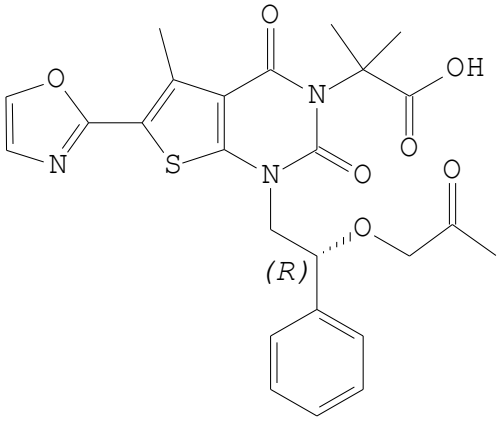
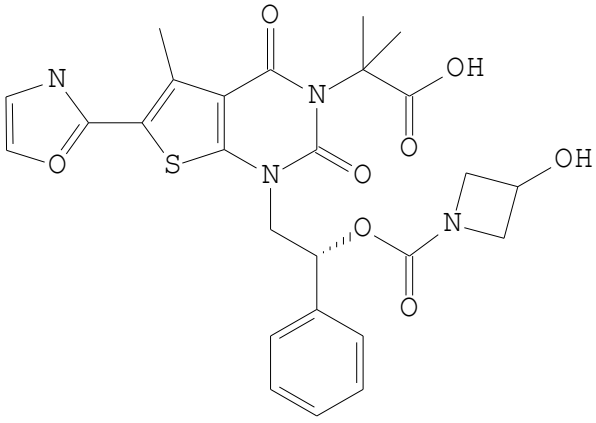
I-213		
I-214		
I-215		

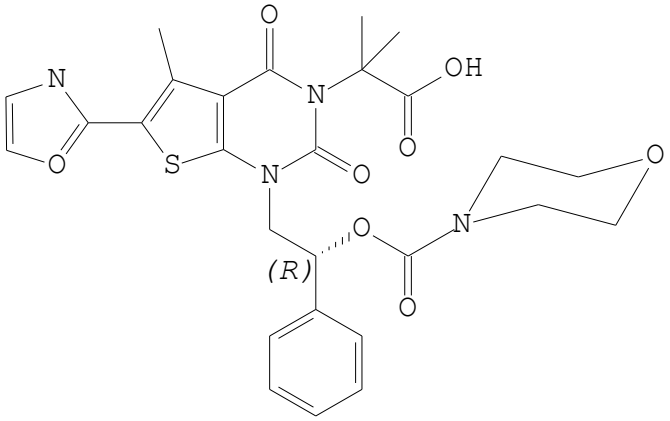
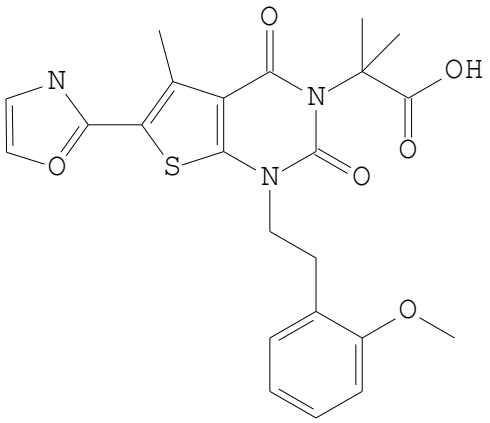
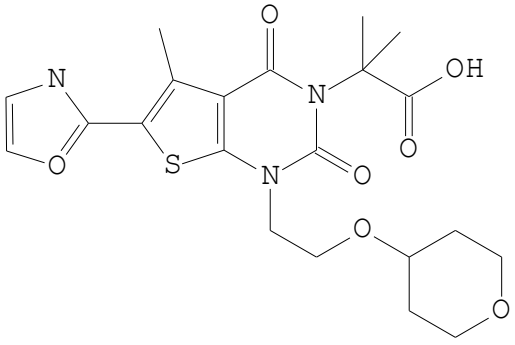
I-216		
I-217		
I-218		

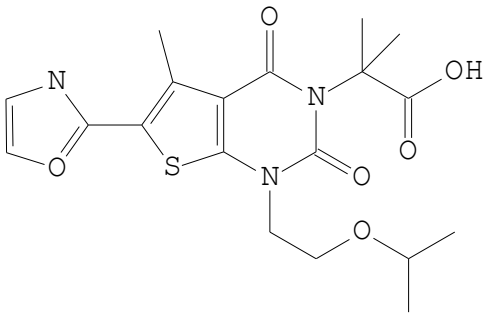
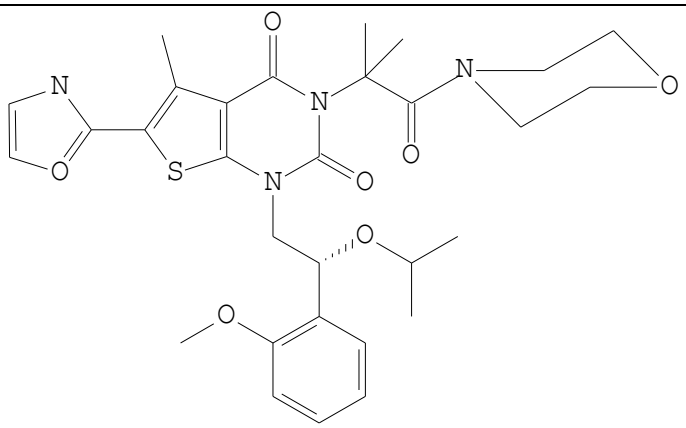
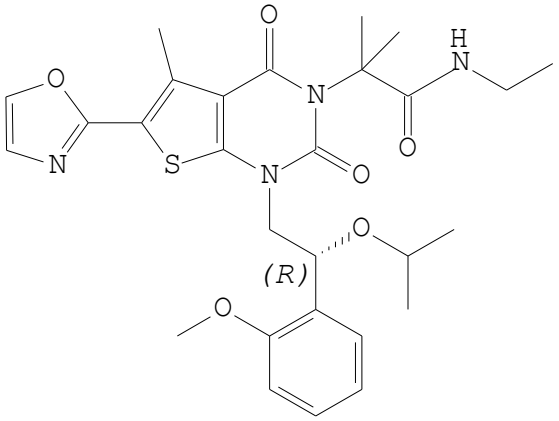
I-219		
I-220		
I-221		

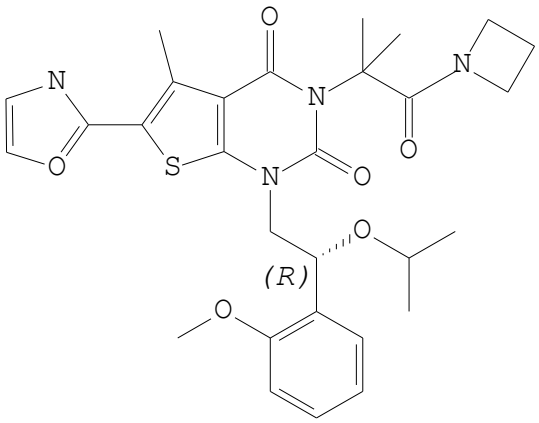
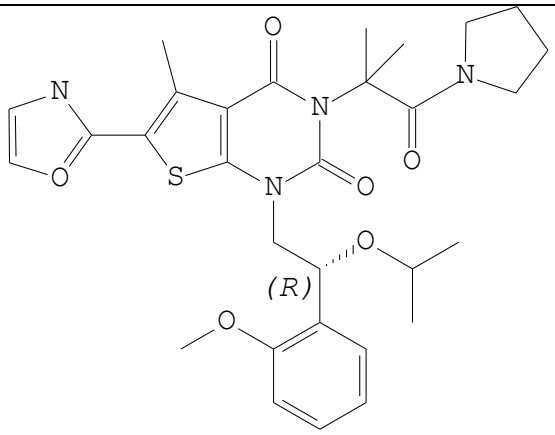
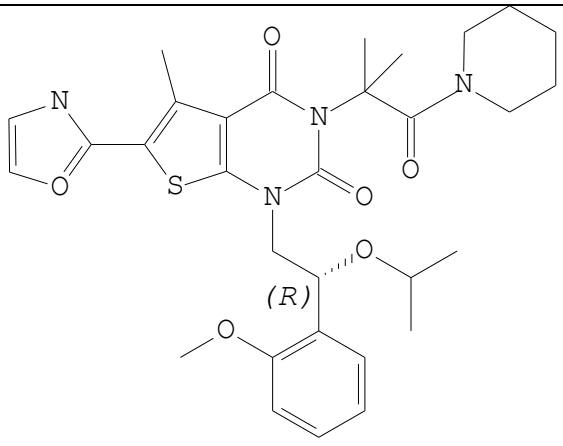
I-222		
I-223		
I-224		

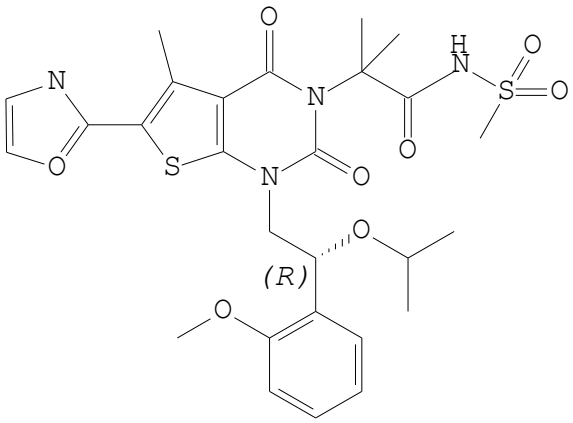
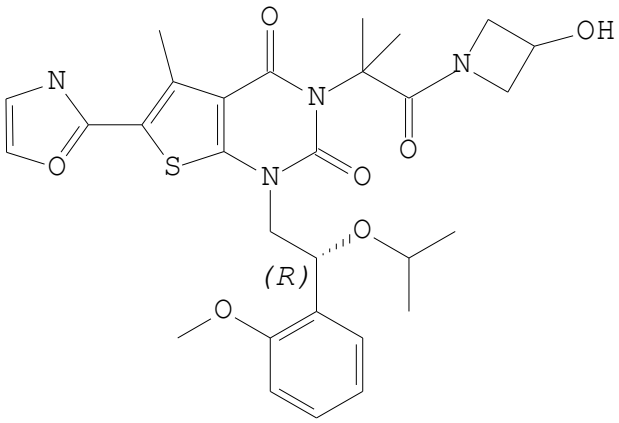
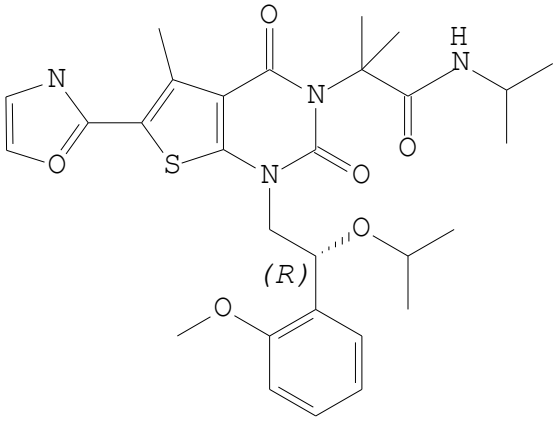
I-225		
I-226		
I-227		526 $(M+H)^+$,

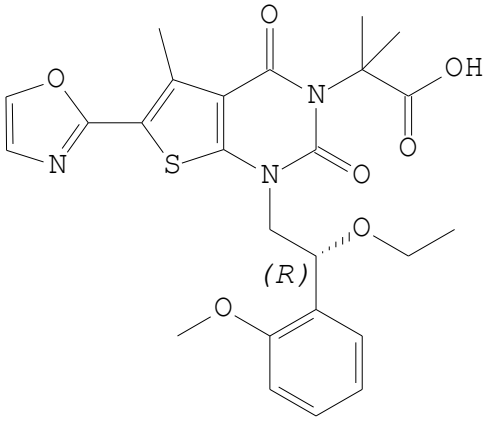
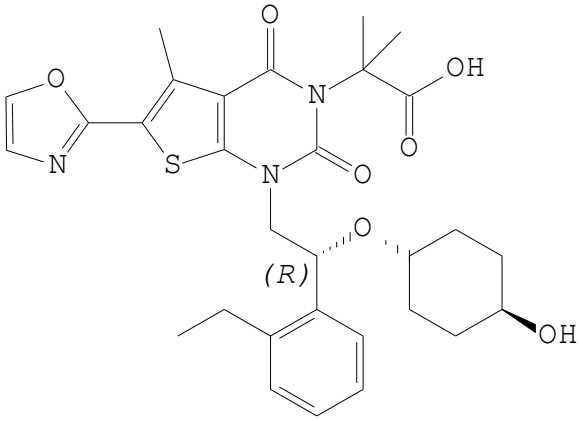
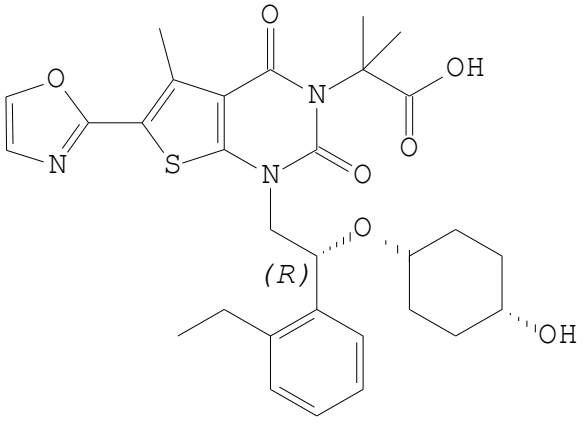
I-228		583 $(M+H)^+$,
I-229		512 $(M+H)^+$,
I-230		555 $(M+H)^+$,

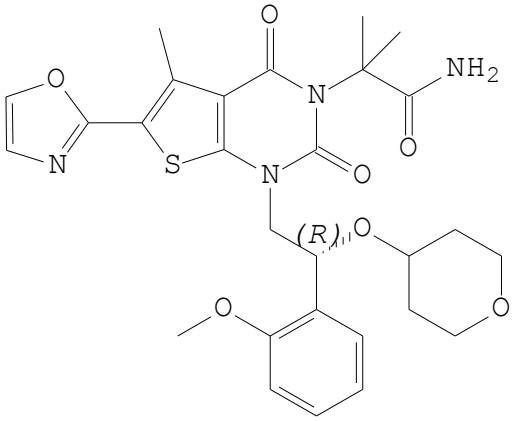
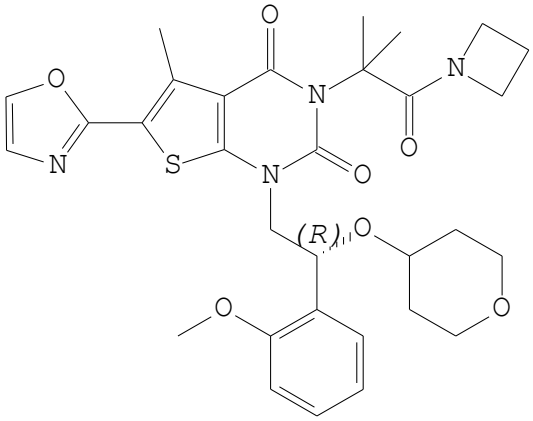
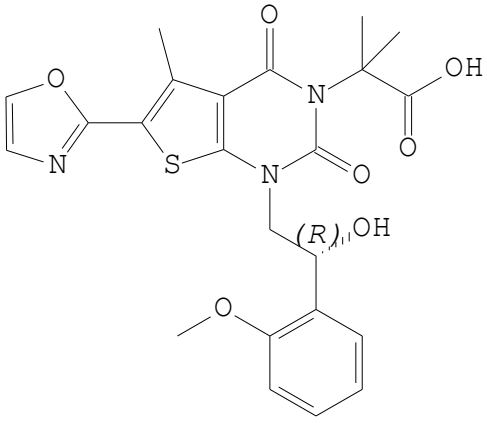
I-231		569 $(M+H)^+$,
I-232		470 $(M+H)^+$,
I-233		464 $(M+H)^+$,

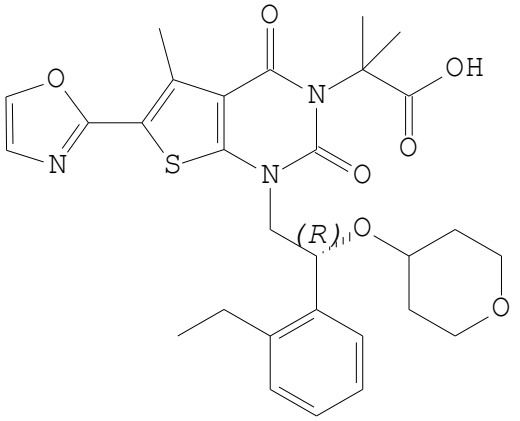
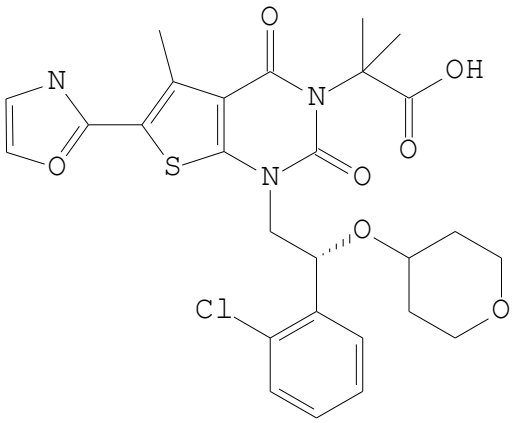
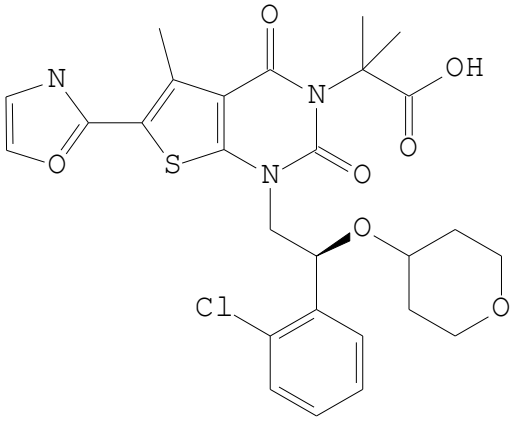
I-234		423 $(M+H)^+$,
I-235		619 $(M+H)^+$,
I-236		577 $(M+H)^+$,

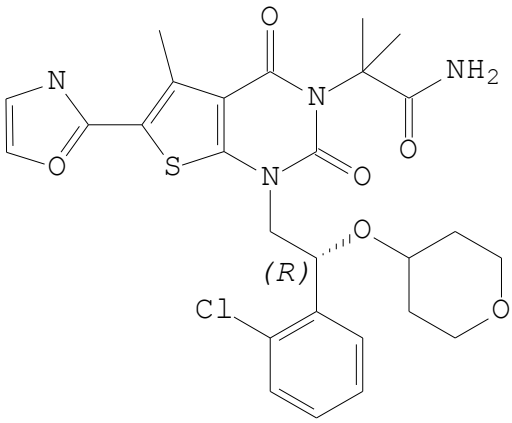
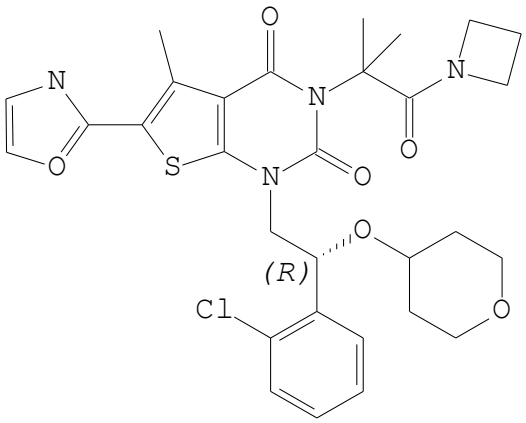
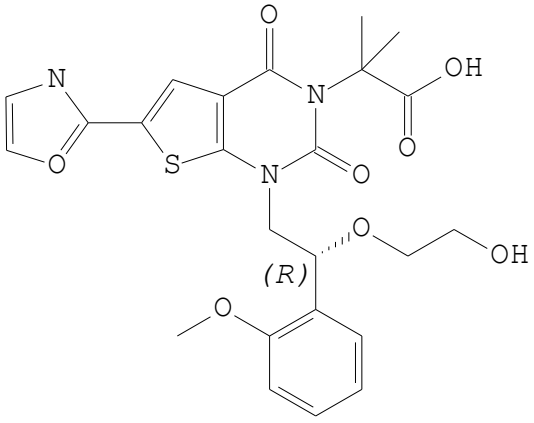
I-237		568 $(M+H)^+$,
I-238		603 $(M+Na)^+$,
I-239		617 $(M+Na)^+$

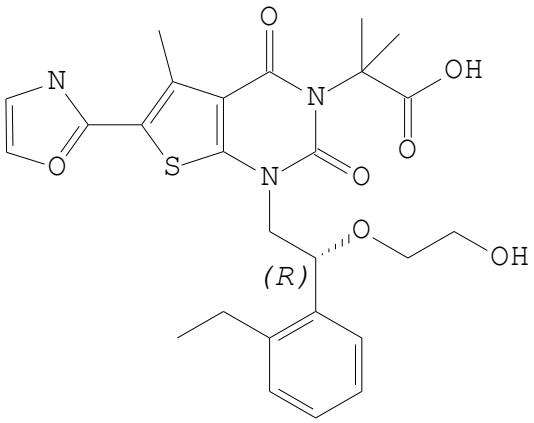
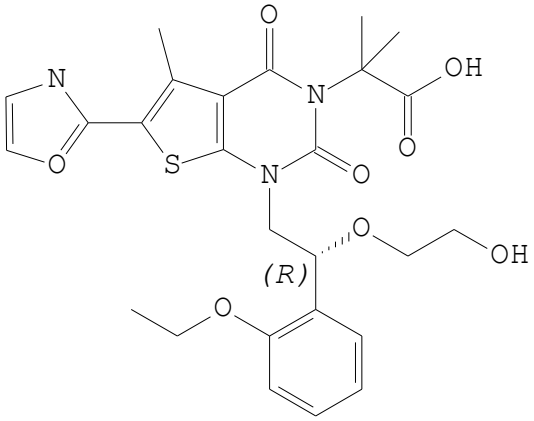
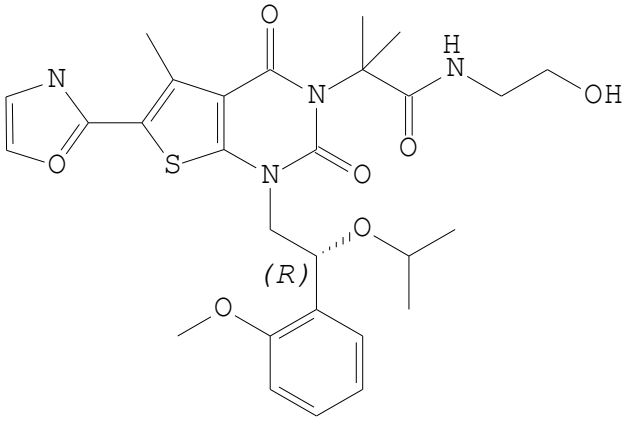
I-240		605 $(M+Na)^+$
I-241		605 $(M+Na)^+$
I-242		591 $(M+Na)^+$

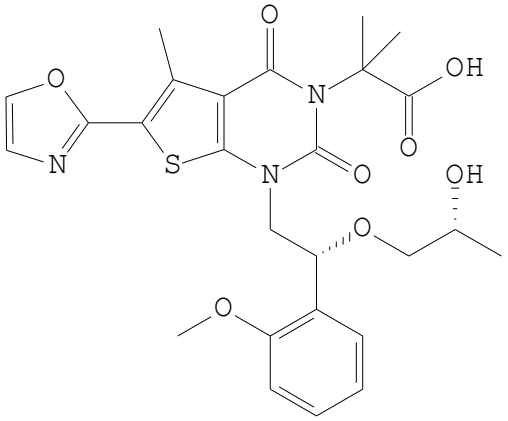
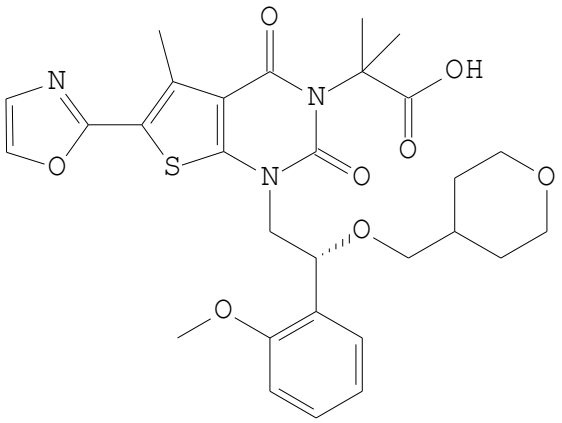
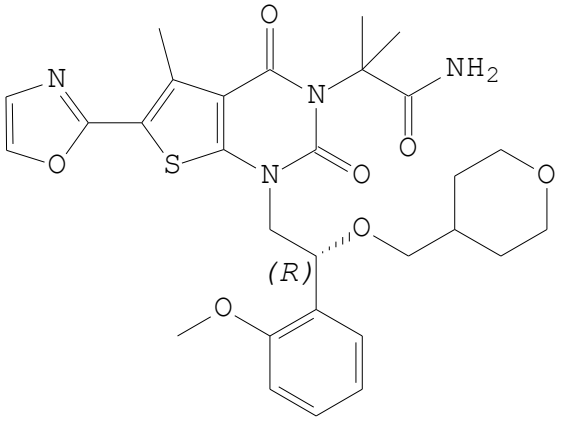
I-243		514 $(M+Na)^+$
I-244		582 $(M+Na)^+$
I-245		582 $(M+Na)^+$

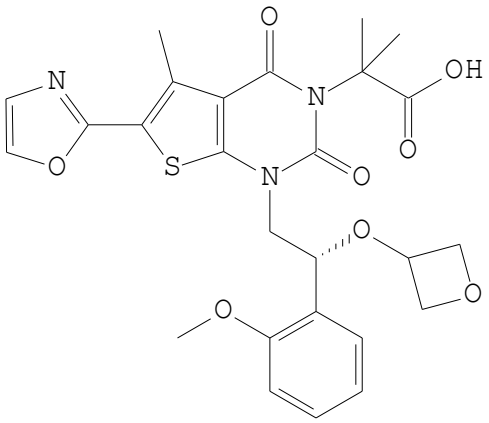
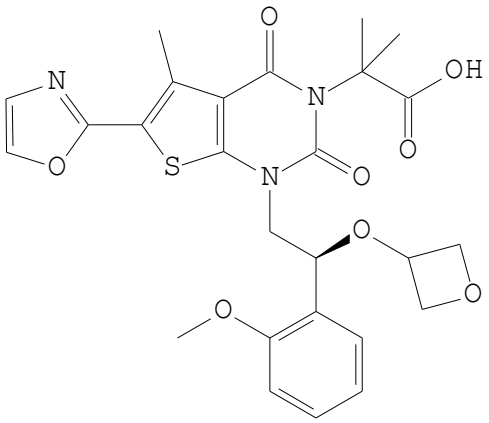
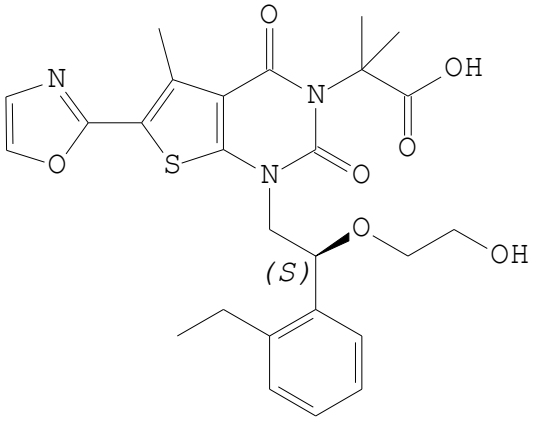
I-246		591 $(M+Na)^+$
I-247		609 $(M+H)^+$
I-248		586 $(M+H)^+$

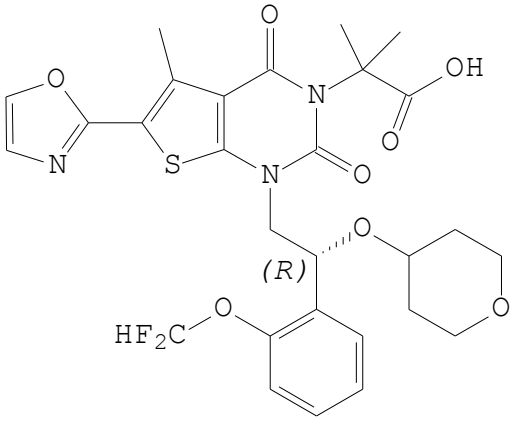
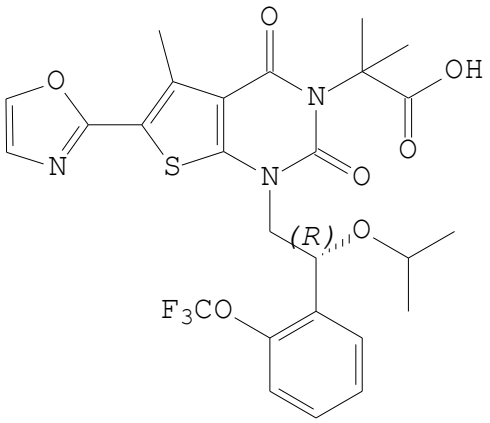
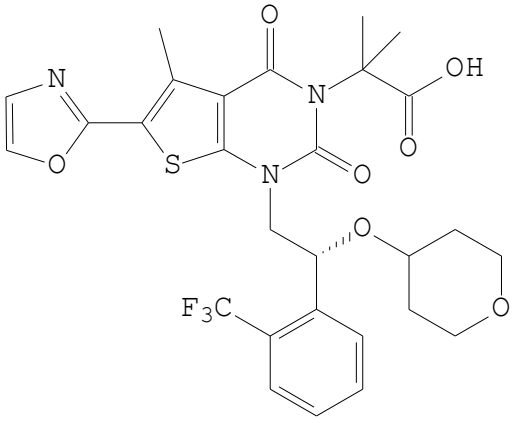
I-249		568 $(M+H)^+$
I-250		574 $(M+Na)^+$
I-251		574 $(M+H)^+$

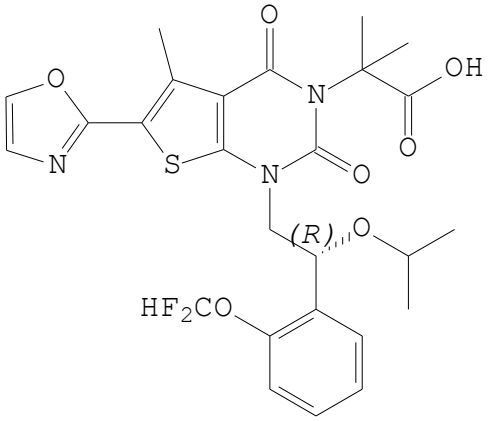
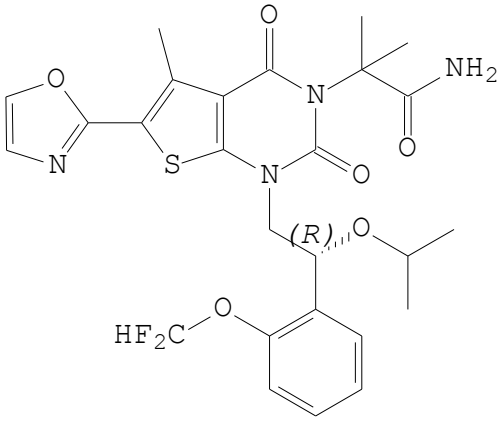
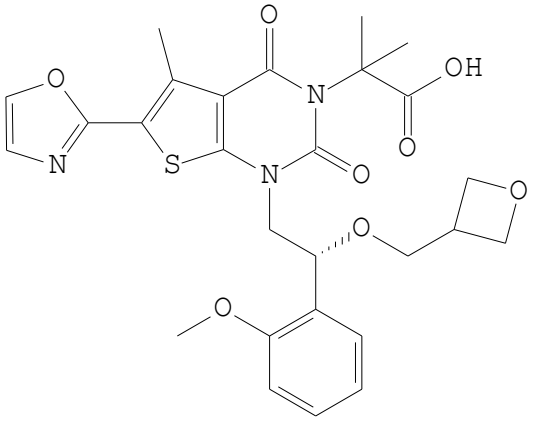
I-252		595 $(M+Na)^+$
I-253		613 $(M+H)^+$
I-254		530 $(M+H)^+$

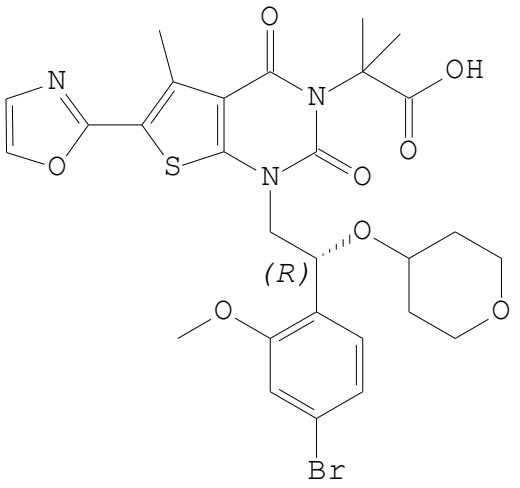
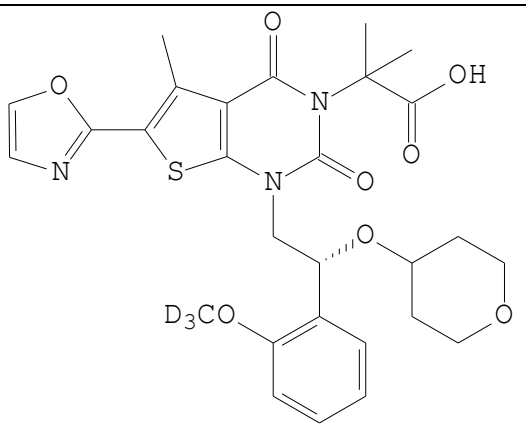
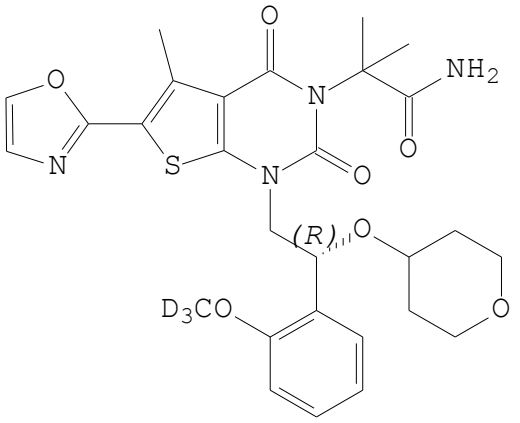
I-255		528 $(M+H)^+$
I-256		544 $(M+H)^+$
I-257		571 $(M+H)^+$

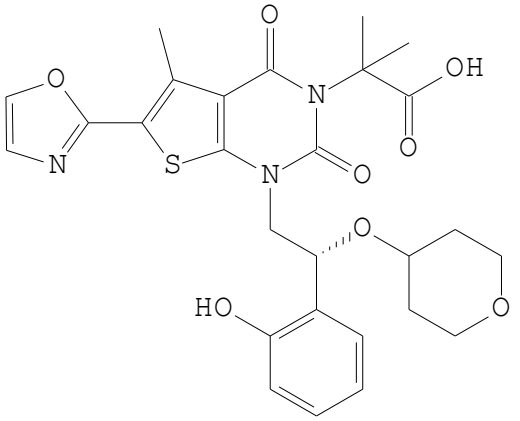
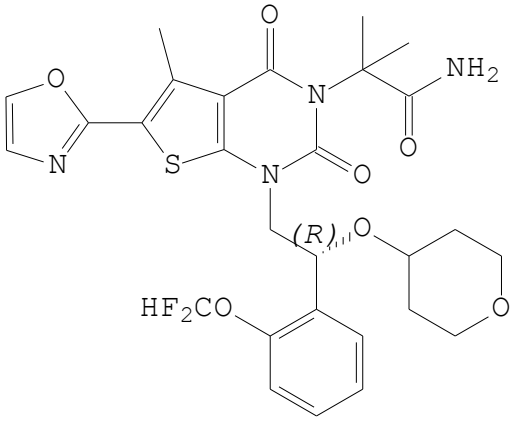
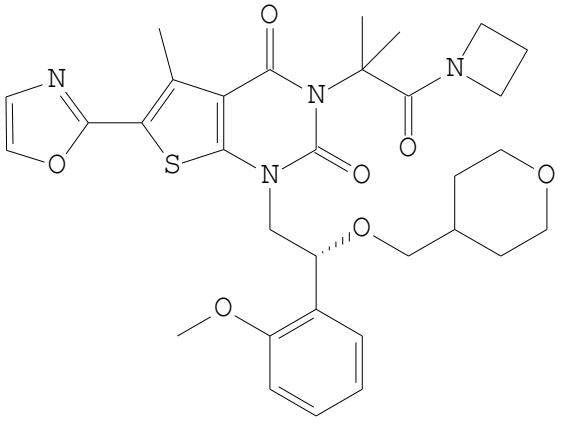
I-258		544 $(M+H)^+$
I-259		584 $(M+H)^+$
I-260		583 $(M+H)^+$

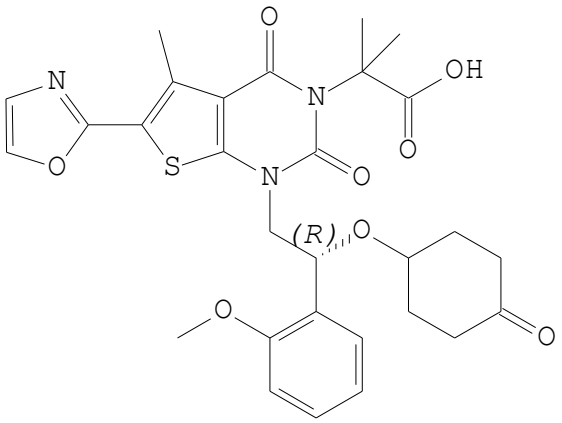
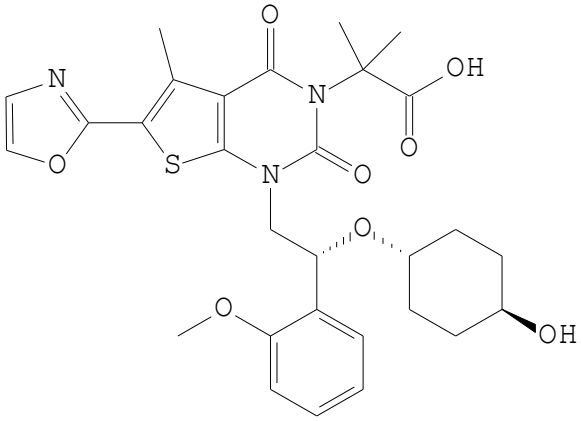
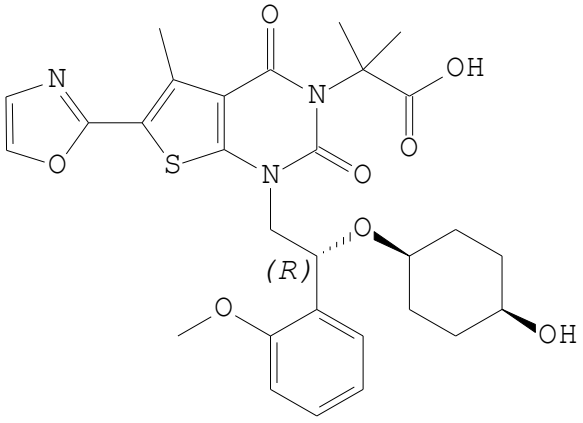
I-261		542 $(M+H)^+$
I-262		542 $(M+H)^+$
I-263		528 $(M+H)^+$

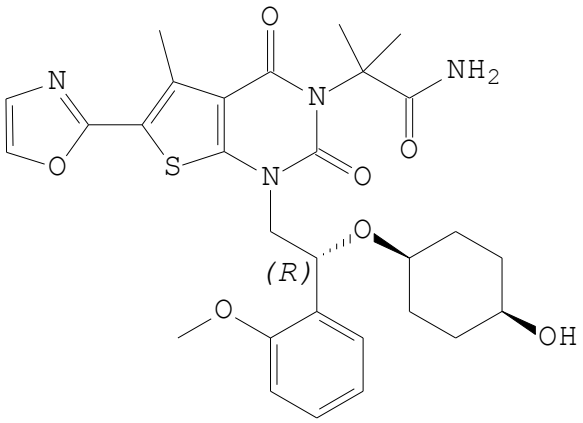
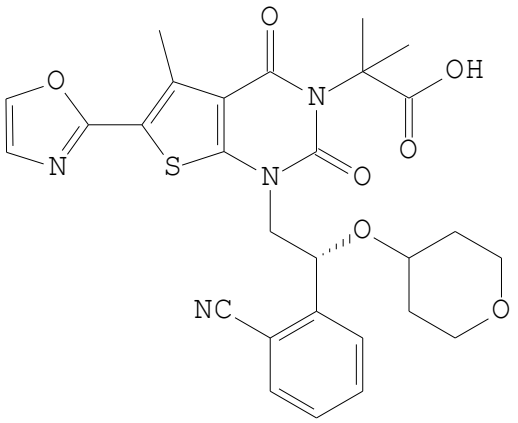
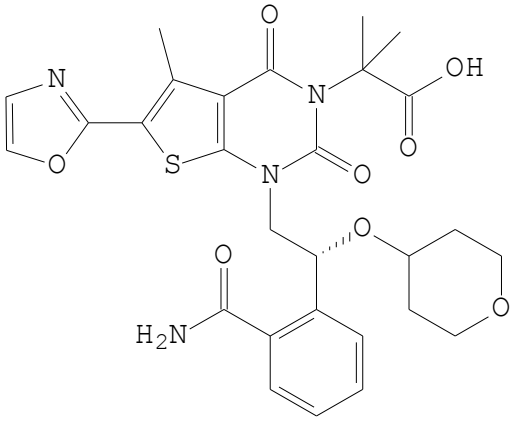
I-264		607 $(M+H)^+$
I-265		582 $(M+H)^+$
I-266		608 $(M+H)^+$

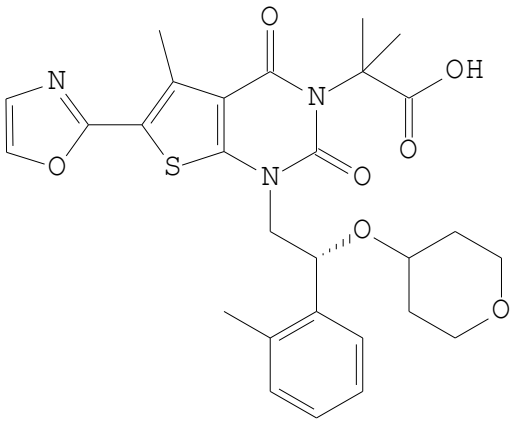
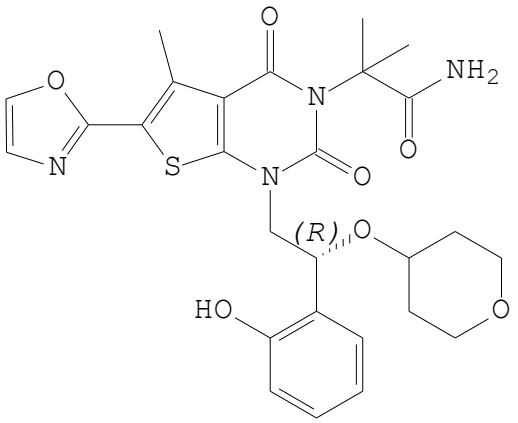
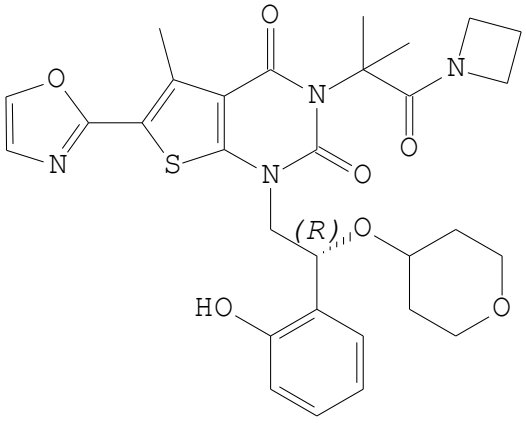
I-267		564 $(M+H)^+$
I-268		563 $(M+H)^+$
I-269		556 $(M+H)^+$

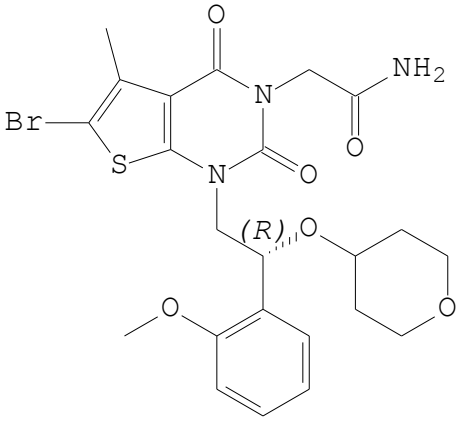
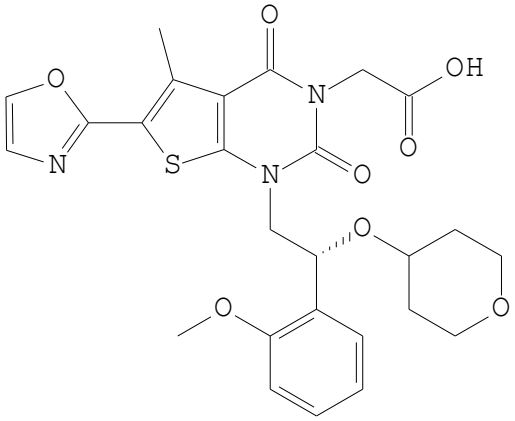
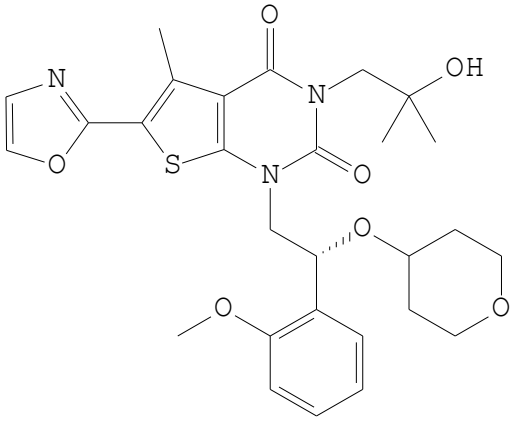
I-270		650 $(M+H)^+$
I-271		573 $(M+H)^+$
I-272		594 $(M+Na)^+$

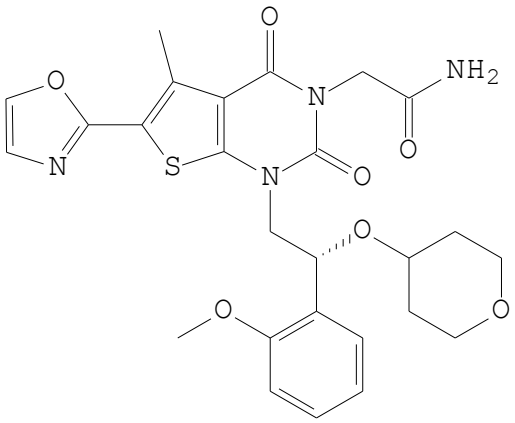
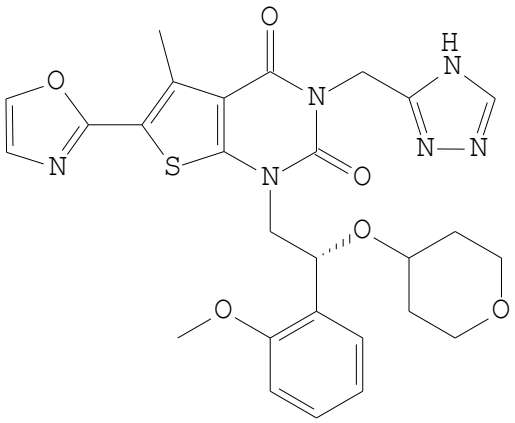
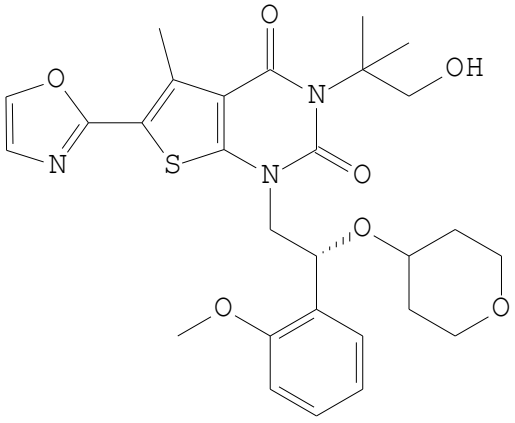
I-273		556 $(M+H)^+$
i-274		627 $(M+Na)^+$
I-275		623 $(M+H)^+$

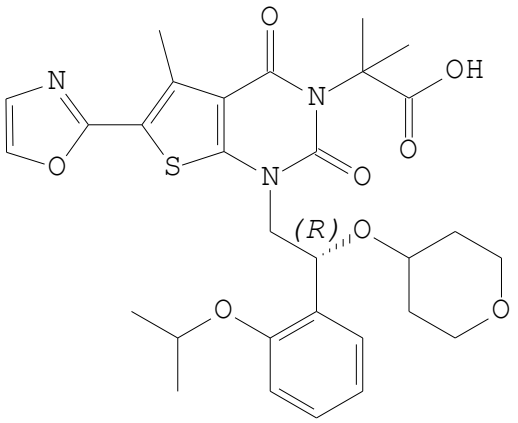
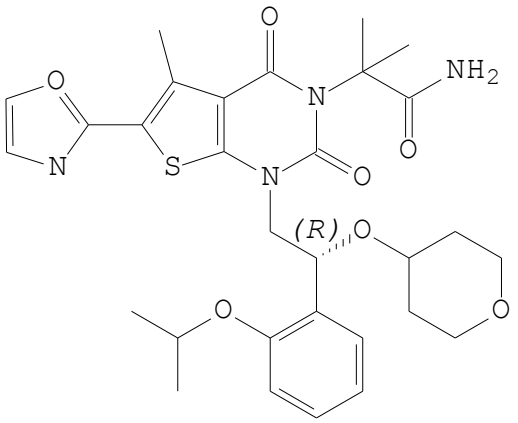
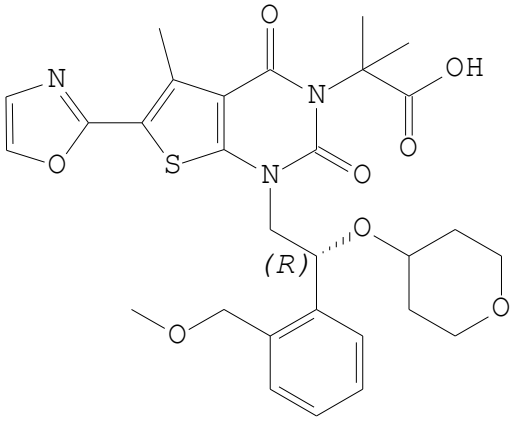
I-276		582 $(M+H)^+$
I-277		584 $(M+H)^+$
I-278		584 $(M+H)^+$

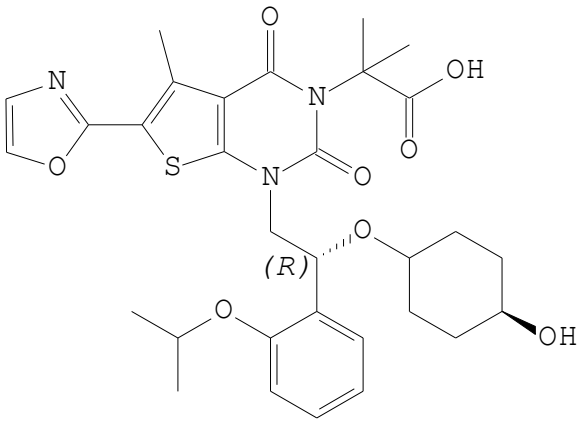
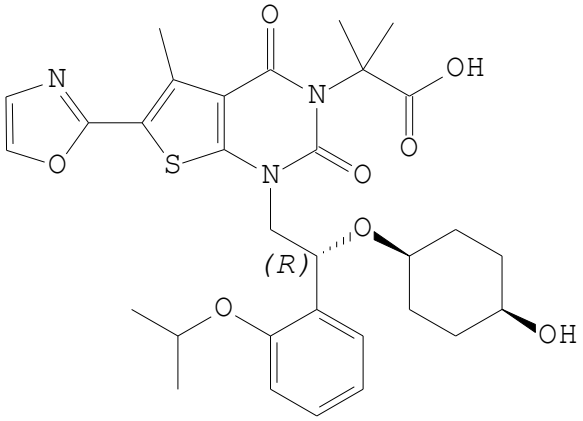
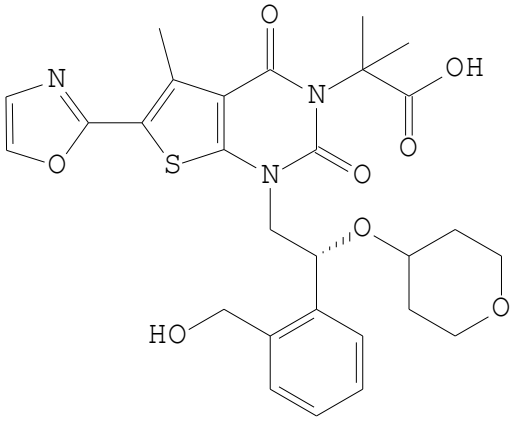
I-279		605 $(M+Na)^+$
I-280		565 $(M+H)^+$
I-281		583 $(M+H)^+$

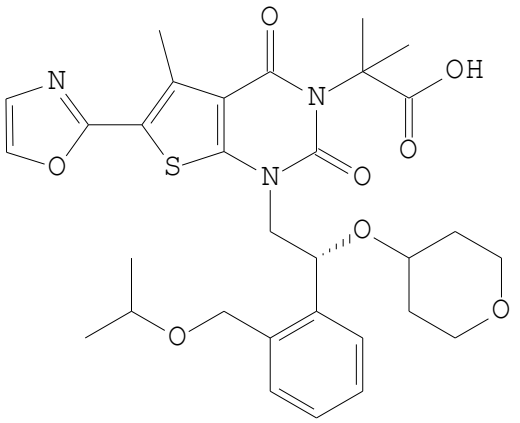
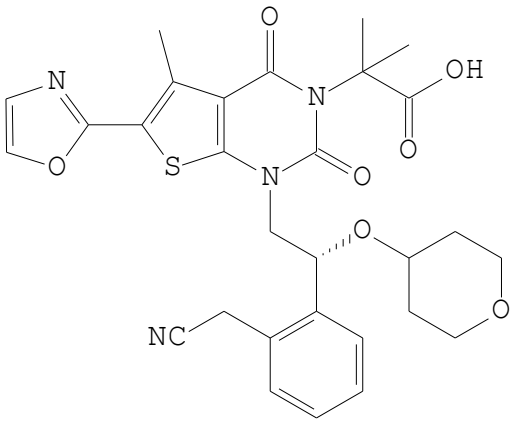
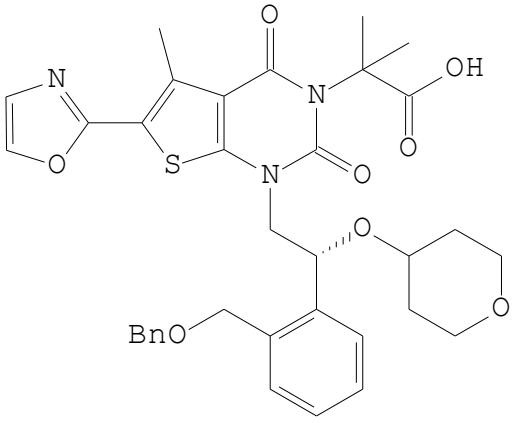
I-282		554 $(M+H)^+$
I-283		577 $(M+Na)^+$
I-284		595 $(M+H)^+$

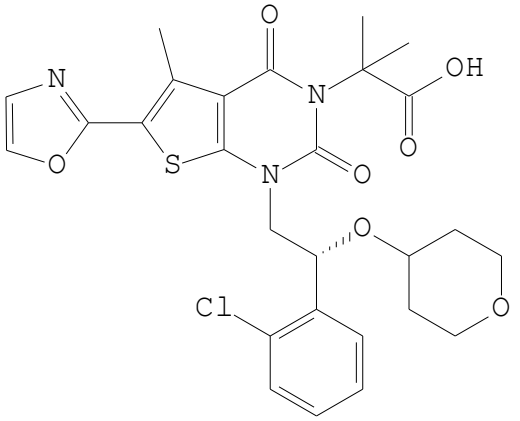
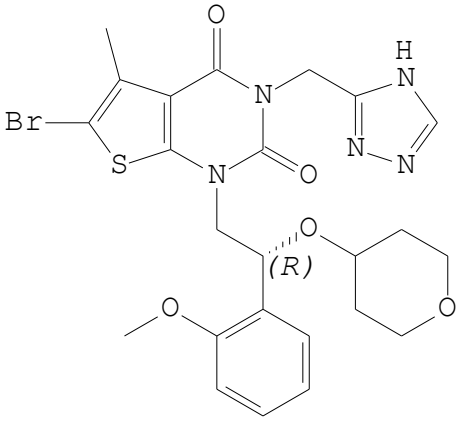
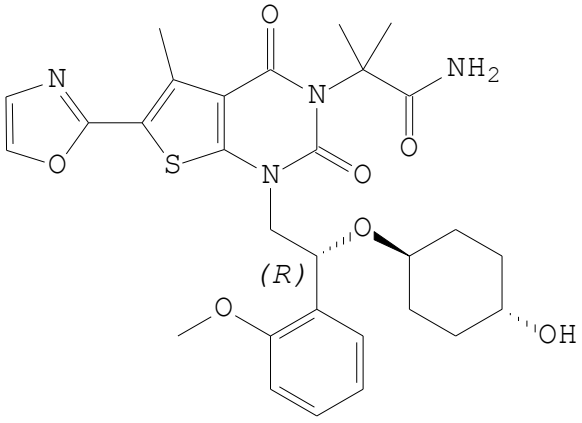
I-285		554, 552 $(M+H)^+$
I-286		542 $(M+H)^+$
I-287		556 $(M+H)^+$

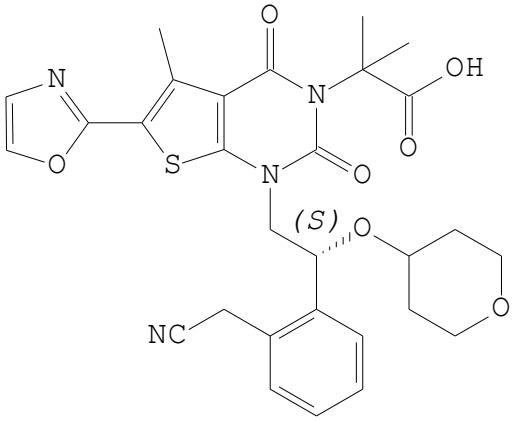
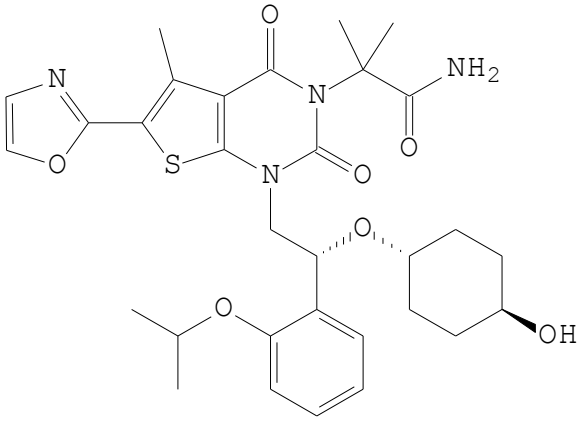
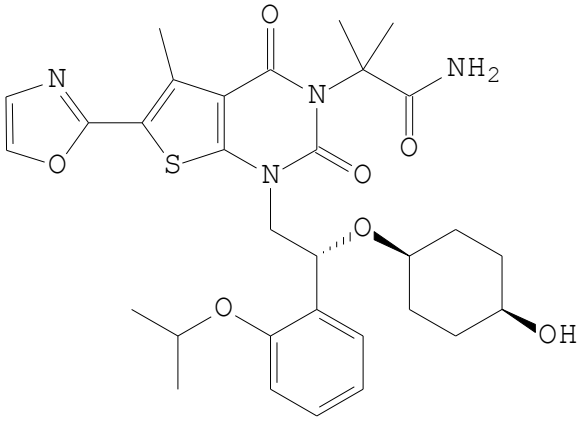
I-288		541 $(M+H)^+$
I-289		565 $(M+H)^+$
I-290		556 $(M+H)^+$

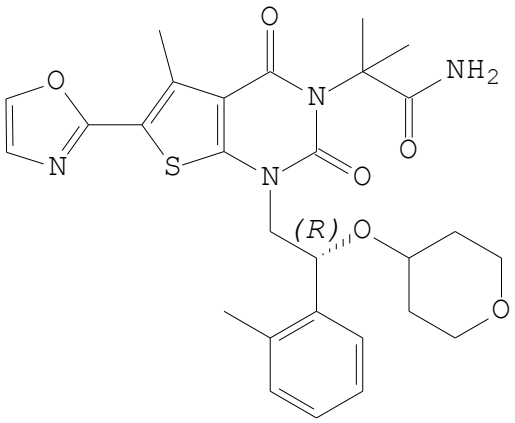
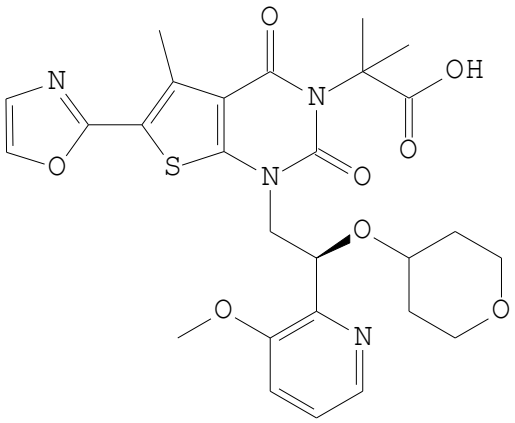
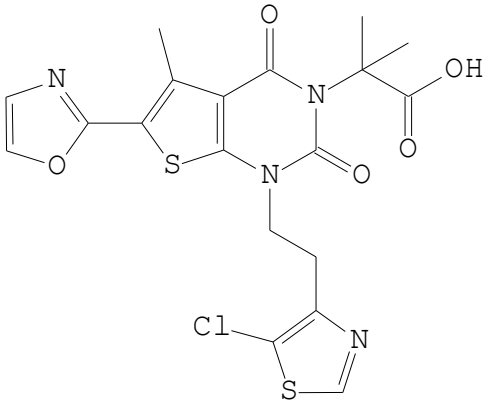
I-291		598 $(M+H)^+$
I-292		619 $(M+Na)^+$
I-293		606 $(M+Na)^+$

I-294		612 $(M+H)^+$
I-295		612 $(M+H)^+$
I-296		592 $(M+Na)^+$

I-297		634 $(M+Na)^+$
I-298		579 $(M+H)^+$
I-299		

I-300		574 $(M+H)^+$
I-301		576 $(M+H)^+$
I-302		605 $(M+Na)^+$

I-303		579 $(M+H)^+$
I-304		633 $(M+Na)^+$
I-305		633 $(M+Na)^+$

I-306		575 $(M+Na)^+$
I-307		593 $(M+Na)^+$
I-308		481 $(M+H)^+$

En ciertas modalidades, la presente invención proporciona cualquier compuesto que se selecciona de los mostrados en la tabla 1 anterior o una sal farmacéuticamente

aceptable del mismo.

4. USOS, FORMULACIÓN Y ADMINISTRACIÓN Y COMPOSICIONES FARMACÉUTICAMENTE ACEPTABLES

De acuerdo con otra modalidad, la invención proporciona una composición que comprende un compuesto de esta invención o las formas farmacéuticamente aceptables de una sal, éster o una sal de éster del mismo y un portador, adyuvante o vehículo farmacéuticamente aceptable. La cantidad de compuestos en composiciones de esta invención es tal que es eficaz para inhibir de manera mensurable ACC en una muestra biológica o en un paciente. En ciertas modalidades, la cantidad de compuesto en composiciones de esta invención es tal que es eficaz para inhibir de manera mensurable ACC, en una muestra biológica o en un paciente. En ciertas modalidades, una composición de esta invención se formula para administración al paciente en necesidad de esta composición. En algunas modalidades, una composición de esta invención se formula para administración oral a un paciente.

El término "paciente", como se utiliza en la presente significa un animal, preferiblemente un mamífero y de manera más preferible un humano.

El término "portador, adyuvante o vehículo farmacéuticamente aceptable" se refiere a un portador, adyuvante o vehículo no tóxico que no destruye la actividad farmacológica del compuesto con el cual está formulado.

Los portadores, adyuvantes o vehículos farmacéuticamente aceptables que se pueden utilizar en composiciones de esta invención incluyen pero no se limitan a intercambiadores de iones, alúmina, estearato de aluminio, lecitina, proteínas de suero tales como albúmina sérica humana, sustancias amortiguadoras tales como fosfatos, glicina, ácido sórbico, sorbato de potasio, mezcla de glicéridos parciales de ácidos grasos vegetales saturados, agua, sales o electrolitos tales como sulfato de protamina, fosfato ácido disódico, fosfato ácido de potasio, cloruro de sodio, sales de zinc, sílice coloidal, trisilicato de magnesio, polivinilpirrolidona, sustancias basadas en celulosa, polietilenglicol, carboximetilcelulosa de sodio, poliacrilatos, ceras, polímeros de bloque de polietileno-polioxipropileno, polietilenglicol y grasa de lana.

Un "derivado farmacéuticamente aceptable" significa cualquier forma no tóxica de sal, éster, sal de un éster u otro derivado de un compuesto de esta invención que, ante la administración a un receptor, es capaz de proporcionar, directa o indirectamente, un compuesto de esta invención o un metabolito activo inhibidor o un residuo del mismo. Como se utiliza en la presente, el término "metabolito activo inhibidor o residuo del mismo" significa que un metabolito o residuo del mismo también es un inhibidor de ACC.

Las composiciones de la presente invención se pueden

administrar por vía oral, parenteral o por inhalación, aspersión, por vía tópica, rectal, nasal, bucal, vaginal o por medio de un depósito implantado. El término "parenteral", como se utiliza en la presente, incluye las vías subcutánea, intravenosa, intramuscular, intraarticular, intrasinovial, intrasternal, intratecal, intrahepática, intralesional e inyección intracraneal o técnicas de infusión. Preferiblemente, las composiciones son administradas por vía oral, intraperitoneal o intravenosa. Las formas inyectables estériles de las composiciones de esta invención pueden ser una suspensión acuosa u oleaginosa. Estas suspensiones se pueden formular de acuerdo con técnicas conocidas en el ámbito utilizando agentes adecuados de dispersión o humedecimiento y agentes de suspensión. La preparación inyectable estéril también puede ser una solución o suspensión inyectable estéril en un diluyente o disolvente parenteralmente aceptable, no tóxico, por ejemplo como una solución en 1,3-butanodiol. Entre los vehículos y disolventes aceptables que se pueden utilizar están en el agua, solución de Ringer o solución isotónica de cloruro de sodio. Además, los aceites fijos estériles se utilizan convencionalmente como un medio disolvente o de suspensión.

Para este propósito, cualquier aceite fijo blando puede ser utilizado que incluye mono- o di-glicéridos sintéticos. Los ácidos grasos tales como ácido oleico y sus

derivados de glicéridos son útiles en la preparación de inyectables así como los aceites naturales farmacéuticamente aceptables tales como aceite de oliva o aceite de ricino, especialmente en sus versiones polioxietiladas. Estas soluciones o suspensiones de aceite también pueden contener un diluyente o dispersante de alcohol de cadena larga tal como carboximetilcelulosa o agentes dispersantes similares que son utilizados habitualmente en la formulación de formas de dosificación farmacéuticamente aceptables que incluyen emulsiones y suspensiones. Otros tensioactivos utilizados comúnmente tales como Tweens, Spans y otros agentes emulsificantes o mejoradores de biodisponibilidad los cuales se utilizan comúnmente en la elaboración de formas de dosificación sólidas, líquidas u otras farmacéuticamente aceptables también se pueden utilizar para los propósitos de la formulación.

Las composiciones farmacéuticamente aceptables de esta invención pueden ser administradas oralmente en una forma de dosificación oralmente aceptable que incluye, pero que no se limita a cápsulas, tabletas, suspensiones o soluciones acuosas. En el caso de tabletas para uso oral, los portadores utilizados habitualmente incluyen lactosa y almidón de maíz. Los agentes lubricantes tales como estearato de magnesio también se agregan típicamente. Para administración oral en forma de cápsula, los diluyentes útiles incluyen lactosa y

almidón de maíz seco. Cuando se requieren suspensiones acuosas para uso oral, el ingrediente activo se combina con agentes emulsificantes y de suspensión. Si se desea, también se pueden agregar ciertos agentes edulcorantes, saborizantes o colorantes.

De manera alternativa, las composiciones farmacéuticamente aceptables de esta invención se pueden administrar en la forma de supositorios para administración rectal. Estos se pueden preparar al mezclar el agente con un excipiente no irritante adecuado que es sólido a temperatura ambiente pero líquido a temperatura rectal y por lo tanto se fundirá en el recto para liberar el fármaco. Estos materiales incluyen manteca de cacao, cera de abejas y polietilenglicoles.

Las composiciones farmacéuticamente aceptables de esta invención también se pueden administrar por vía tópica, especialmente cuando el objetivo de tratamiento incluye áreas u órganos accesibles fácilmente por aplicación tópica que incluyen enfermedades de los ojos, la piel o el tracto intestinal inferior. Las formulaciones tópicas adecuadas se preparan fácilmente para cada una de estas áreas u órganos.

La aplicación total para el tracto intestinal inferior se puede llevar a cabo en una formulación de supositorio rectal (véase antes) o en una formulación de enema adecuada. También se pueden utilizar parches tópicamente

transdérmicos.

Para aplicaciones tópicas, las composiciones farmacéuticamente aceptables proporcionadas se pueden formular en un ungüento adecuado que contenga el componente activo suspendido o disuelto en uno o más portadores. Los portadores para administración tópica de compuestos de esta invención incluyen, pero no se limitan a aceite mineral, petrolato líquido, petrolato blanco, propilenglicol, polioxietileno, compuesto de polioxipropileno, cera emulsificante y agua. De manera alternativa, las composiciones farmacéuticamente aceptables proporcionadas se pueden formular en una loción o crema adecuada que contenga los componentes activos suspendidos o disueltos en uno o más portadores farmacéuticamente aceptables. Los portadores adecuados incluyen, pero no se limitan a aceite mineral, monoestearato de sorbitán, polysorbate 60, cera de ésteres de cetilo, alcohol cetearílico, 2-octildodecano, alcohol bencílico y agua.

Para uso oftálmico, las composiciones farmacéuticamente aceptables proporcionadas se pueden formular como suspensiones micronizadas en solución salina estéril ajustada de pH, isotónica o, preferiblemente, como soluciones en solución salina estéril ajustada de pH isotónica, ya sea con o sin un conservador tal como cloruro de benzalconio. De manera alternativa, para usos oftálmicos, las composiciones

farmacéuticamente aceptables se pueden formular en un ungüento tal como petrolato.

Las composiciones farmacéuticamente aceptables de esta invención también se pueden administrar por aerosol nasal o inhalación. Tales composiciones se preparan de acuerdo con técnicas bien conocidas en el ámbito de la formulación farmacéutica y se pueden preparar como soluciones en solución salina, utilizando alcohol bencílico u otros conservadores adecuados, promotores de absorción para mejorar la biodisponibilidad, fluorocarburos y/u otros agentes convencionales solubilizantes o dispersantes.

De manera más preferible, las composiciones farmacéuticamente aceptables de esta invención se formulan para administración oral. Estas formulaciones se pueden administrar con o sin alimentos. En algunas modalidades, las composiciones farmacéuticamente aceptables de esta invención se administran sin alimentos. En otras modalidades, las composiciones farmacéuticamente aceptables de la invención se administran con alimentos.

La cantidad de compuestos de la presente invención que se pueden combinar con los materiales portadores para producir una composición en una forma de dosificación única variarán dependiendo del hospedador tratado, el modo de administración particular. De manera preferible, las composiciones que se proporcionan se deben formular de manera

que se pueda administrar una dosificación de entre 0.01 a 100 mg/kg de peso corporal/día del inhibidor a un paciente que recibe las composiciones.

También debe entenderse que una dosificación específica y un régimen de tratamiento para cualquier paciente particular dependerá de una diversidad de factores que incluyen la actividad del compuesto específico utilizado, la edad, el peso corporal, la salud general, sexo, dieta, hora de administración, velocidad de excreción, combinación con otros fármacos y el juicio del médico que suministra el tratamiento así como la gravedad de la enfermedad particular que es tratada. La cantidad de un compuesto de la presente invención en la composición también dependerá del compuesto particular en la composición.

USO DE COMPUESTOS Y COMPOSICIONES FARMACÉUTICAMENTE ACEPTABLES

La acetil-CoA carboxilasa (ACC) cataliza la carboxilación dependiente de ATP de acetil-CoA para formar malonil-CoA. Esta reacción, la cual se lleva a cabo en dos semi-reacciones, una reacción de biotina carboxilasa (BC) y una reacción de carboxiltransferasa (CT) es la primera etapa obligada en la biosíntesis de ácido graso (FA) y es la reacción limitante de velocidad para la vía. Además de su papel como un sustrato en la biosíntesis de FA, el malonil-CoA, el producto de una reacción catalizada por ACC también juega un papel regulador importante para controlar la

captación de FA mitocondrial a través de inhibición alostérica de carnitina palmitoil transferasa I (CPT-I), la enzima que cataliza la primera etapa obligada en la oxidación mitocondrial de FA. Por lo tanto, el malonil-CoA es una señal metabólica clave para el control de la producción y utilización de FA en respuesta a cambios en la dieta y requerimientos nutricionales alterados en animales, por ejemplo durante el ejercicio y por lo tanto juega un papel clave en el control del cambio entre la utilización de carbohidratos y grasas en hígado y músculo esquelético [Hardwood, 2005].

En mamíferos, ACC existe como dos isozimas específicas de tejido, ACC1, la cual está presente en tejidos lipogénicos (hígado, tejido adiposo) y ACC2, la cual está presente en tejidos oxidativos (hígado, corazón, músculo esquelético). ACC1 y ACC2 son codificados por genes separados, muestran distribuciones celulares distintas y comparten 75% de la identidad de secuencia de aminoácidos total, excepto por una extensión en la parte N-terminal de ACC2 que dirige a ACC2 a la membrana mitocondrial. ACC1, la cual carece de esta secuencia de direccionamiento, se localiza hacia el citoplasma. En el corazón y músculo esquelético, los cuales tienen una capacidad limitada para sintetizar ácidos grasos, el malonil-CoA formado por ACC2 funciona para regular la oxidación de FA. En el hígado, el malonil-CoA formado en el

citoplasma a través de las acciones de ACC1 se utiliza para la síntesis de FA y alargamiento, lo que lleva a la formación de triglicéridos y producción de VLDL, mientras que el malonil-CoA formado en la superficie mitocondrial por ACC2 actúa para regular la oxidación de FA [Tong and Hardwood, *J. Cellular Biochem*. 99: 1476, 2006]. Esta distribución en compartimientos de malonil-CoA resulta de una combinación de proximidad de síntesis [Abu-Elheiga *et al.*, PNAS (USA) 102: 12011, 2005] y la acción rápida de malonil-CoA descarboxilasa [Cheng *et al.*, *J. Med, Chem.* 49:1517, 2006].

La inhibición simultánea de las actividades enzimáticas de ACC1 y ACC2 proporciona la capacidad para inhibir la producción FA *de novo* en tejidos lipogénicos (por ejemplo, hígado y tejido adiposo) mientras que al mismo tiempo estimula la oxidación de FA en tejidos oxidativos (por ejemplo hígado y músculo esquelético) y por lo tanto proporciona una modalidad atractiva para alterar de manera favorable, de una manera concertada, una multitud de factores de riesgo cardiovasculares asociados con obesidad, diabetes, resistencia a insulina y síndrome metabólico.

Varias líneas de evidencia fundamentan fuertemente el concepto de la inhibición directa de la actividad de ACC como un objetivo terapéutico importante para tratar obesidad, diabetes, resistencia a insulina y el síndrome metabólico.

Abu-Elheiga *et al. [Proc. Natl. Acad. Sci.* USA

100:10207-10212, 2003] demostraron que ratones en donde se bloquea la expresión de ACC2 presentan una reducción en malonil-CoA en músculo esquelético y cardíaco, oxidación de FA en músculo aumentada, grasa hepática reducida, grasa corporal total reducida, desacoplamiento de músculo esquelético elevado de proteína-3 (UCP3) lo cual es indicativo de gasto de energía aumentado, peso corporal reducido, plasma reducido libre de FAs, glucosa en plasma reducida y glucógeno en tejido reducido y están protegidos de diabetes y obesidad inducida por dieta.

Savage *et al. [J. Clin. Invest.* 116:817, 2006], utilizando oligonucleótidos antisentido para ACC1 y ACC2 demostraron estimulación de oxidación de FA en hepatocitos de rata aislados y en ratas alimentadas con dietas alta en grasa y disminución de triglicéridos hepáticos, mejora en la sensibilidad de insulina, reducciones en la producción de glucosa hepática e incrementos en ARNm para UCP1 en ratas alimentadas con una dieta alta en grasa. Estos efectos fueron mayores cuando la expresión de ACC1 y ACC2 se suprime en comparación a cuando se suprime únicamente la expresión de ACC1 o ACC2.

Hardwood *et al. [J. Biol. Chem.* 278:37099, 2003] demostraron que el inhibidor de ACC no selectivo a isozima, CP-640186, el cual inhibe por igual a ACC1 y ACC2 (CI_{50} = ~60 nM) aislado de rata, ratón, mono y humano sin inhibir ya sea la piruvato carboxilasa o la propionil-CoA carboxilasa,

redujo la síntesis de FA, síntesis de triglicéridos y secreción en células Hep-G2 sin afectar la síntesis de colesterol y la secreción reducida de apoB sin afectar la secreción de apoA1. El compuesto CP-640186 también estimula la oxidación de FA en células C2C12 y en cortes de músculo de rata y aumenta la actividad de CPT-1 en células Hep-G2. En animales experimentales, el compuesto CP-640186 reduce de manera aguda la concentración de malonil-CoA en tejidos tanto lipogénicos como oxidativos tanto en estado alimentado como en ayuno, reduce la síntesis de FA en hígado y tejido adiposo e incrementa la oxidación de FA corporal total. En ratas alimentadas con sacarosa, tratadas con CP-640186 durante tres semanas, el compuesto CP-640186 reduce de una manera dependiente tanto del tiempo como de la dosis los triglicéridos en hígado, músculo y tejido adiposo, reduce el peso corporal debido a la reducción selectiva de grasa sin reducir la masa corporal magra, reduce los niveles de lectina, reduce la hiperinsulinemia producida por una dieta alta en sacarosa sin cambiar los niveles de glucosa en plama y mejora la sensibilidad a insulina.

Saha *et al. [Diabetes* 55:A288, 2006] demostraron estimulación de sensibilidad a insulina en tejido de músculo de rata resistente a insulina por el compuesto CP-640186 en los siguientes 30 min a partir de la administración del compuesto y los estudios de Furler et al. [*Diabetes* 55:A333,

2006] utilizaron análisis de trazador doble para mostrar que un tratamiento agudo (46 min) de ratas con el compuesto CP-640186 estimula la depuración de FA sin disminuir la depuración de glucosa.

ACC es una enzima limitante de velocidad en la síntesis de ácido graso y su producto, malonil-CoA, sirve como un regulador importante de la oxidación de ácidos grasos. Por lo tanto, los inhibidores de ACC reducen la síntesis de lípido *de novo* y promueven la oxidación de la grasa existente. Este efecto doble sobre el metabolismo de lípidos incrementa la posibilidad de que los inhibidores de ACC sean sustancialmente más eficaces en reducir la grasa en exceso en comparación con otros mecanismos. Además, los inhibidores de ACC tienen impacto en la sensibilidad en insulina, triglicéridos en plasma y tejido y glucosa plasmática en ayuno como una consecuencia de una reducción en la masa grasa tanto del cuerpo completo como específica de tejido sin la necesidad de administración de diversas sustancias farmacéuticas.

Los inhibidores de ACC únicamente necesitan tener acceso al hígado y músculo en el compartimiento periférico. El evitar el SNC resuelve muchos de los efectos secundarios asociados con programas de obesidad de etapa tardía dirigidos a los receptores de SNC. Los inhibidores de ACC también se espera que tengan perfiles de seguridad superiores a los agentes de enfermedad metabólicos existentes. Por ejemplo, es

poco probable que un inhibidor de ACC precipite hipoglucemia que ponga en peligro la vida como con frecuencia se observa en miméticos de insulina, secretagogos de insulina e inhibidores de degradación de insulina. Además, puesto que los inhibidores de ACC reducen la masa grasa corporal completa, serán superiores a las glitazonas que incrementen la masa grasa corporal completa como parte de su mecanismo de acción.

Un agente que actúa periféricamente que provoca pérdida de peso significativa y que mejora otros criterios de valoración metabólicos se acopla bien dentro de los requerimientos de la FDA de los Estados Unidos para su aprobación como un nuevo agente contra la obesidad. No obstante, si la aprobación para la obesidad continúa siendo un reto en los siguientes 5 a 7 años, los inhibidores de ACC serán aprobados para hiperlipidemia combinada familiar y esteatohepatitis no alcohólica (NASH, por sus siglas en inglés). Actualmente no hay inhibidores de ACC comercializados de manera que un inhibidor de isozima no selectivo de ACC representaría un tratamiento primero en su clase para tratar obesidad y síndrome metabólico.

La actividad de un compuesto utilizado en esta invención como un inhibidor de ACC o para tratamiento de obesidad o síndrome metabólico se puede analizar *in vitro* o *in vivo*. Una determinación *in vivo* de la eficacia de los compuestos de la invención se puede realizar utilizando un

modelo animal de obesidad o síndrome metabólico, por ejemplo un modelo en roedor o en primate. Se pueden realizar análisis basados en células utilizando, por ejemplo, una línea de célula aislada de un tejido que expresa ACC. Adicionalmente, los análisis bioquímicos o basados en mecanismos, por ejemplo análisis de transcripción utilizando una proteína purificada, transferencia Northern, RT-PCR, etc., se pueden llevar a cabo. Los análisis *in vitro* incluyen análisis que determinan morfología de células, expresión de proteínas y/o la citotoxicidad, actividad inhibidora de enzimas y/o las consecuencias funcionales subsecuentes de tratamiento de células con compuestos de la invención. Los análisis *in vitro* alternativos cuantifican la capacidad del inhibidor para unir la proteína o moléculas de ácido nucleico dentro de la célula. La unión de inhibidor se puede medir por radiomarcado del inhibidor antes de la unión, aislamiento del complejo de inhibidor/molécula objetivo y determinación de la cantidad de radiomarca unida. De manera alternativa, la unión de inhibidor se puede determinar al llevar a cabo un experimento de competencia en donde se incuban inhibidores nuevos con proteínas purificadas o ácidos nucleicos unidos a radioligandos conocidos. Las condiciones detalladas para los análisis de un compuesto utilizado en esta invención como un inhibidor de ACC se establecen en los ejemplos más adelante. Los análisis mencionados en lo anterior son ejemplares y no se

pretende que limiten el alcance de la invención. Los expertos en el ámbito pueden apreciar que se pueden realizar modificaciones a los análisis convencionales para desarrollar análisis equivalentes para obtener el mismo resultado.

Como se utiliza en la presente, los términos "tratamiento", "tratar" y "tratado" se refieren a revertir, aliviar, retrasar el inicio de o inhibir el progreso de una enfermedad de trastorno, o uno o más síntomas de los mismos, como se describe en la presente. En algunas modalidades, el tratamiento se puede administrar después de que se han desarrollado uno o más síntomas. En otras modalidades, el tratamiento se puede administrar en ausencia de síntomas. Por ejemplo, el tratamiento se puede administrar a un individuo susceptible antes del inicio de los síntomas (por ejemplo tomando en consideración los antecedentes de los síntomas y/o tomando en consideración factores genéticos o de otra susceptibilidad). El tratamiento también puede continuar después de que los síntomas se hayan resuelto, por ejemplo, para evitar o retrasar su recurrencia.

Los compuestos y composiciones de acuerdo con el método de la presente invención se pueden administrar utilizando cualquier cantidad y cualquier vía de administración eficaz para tratar o disminuir la gravedad de un trastorno metabólico o condición, cáncer, una infección bacteriana, una infección micótica, una infección parasitaria

(por ejemplo, paludismo), un trastorno autoinmune, un trastorno neurodegenerativo o neurológico, esquizofrenia, un trastorno relacionado con los huesos, enfermedad hepática o un trastorno cardíaco.

En algunas modalidades, los compuestos y composiciones de acuerdo con el método de la presente invención se pueden administrar utilizando cualquier cantidad y cualquier vía de administración eficaz para tratar o disminuir la gravedad de una enfermedad asociada con ACC (Tong, *et al*. "Acetil-coenzima A carboxylase: crucial metabolic enzyme and attractive target for drug discovery" Cell and Molecular Life Sciences (2005) 62, 1784, 1803).

En algunas modalidades, los compuestos y composiciones de acuerdo con el método de la presente invención se pueden administrar utilizando cualquier cantidad y cualquier vía de administración eficaz para tratar o disminuir la gravedad de un trastorno metabólico, enfermedad o condición. En algunas modalidades, el trastorno o metabólico es obesidad, síndrome metabólico, diabetes o trastornos relacionados con diabetes que incluyen diabetes tipo 1 (diabetes mellitus dependiente de insulina, IDDM) y diabetes tipo 2 (diabetes mellitus no dependiente de insulina, NIDDM), tolerancia deteriorada a la glucosa, resistencia a insulina, hiperglucemia, complicaciones diabéticas que incluyen pero que no se limitan a aterosclerosis, enfermedad cardiaca coronaria,

apoplejía, enfermedad vascular periférica, nefropatía, hipertensión, neuropatía y nefropatía; comorbilidades de obesidad que incluyen pero que no se limitan a síndrome metabólico, dislipidemia, hipertensión, resistencia a la insulina, diabetes (que incluye diabetes tipo 1 y tipo 2), enfermedad de arteria coronaria y fallo cardíaco. En algunas modalidades, el trastorno metabólico, la enfermedad o condición es enfermedad de hígado graso no alcohólico o resistencia a insulina hepática.

En algunas modalidades, la presente invención proporciona un método para tratar un trastorno metabólico, enfermedad o condición descrito en la presente que comprende administrar un compuesto de la invención junto con uno o más agentes farmacéuticos. Los agentes farmacéuticos adecuados que se pueden utilizar en combinación con los compuestos de la presente invención incluyen agentes contra la obesidad (que incluye supresores del apetito), agentes antidiabéticos, agentes antihiperglucémicos, agentes que disminuyen lípidos y agentes antihipertensivos.

Los agentes que disminuyen lípidos adecuados que se pueden utilizar junto con los compuestos de la presente invención incluyen pero no se limitan a secuestrantes de ácido biliar, inhibidores de HMG-CoA reductasa, inhibidores de HMG-CoA sintasa, inhibidores de absorción de colesterol, inhibidores de acil coenzima A-colesterol acil transferasa

(ACAT), inhibidores de CETP, inhibidores de escualeno sintetasa, agonistas de PPAR-alfa, moduladores de receptor de FXR, moduladores de receptor de LXR, inhibidores de síntesis de lipoproteínas, inhibidores del sistema renina-angiotensina, agonistas parciales de PPAR-delta, inhibidores de reabsorción de ácido biliar, agonistas de PPAR-gamma, inhibidores de síntesis de triglicéridos, inhibidores del transporte de triglicéridos microsomal, moduladores de transcripción, inhibidores de escualeno o epoxidasa, inductores de receptor de lipoproteína de baja densidad, inhibidores de agregación plaquetaria, inhibidores de 5-LO o FLAP, niacina y cromo unido a niacina.

Los agentes antihipertensivos adecuados que pueden ser utilizados junto con los compuestos de la presente invención incluyen pero no se limitan a diuréticos, bloqueadores beta-adrenérgicos, bloqueadores de canal de calcio, inhibidores de la enzima convertidora de angiotensina (ACE), inhibidores de endopeptidasa neutral, antagonistas de endotelina, vasodilatadores, antagonistas de receptor de angiotensina II, bloqueadores adrenérgicos alfa/beta, bloqueadores alfa-1, agonistas alfa 2, inhibidores de aldosterona, inhibidores de receptor de mineralocorticoides, inhibidores de renina y agentes de unión de angiopoyetina 2.

Los agentes antidiabéticos adecuados que se pueden utilizar junto con los compuestos de la presente invención

incluyen pero no se limitan a otros inhibidores de acetil-CoA carboxilasa (ACC), inhibidores de DGAT-1, AZD7687, LCQ908, inhibidores de DGAT-2, inhibidores de monoacilglicerol O-aciltransferasa, inhibidores de PDE-10, activadores de AMPK, sulfonilureas (por ejemplo acetohexamida, clorpropamida, diabinese, glibenclamida, glipizida, gliburida, blimpirida, gliclazida, glipentida, gliquidona, glisolamida, tolazamida, tolbutamida), meglitinidas, inhibidores de alfa-amilasa (por ejemplo tendamistat, treastatina, AL-3688), inhibidores de alfa-glucósido hidrolasa (por ejemplo, acarbosa), inhibidores de alfa-glucosidasa (por ejemplo adiposina, camiglibosa, emiglitato, miglitol, voglibosa, pradimicina-1, sarbostatina), agonistas de PPAR-gamma (por ejemplo balaglitazona, ciglitazona, darglitazona, englitazona, isaglitazona, pioglitazona, rosiglitazona, troglitazona), agonistas de PPAR-alfa/gamma (por ejemplo CLX-0940, GW-1536, GW-1929, GW-2433, KRP-297, L-796449, LR-90, MK-0767, SB-219994), biguanidas (por ejemplo metformina, buformina), moduladores de GLP-1 (exendina-3, exendina-4), liraglutida, albiglutida, exenatida (Byetta), taspoglutida, lixisenatida, dulaglutida, semaglutida, N,N-9924, TTP-054, inhibidores de PTP-1B (trodusquemina, extracto de hirtiosal), inhibidores de SIRT-1 (por ejemplo, resveratrol, GSK2245840, GSK184072), inhibidores de DPP-IV (por ejemplo sitagliptina, vildagliptina, alogliptina, dutogliptina, linagliptina, saxagliptina),

secretagogos de insulina, inhibidores de oxidación de ácido graso, antagonistas de A2, inhibidores de JNK, activadores de glucocinasa (por ejemplo TTP-399, TTP-355, TTP.547, AZD1656, ARRY403, MK-0599, TAK-329, AZD5658, GKM-001), insulina, miméticos de insulina, inhibidores de glucógeno fosforilasa (por ejemplo GSK1362885), agonitas del receptor de VPAC2, inhibidores de SGLT2 (dapagliflozina, canaglifozina, BI-10733, tofoglifozina, ASP-1941, THR1474, TS-071, ISIS388626, LX4211), moduladores de receptor de glucagón, moduladores de GPR119 (por ejemplo MBX-2982, GSK1292263, APD597, PSN821), derivados de FGF21, agonistas del receptor de TGR5 (GPBAR1), (por ejemplo INT777), agonistas de GPR40 (por ejemplo, TAK-875), agonistas de GPR120, activadores del receptor de ácido nicotínico (HM74A), inhibidores de SGLT1 (por ejemplo GSK1614235), inhibidores de la enzima carnitina palmitoil transferasa, inhibidores de fructosa 1,6-difosfatasa, inhibidores de aldosa reductasa, inhibidores de receptor de mineralocorticoide, inhibidores de TORC2, inhibidores de CCR2, inhibidores de CCR5, inhibidores de PKC (por ejemplo PKC-alfa, PKC-beta, PKC-gamma), inhibidores de ácido graso sintetasa, inhibidores de serina palmitoil transferasa, moduladores de GPR81, moduladores de GPR39, moduladores de GPR43, moduladores de GPR41, moduladores de GPR105, inhibidores de Kv1.3, inhibidores de proteína 4 de unión de retinol, moduladores de receptor de glucocorticoide, inhibidores de receptor de

somatostatina (por ejemplo SSTR1, SSTR2, SSTR3, SSTR5), inhibidores de PDHK2, inhibidores de PDHK4, inhibidores de MAP4K4, moduladores de IL1-beta y moduladores de RXR-alfa.

Los agentes antiobesidad adecuados incluyen pero no se limitan a inhibidores de 11-beta-hidroxiesteroide deshidrogenasa, inhibidores de estearoil-CoA desaturasa (SCD-1), agonistas de MCR-4, agonistas de CCK-A, inhibidores de recaptación de monoamina (por ejemplo sibutramina), agentes simpatomiméticos, agonistas del receptor beta-3-adrenérgico, agonistas del receptor de dopamina (por ejemplo, bromocriptina), hormona estimulante de melanocitos y análogos de la misma, agonistas de $5\text{-}HT_{2C}$ (por ejemplo lorcaserina/Belviq), agonistas de hormona concentradora de melamina, leptina, análogos de leptina, agonistas de leptina, antagonistas de galanina, inhibidores de lipasa (por ejemplo tetrahidrolipstatina/orlistat), agentes anoréxicos (por ejemplo, agonistas de bombesina), antagonistas de NPY (por ejemplo velneperit), PYY_{3-36} (y análogos de la misma), moduladores de BRS3, antagonistas mixtos de receptor de opioide, agentes tiromiméticos, deshidroepiandrosterona, agonistas o antagonistas de glucocorticoide, antagonistas de orexina, agonistas de GLP-1, factor neutrófico ciliar (por ejemplo axocina), inhibidores de proteína relacionada con agouti humana (AGRP), antagonistas H3 o agonistas inversos, agonistas de neuromedina U, inhibidores de MTP/ApoB (por

ejemplo, inhibidores de MTP selectivos de intestino tales como dirlotapida, JTT130, Usistapida, SLX4090), inhibidores de MetAp2 (por ejemplo, ZNG-433), agentes con actividad moduladora mixta en dos o más de receptores de glucagón, GIP y GLP1 (por ejemplo, MAR-701, ZP2929), inhibidores de recaptación de norepinefrina, antagonistas opiodes (por ejemplo naltrexona), antagonistas de receptor CB1 o agonistas de inversos, agonistas de o antagonistas de grelina, oxintomodulina y análogos de la misma, inhibidores de captación de monoamina (por ejemplo tesofensina) y agentes de combinación (por ejemplo buproprion más zonisamida (Empatic), pramlintida más metreleptina, buproprion más naltrexona (Contrave), fentermina más topiramato (Qsymia).

En algunas modalidades, los agentes antiobesidad utilizados en combinación con los compuestos de la invención se seleccionan de inhibidores de MTP selectivos de intestino (por ejemplo dirlotapida, mitratapida, implitapida, R56918), agonistas de CCK-A, agonistas de $5\text{-}HT_{2C}$ (por ejemplo lorcaserina/Belviq), agonistas de MCR4, inhibidores de lipasa (por ejemplo Cetilistat), PYY_{3-36} (que incluye análogos y análogos PEGilados de los mismos), antagonistas opioides (por ejemplo, naltrexona), oleoil estrona, obinepitida, pramlintida, tesofensina, leptina, bromocriptina, orlistat, AOD-9604 y sibutramina.

En algunas modalidades, los compuestos y

composiciones de acuerdo con el método de la presente invención se pueden administrar utilizando cualquier cantidad y cualquier vía de administración eficaz para tratar o disminuir la gravedad de una enfermedad asociada con LKB1 o Kras. En algunas modalidades, la enfermedad asociada con LKB1 o Kras se selecciona de carcinoma hepatocelular canceres mutante de LKB1, canceres activados por pérdida de condición heterocigota (LOH) de LKB1, canceres mutantes de Kras, síndrome de Peutz-Jeghers (PJS, por sus siglas en inglés), enfermedad de Cowden (CD, por sus siglas en inglés) y esclerosis tubeousa (TS, por sus siglas en inglés) (makowski et al. “Role of LKB1 in Lung Cancer development” British Journal of Cancer (2008) 99, 683-688). En algunas modalidades, la enfermedad asociada a LKB1 o Kras es un tumor de pulmón positivo a Kras/deficiente en LKB1.

En algunas modalidades, los compuestos y composiciones de acuerdo con el método de la presente invención se pueden administrar utilizando cualquier cantidad y cualquier vía de administración eficaz para tratar o disminuir la gravedad de un cáncer o para inhibir el crecimiento o para inducir apoptosis en células de cáncer (Wang et al. “Acetyl-CoA Carboxylase-alpha Inhibitor TOFA Induces Human Cancer Cell Apoptosis” Biochem Biophys res Commun. (2009) 385(3), 302-306; Chajes et al. "Acetyl-CoA Carboxilase alpha Is Essential to Breast Cancer Cell Survival" Cancer Res. (2006) 66, 5287-5294; Beckers et al. "Chemical

Inhibition of Acetyl-CoA Carboxilase Induces Growth Arrest and Cytotoxicity Selectivity in Cancer Cells" Cancer Res. (2007) 8180-8187; Brusselmans et al. "RNA interference-Mediated Silencing of the Acetyl-CoA-Carboxilase-alpha Gene Induces Growth Inhibition and Apoptosis of Prostate Cancer cells" Cancer res. (2005) 65, 6719-6725; Brunet et al. "BRCA1 and Acetyl-CoA Carboxilase: The Metabolic Syndrom of Breast Cancer" Molecular Carcinogenesis (2008) 47, 157-163; Cairns et al. "Regulation of Cancer Cell Metabolism" (2011) 11, 85-95; Chiaradonna et al. "From Cancer Metabolism to New Biomarkers and Drug Targets" Biotechnology Advances (2012) 30, 30-51).

En algunas modalidades, los compuestos y composiciones de acuerdo con el método de la presente invención se pueden administrar utilizando cualquier cantidad y cualquier vía de administración eficaz para tratar o disminuir la gravedad de un melanoma. En algunas modalidades, el melanoma es uno que presenta una vía MAPK activada (Petti et al. "AMPK activators inhibit the proliferation of human melanomas bearing the activated MAPK pathway" Melanoma Research (2012) 22, 341-350).

Los compuestos de la presente invención encuentran utilidad especial en cáncer de mama triple negativo, como la proteína supresora de tumor BRCA1 se une y estabiliza la forma inactiva de ACC, y por lo tanto regula por aumento la síntesis de lípidos de novo, lo que resulta en proliferación de células

de cáncer Brunet et al. "BRCA1 and acetyl-CoA carboxylase: the metabolic syndrome of breast cancer" Mol. Carcinog. (2008) 47(2), 157-163.

En algunas modalidades, los compuestos y composiciones de acuerdo con el método de la presente invención se pueden administrar utilizando cualquier cantidad y cualquier vía de administración eficaz para tratar o disminuir la gravedad de un liposarcoma. Se ha demostrado que los liposarcomas dependen de la síntesis de ácido graso de cadena larga de novo para su crecimiento, y la inhibición de ACC por soraphen A inhiben la lipogénesis así como el crecimiento de células tumorales (Olsen et al. "Fatty acid synthesis is a therapeutic target in human liposarcoma" International J. of Oncology (2010) 36, 1309-1314).

En algunas modalidades, los compuestos y composiciones de acuerdo con el método de la presente invención se pueden administrar utilizando cualquier cantidad y cualquier vía de administración eficaz para tratar o disminuir la gravedad de una enfermedad hepática. En algunas modalidades, la enfermedad hepática se selecciona de hepatitis C, carcinoma hepatocelular, hiperlipidemia combinada familiar y esteatohepatitis no alcohólica (NASH, por sus siglas en inglés), cáncer de hígado, colangiocarcinoma, angiosarcoma, hemangiosarcoma y colestasis intrahepática familiar progresiva.

En algunas modalidades, los compuestos y composiciones de acuerdo con el método de la presente invención se pueden administrar utilizando cualquier cantidad y cualquier vía de administración eficaz para tratar o disminuir la gravedad de una infección bacteriana o para inhibir el crecimiento de bacterias.

En algunas modalidades, los compuestos y composiciones de acuerdo con el método de la presente invención se pueden administrar utilizando cualquier cantidad y cualquier vía de administración eficaz para tratar o disminuir la gravedad de una infección micótica o para inhibir el crecimiento de células micóticas (Shen et al. "A Mechanism for the Potent Inhibition of Eukaryotic Acetyl-Coenzyme A Carboxylase by Soraphen A, a Macrocyclic Polyketide Natural Product" Molecular Cell (2004) 16, 881-891).

En algunas modalidades, los compuestos y composiciones de acuerdo con el método de la presente invención se pueden administrar utilizando cualquier cantidad y cualquier vía de administración eficaz para tratar o disminuir la gravedad de una infección bacteriana (Tong, L. et al. J. Cell. Biochem. (2006) 99, 1476-1488).

En algunas modalidades, los compuestos y composiciones de acuerdo con el método de la presente invención se pueden administrar utilizando cualquier cantidad y cualquier vía de administración eficaz para tratar o

disminuir la gravedad de una infección viral (Munger et al. Nat. Biotechnol. (2008) 26, 1179-1186). En algunas modalidades, la infección viral es hepatitis C.

En algunas modalidades, el compuesto y las composiciones de acuerdo con el método de la presente invención se pueden administrar utilizando cualquier cantidad y cualquier vía de administración eficaz para tratar o disminuir la gravedad de una enfermedad neurológica (Henderson et al. Neurotherapeutics (2008) 5, 470-480; Costantini et al. Neurosci. (2008) 9 Suppl. 2: S16; Baranano et al. Curr. Treat. Opin. Naurol. (2008) 10, 410-419).

En algunas modalidades, los compuestos y composiciones de acuerdo con el método de la invención se pueden administrar utilizando cualquier cantidad y cualquier vía de administración eficaz para tratar o disminuir la gravedad de una infección parasitaria o para inhibir el crecimiento de parásitos (por ejemplo paludismo o toxoplasma: Gornicki et al. "Apicoplast fatty acid biosynthesis as a target for medical intervention in apicomplexan aparasites" International journal of Parasitology (2003) 33, 885-896; Zuther et al. "Growth of *Toxoplasma gondii* is inhibited by ariloxyphenoxypropionate herbicides targeting acetyl-CoA carboxylase" PNAS (1999) 96 (23) 13387-13392).

En algunas modalidades, los compuestos y composiciones de acuerdo con el método de la presente

invención se pueden administrar utilizando cualquier cantidad y cualquier vía de administración eficaz para tratar o disminuir la gravedad de un trastorno cardíaco. En algunas modalidades, el trastorno cardíaco es hipertrofia cardíaca. En algunas modalidades, el trastorno cardíaco es tratado o su gravedad se disminuye por el mecanismo cardiprotector que resulta de oxidación aumentada de ácidos grasos por medio de inhibición de ACC (Kolwicz et al. "Cardiac-specific deletion of acetyl CoA carboxilase 2 (ACC2) prevents metabolic remodeling during pressure-overload hypertrophy" Circ. Res. (2012); DOI: 10.1161/CIRCRESAHA.112.268128).

En ciertas modalidades, los compuestos y composiciones de acuerdo con el método de la presente invención se pueden utilizar como herbicidas. En algunas modalidades, la presente invención proporciona un método para inhibir el crecimiento o viabilidad de plantas que comprende tratar a las plantas con compuestos de la presente invención. En algunas modalidades de la presente invención, los compuestos de la presente invención se pueden utilizar para inhibir el crecimiento o viabilidad de plantas al inhibir ACC. En algunas modalidades, el método de la presente invención comprende utilizar compuestos de la presente invención para inhibir la producción de ácidos grasos o para incrementar la oxidación de ácidos grasos en plantas.

La cantidad exacta requerida variará de un sujeto a

otro, dependiendo de la especie, edad y condición general del sujeto, la gravedad de infección, el agente particular, su modo de administración y similar. Los compuestos de la invención preferiblemente se formulan en forma de dosificación unitaria para facilidad de administración y uniformidad de dosificación. La expresión "forma de dosificación unitaria", como se utiliza en la presente, se refiere a una unidad físicamente separada de un agente apropiado para el paciente que va a ser tratado. No obstante, se entenderá que el uso del diario total de los compuestos y composiciones de la presente invención lo decidirá el médico que atiende dentro del ámbito y el buen juicio del médico. El nivel de dosis eficaz específico para cualquier paciente u organismo particular dependerá de una diversidad de factores que incluyen el trastorno que es tratado y la gravedad del trastorno, la actividad del compuesto específico utilizado, la composición específica utilizada; la edad, peso corporal, salud general, sexo y dieta del paciente; la hora de administración, la vía de administración, y la velocidad de expresión del compuesto específico utilizado; la duración del tratamiento; los fármacos utilizados en combinación o de modo coincidente con el compuesto específico utilizado y factores similares bien conocidos en los ámbitos médicos. El término "paciente", como se utiliza en la presente, significa un animal, preferiblemente un mamífero y de manera más preferible un

humano.

Las composiciones farmacéuticamente aceptables de esta invención se pueden administrar a humanos y otros animales por vía oral, rectal, parenteral, intracisternal, intravaginal, intraperitonealmente, tópica (por ejemplo, por polvos, ungüentos o gotas), bucalmente, como una aspersión oral o nasal o similar, dependiendo de la gravedad de la infección que es tratada. En algunas modalidades, los compuestos de la invención se pueden administrar por vía oral o parenteral a niveles de dosificación de aproximadamente 0.01 mg/kg a aproximadamente 50 mg/kg y de manera preferible de aproximadamente 1 mg/kg a aproximadamente 25 mg/kg del peso corporal del sujeto al día, una o más veces al día, para obtener el efecto terapéutico deseado.

Las formas de dosificación líquidas para administración oral incluyen, pero no se limitan a emulsiones farmacéuticamente aceptables, microemulsiones, soluciones, suspensiones, jarabes y elíxires. Además de los compuestos activos, las formas de dosificación líquida pueden contener diluyentes inertes utilizados habitualmente en el ámbito tales como, por ejemplo, agua u otros disolventes, agentes solubilizantes y emulsificantes tales como alcohol etílico, alcohol isopropílico, carbonato de etilo, acetato de etilo, alcohol bencílico, benzoato de bencilo, propilenglicol, 1,3-butilenglicol, dimetilformamida, aceites (en particular

aceite de semilla de algodón, aceite de nuez molida, de maíz, de germen, de oliva, de recino y de ajonjolí), glicerol, alcohol tetrahidrofurfurilico, polietielenglicoles y ésteres de ácido graso de sorbitan y mezclas de los mismos. Además de los diluyentes inertes, las composiciones orales también pueden incluir adyuvantes tales como agentes humectantes, agentes emulsificantes y que mejoren la suspensión, edulcorantes, saborizantes y agentes que proporcionen perfume.

Las preparaciones inyectables, por ejemplo, suspensiones acuosas o oleaginosas inyectables estériles se pueden formular de acuerdo con la técnica conocida utilizando agentes adecuados dispersantes o de humedecimiento y agentes que mejoren la suspensión. La preparación inyectable estéril también puede ser una solución inyectable estéril, una suspensión o una emulsión en un diluyente o disolvente no tóxico parenteralmente aceptable, por ejemplo, como una solución en 1,3-butanodiol. Entre los vehículos y disolventes aceptables que se pueden utilizar están en agua, solución de Ringer, U.S.P. y solución isotónica de cloruro de sodio. Además, los aceites fijos estériles se utilizan convencionalmente como un disolvente o medio de suspensión. Para este propósito se puede utilizar cualquier aceite fijo blando que incluye mono-o di- glicéridos sintéticos. Además, los ácidos grasos tales como ácido oleico se utilizan en la preparación de inyectables.

Las formulaciones inyectables se pueden esterilizar, por ejemplo, por filtración a través de un filtro para retener bacterias o al incorporar agentes esterilizantes en forma de composiciones sólidas estériles las cuales se pueden disolver o dispersar en agua estéril u otro medio inyectable estéril antes de su uso.

Con el fin de prolongar el efecto de un compuesto de la presente invención con frecuencia es deseable frenar la absorción del compuesto desde la inyección subcutánea o intramuscular. Esto se puede llevar a cabo mediante el uso de una suspensión líquida de material cristalino o amorfo con poca hidrosolubilidad. La velocidad de absorción del compuesto depende entonces de su velocidad de disolución que, a su vez, puede depender del tamaño del cristal y la forma cristalina. De manera alternativa, la absorción retrasada de una forma de compuesto administrado parenteralmente se lleva a cabo al disolver o suspender el compuesto en un vehículo oleoso. Las formas de depósito inyectables se elaboran al formar matrices microencapsuladas del compuesto en polímeros biodegradables tales como poliláctida-poliglicolida. Dependiendo de la relación del compuesto respecto a polímero y la naturaleza del polímero particular utilizado, la velocidad de liberación del compuesto se puede controlar. Los ejemplos de otros polímeros biodegradables incluyen poli(ortoésteres) y poli(anhídridos). Las formulaciones del depósito inyectables también se pueden

preparar al atrapar al compuesto en liposomas o microemulsiones que sean compatibles con los tejidos corporales.

Las composiciones para administración rectal o vaginal son preferiblemente supositorios los cuales se pueden preparar al mezclar los compuestos de esta invención con excipientes o portadores no irritantes adecuados tales como manteca de cacao, polietilenglicol o una cera de supositorio la cual es sólida a temperatura ambiente pero líquida a temperatura corporal y por lo tanto se funde en el recto o en cavidad vaginal y libera el compuesto activo.

Las formas de dosificación sólida para administración oral incluyen cápsulas, tabletas, píldoras, polvos y gránulos. En estas formas de dosificación sólidas, el compuesto activo se mezcla con por lo menos un excipiente o portador inerte, farmacéuticamente aceptable tal como citrato de sodio o fosfato dicálcico y/o a) rellenos o diluyentes tales como almidones, lactosa, sacarosa, glucosa, manitol y ácido silícico, b) aglutinantes tales como, por ejemplo, carboximetilcelulosa, alginatos, gelatina, polivinilpirrolidinona, sacarosa y goma acacia, c) humectantes tales como glicerol, d) agentes desintegrantes tales como agar-agar, carbonato de calcio, almidón de papa o de tapioca, ácido algínico, ciertos silicatos y carbonato de sodio, e) agentes que retardan la solución tal como parafina, f)

aceleradores de absorción tales como compuestos de amonio cuaternario, g) agentes humectantes tales como, por ejemplo alcohol cetílico y monoestearato de glicerol, h) absorbentes tales como caolín y arcilla de bentonita, e i) lubricantes tales como talco, estearato de calcio, estereato de magnesio, polieltilenglicoles sólidos, laurilsulfato de sodio y mezclas de los mismos. En el caso de cápsulas, tabletas y píldoras, la forma de dosificación también puede comprender agentes amortiguadores.

Las composiciones sólidas de un tipo similar también se puede utilizar como materiales de relleno en cápsulas de gelatina de relleno suave y duro utilizando excipientes tales como lactosa o azúcar de leche así también como polietilenglicoles de peso molecular alto y similares. Las formas de dosificación sólidas de tabletas, grageas, cápsulas, píldoras y gránulos se pueden preparar con recubrimientos y tabletas tales como recubrimientos entéricos y otros recubrimientos bien conocidos en la técnica de formulación farmacéutica. Opcionalmente pueden contener agentes opacificantes y también pueden ser de una composición que libere uno o varios de los ingredientes activos únicamente o del modo preferencial en cierta parte del tracto intestinal, opcionalmente de una manera retrasada. Los ejemplos de composiciones incrustadas que se pueden utilizar incluyen sustancias poliméricas y ceras. Las composiciones sólidas de

un tipo similar también se pueden utilizar como rellenos en cápsulas de gelatina de rellenado suave y duro utilizando excipientes tales como lactosa o azúcar de leche así como polietilenglicoles de peso molecular alto y similares.

Los compuestos activos también pueden estar en forma microencapsulada con uno o más excipientes como se indica en lo anterior. Las formas de dosificación sólidas de tabletas, grageas, cápsulas, píldoras y gránulos se pueden preparar con recubrimientos y cubiertas tales como recubrimientos entéricos, recubrimientos de control de liberación y otros recubrimientos bien conocidos en el ámbito de formulación farmacéutica. En estas formas de dosificación sólidas el compuesto activo se puede mezclar con por lo menos un diluyente inerte tal como sacarosa, lactosa o almidón. Estas formas de dosificación también pueden comprender, como en la práctica normal, sustancias adicionales diferentes de diluyentes inertes, pro ejemplo lubricantes de tableteado y otros auxiliares de tableteado tales como estearato de magnesio y celulosa microcristalina. En el caso de cápsulas, tabletas y píldoras, la forma de dosificación también puede comprender agentes amortiguadores. Opcionalmente también pueden contener agentes opacificantes y también pueden ser de una composición que libere uno o varios de los ingredientes activos únicamente o de modo preferencial, en cierta parte del tracto intestinal, opcionalmente de una manera retrasada. Los

ejemplos de composiciones incrustadas que se pueden utilizar incluyen sustancias poliméricas y ceras.

Las formas de dosificación para administración tópica o transdérmica de un compuesto de esta invención incluyen ungüentos, pastas, cremas, lociones, geles, polvos, soluciones, aspersiones, inhalantes o parches. El componente activo se mezcla bajo condiciones estériles con un portador farmacéuticamente aceptable y cualquier conservador o amortiguador necesario que se pueda requerir. La formulación oftálmica, gotas para los oídos y gotas para los ojos también se contemplan como dentro del alcance de esta invención. Adicionalmente, la presente invención contempla el uso de parches transdérmicos los cuales tienen la ventaja agregada de proporcionar suministro controlado de un compuesto al cuerpo. Estas formas de dosificación se pueden elaborar al disolver o suministrar el compuesto en el medio apropiado. Los mejoradores de absorción también se pueden utilizar para incrementar el flujo del compuesto a través de la piel. La velocidad se puede controlar ya sea al proporcionar una membrana de control de velocidad o al dispersar el compuesto en una matriz polimérica o en un gel.

De acuerdo con una modalidad, la invención se relaciona con un método para inhibir ACC en una muestra biológica que comprende la etapa de poner en contacto la muestra biológica con un compuesto de esta invención o una

composición que comprende al compuesto.

En ciertas modalidades, la invención se relaciona con un método para modular los niveles de ácido graso en una muestra biológica que comprende la etapa de poner en contacto la muestra biológica con un compuesto de esta invención o una composición que comprende al compuesto.

El término "muestra biológica", como se utiliza en la presente, incluye, sin limitación, cultivos de células o extractos de los mismos; material de biopsia obtenido de un mamífero o extractos de los mismos; y sangre, saliva, orina, heces, semen, lagrimas u otros fluidos corporales o extractos de los mismos.

La inhibición de enzimas en una muestra biológica es útil para una diversidad de propósitos que son conocidos por una persona experta en el ámbito. Los ejemplos de estos propósitos incluyen, pero no se limitan a análisis biológicos, estudios de expresión de genes e identificación de objetivo biológico.

Otra modalidad de la presente invención se relaciona con un método para inhibir ACC en un paciente, que comprende la etapa de administrar al paciente un compuesto de la presente invención o una composición que comprende el compuesto.

De acuerdo con otra modalidad, la invención se relaciona con un método para inhibir la producción de ácido

graso, estimular la oxidación de ácido graso o ambas cosas en un paciente, que comprende la etapa de administrar al paciente un compuesto de la presente invención o una composición que comprende el compuesto. De acuerdo con ciertas modalidades, la invención se relaciona con un método para inhibir la producción de ácido graso, estimular la oxidación de ácido graso o ambos en un paciente, dirigirse a disminuir la obesidad o aliviar los síntomas de síndrome metabólico, que comprende la etapa de administrar al paciente un compuesto de la presente invención o una composición que comprende el compuesto. En otras modalidades, la presente invención proporciona un compuesto para tratar un trastorno mediado por ACC en un paciente en necesidad del mismo, que comprende la etapa de administrar al paciente un compuesto de acuerdo con la presente invención o una composición farmacéuticamente aceptable del mismo. Estos trastornos se describen con detalle en la presente.

En algunas modalidades los compuestos y composiciones de la presente invención se pueden utilizar en un método para tratar obesidad u otro trastorno metabólico. En ciertas modalidades, los compuestos y composiciones de la presente invención se pueden utilizar para tratar obesidad u otro trastorno metabólico en un mamífero. En ciertas modalidades el mamífero es un paciente humano. En ciertas modalidades los compuestos y composiciones de la presente

invención se pueden utilizar para tratar obesidad u otro trastorno metabólico en un paciente humano.

En algunas modalidades, la presente invención proporciona un método para tratar obesidad u otro trastorno metabólico, que comprende administrar un compuesto o composición de la presente invención a un paciente con obesidad u otro trastorno metabólico. En ciertas modalidades, el método de tratamiento de obesidad u otro trastorno metabólico comprende administrar compuestos y composiciones de la presente invención a un mamífero. En ciertas modalidades el mamífero es un humano. En algunas modalidades el trastorno metabólico es dislipidemia o hiperlipidemia. En algunas modalidades la obesidad es un síntoma del síndrome de Prader-Willi, del síndrome de bardet-Biedl, del síndrome de Cohen o del síndrome MOMO. En algunas modalidades la obesidad es un efecto secundario de la administración de otro medicamento que incluye pero que no se limita a insulina, sulfonilureas, tiazolidinedionas, antipsicóticos, antidepresivos, esteroides, anticonvulsivantes (que incluyen fenitoína y valproato), pizotifeno o anticonceptivos hormonales.

En ciertas modalidades, la presente invención proporciona un método para tratar cáncer u otro trastorno proliferativo que comprende administrar a un compuesto composición de la presente invención a un paciente con cáncer u otro trastorno proliferativo. En ciertas modalidades, el

método de tratar cáncer u otro trastorno proliferativo comprende administrar compuestos y composiciones de la presente invención a un mamífero. En ciertas modalidades, el mamífero es un humano.

Como se utiliza en la presente, los términos "inhibición de cáncer" e "inhibición de proliferación de células cancerosas" se refiere a la inhibición del crecimiento, división, maduración o viabilidad de células cancerosas y/o causa de muerte de células cancerosas, individualmente o en un agregado con otras células cancerosas por citotoxicidad, supresión de nutrientes o inducción de apoptosis.

Los ejemplos de tejidos que contienen células cancerosas cuya proliferación se inhibe por los compuestos y composiciones que aquí se describen y contra los cuales los métodos aquí descritos son útiles e incluyen, pero no se limitan a mama, próstata, cerebro, sangre, médula ósea, hígado, páncreas, piel, riñón, colon, ovario, pulmón, testículo, pene, tiroides, paratiroides, hipófisis, timo, retina, uvea, conjuntiva, bazo, cabeza, cuello, traquea, vesícula biliar, recto, glándula salival, glándulas suprarrenales, garganta, esófago, nódulos linfáticos, glándulas sudoríparas, glándulas sebáceas, músculo, corazón y estómago.

En algunas modalidades, el cáncer tratado por

compuestos o composiciones de la invención es un melanoma, liposarcoma, cáncer de pulmón, cáncer de mama, cáncer de próstata, leucemia, cáncer renal, cáncer esofágico, cáncer cerebral, linfoma o cáncer de colon. En ciertas modalidades, el cáncer es un linfoma de efusión primaria (PEL, por sus siglas en inglés). En ciertas modalidades preferidas el cáncer que se va a tratar por compuestos o composiciones de la invención es uno que presenta una vía MAPK activada. En algunas modalidades, el cáncer que presenta una vía MAPK es un melanoma. En ciertas modalidades preferidas el cáncer tratado por compuestos o composiciones de la invención es uno asociado con la mutación BRCA1. En una modalidad preferida especialmente, el cáncer tratado por compuestos o composiciones de la invención es un cáncer de mama triple negativo.

En ciertas modalidades, la enfermedad la cual puede ser tratada por compuestos de la invención son trastornos neurológicos. En algunas modalidades, el trastorno neurológico es enfermedad de Alzheimer, enfermedad de parkinson, epilepsia, isquemia, deterioro de memoria asociado con la edad, deterioro cognitivo ligero, ataxia de Friedreich, epilepsia deficiencia de GLUT1, leprechaunismo, síndrome de Rabson-Mendenhall, demencia por injerto de derivación arterial coronario, pérdida de memoria inducida por anestesia, esclerosis lateral amiotrófica, corea de Huntington gliomaor.

En ciertas modalidades, la enfermedad la cual puede ser tratada por compuestos de la invención es una enfermedad infecciosa. En algunas modalidades, la enfermedad infecciosa es una infección viral. En algunas modalidades la infección viral es infección por citomegalovirus o infección por influenza. En algunas modalidades, la enfermedad infecciosa es una infección micótica. En algunas modalidades, la enfermedad infecciosa es una infección bacteriana.

En algunas modalidades, los compuestos de la presente invención se pueden utilizar en el tratamiento de cualquiera de las enfermedades aquí citadas.

Dependiendo de la condición o enfermedad particular que va a ser tratada, agentes terapéuticos adicionales, los cuales normalmente se administran para tratar esa condición, se pueden administrar en combinación con compuestos y composiciones de esta invención. Como se utiliza en la presente, agentes terapéuticos adicionales que normalmente se administran para tratar una enfermedad o condición particular se conocen como “apropiados para la enfermedad o condición que es tratada”.

En ciertas modalidades, se proporciona un compuesto o una composición del mismo que se administre en combinación con otro inhibidor de ACC o agente antiobesidad. En algunas modalidades se proporciona un compuesto o composición del mismo, que se administre en combinación con uno o más agentes

terapéuticos adicionales. Estos agentes terapéuticos incluyen, pero no se limitan a agentes tales como orlistat (Xenical), estimulantes del SNC, Qsymia o Belviq.

En ciertas modalidades se proporciona un compuesto o una composición del mismo que se administra en combinación con otro agente anticancerígeno, citotoxina o agente quimioterapéutico a un paciente en necesidad del mismo.

En ciertas modalidades, el agente anticancerígeno o los agentes quimioterapéuticos utilizados en combinación con compuestos o composiciones de la invención incluyen, pero no se limitan a metformina, fenformina, buformina, imatinib, nilotinib, gefitinib, sunitinib, carfilzomib, salinosporamida A, ácido retinoico, cisplatino, carboplatino, oxaliplatino, mecloretamina, ciclofosfamida, clorambucilo, ifosfamida, azatioprina, mercaptopurina, doxifluridina, fluorouracilo, gemcitabina, metotrexato, tioguanina, vincristina, vinblastina, vinorelbina, vindesina, podofilotoxina, etopósido, tenipósido, taflupósido, paclitaxel, docetaxel, irinotecano, topotecano, amsacrina, actinomicina, doxorrubicina, daunorrubicina, valrrubicina, idarrubicina, epirrubicina, plicamicina, mitomicina, mitoxantrona, melfalano, busulfano, capecitabina, pemetrexed, epotilonas, ácido 13-cis-retinoico, 2-CdA, 2-clorodesoxiadenosina, 5-azaitidina, 5-fluorouracilo, 5-FU, 6-mercaptopurina, 6-MP, 6-TG, 6-tioguanina, abraxane, Accutane^{MR}, actinomicina D,

Adriamycin[MR], Adrucil[MR], Afinitor[MR], Agrylin[MR], Ala-Cort[MR] aldesleucina, alemtuzumab, ALIMTA, alitretinoína, Alkaban-AQ[MR], Alkeran[MR], ácido todo-transretinoico, interferón alfa, altretamina, ametopterina, amifostina, aminoglutetimida, anagrelida, Anandron[MR], anastrozol, arabinosilcitosina, Ara-C, Aranesp[MR], Aredia[MR], Arimidex[MR], Aromasin[MR], Arranon[MR], trióxido de arsénico, Arzerra[MR], asparaginasa, ATRA, Avastin[MR], azacitidina, BCG, BCNU, bendamustina, bevacizumab, bexaroteno, BEXXAR[MR], bicalutamida, BiCNU, Blenoxane[MR], bleomicina, bortezomib, busulfano, Bulsulfex[MR], C225, leucovorina de calcio, Campath[MR], Camptosar[MR], campotecina-11, capecitabina, Carac[MR], carboplatino, carmustina, oblea de carmustina, Casodex[MR], CC-5013, CCI-779, CCNU, CDDP, CeeNu, Cerubidine[MR],cetuximan, clorambucilo, factor de citrovorum, cladribina, cortisona, Cosmegen[MR], CPT-11, Cytraden[MR], Cytosar-U[MR],cytoxan[MR], dacarbazina, dacogen, dactinomicina, darbepoyetina alfa, dasatinib, daunomicina, clorhidrato de daunorrubicina, daunorrubicina liposómica, DaunoXome[MR], decadrón, decitabina, Delta-Cortef[MR], Deltasone[MR], denileucina, diftitox, DepoCyt[MR], dexametasona, acetato de dexametasona, fosfato de dexametasona de sodio, dexasona, dexrazoxano, DHAD, DIC, diodex, docetaxel, Doxil[MR], doxorrubicina, doxorrubicina liposómica, Droxia[MR], DTIC, DTIC-Dome[MR], Duralone[MR], Efudex[MR], Eligard[MR], Ellence[MR], Eloxatin[MR], Elspar[MR], Emcyt[MR], epirrubicina, epoyetina alfa, erbotux, erlotinib,

L-asparaginasa de Erwinia, estramustina, etiol, Etopophos[MR], etopósido, fosfato de etopósido, Eulexin[MR], everolimus, Evista[MR], exemestano, Fareston[MR], Faslodex[MR], Femara[MR], filgrastim, fluxuridina, Fludara[MR], fludarabina, Fluoroplex[MR], fluorouracilo, fluorouracilo (crema), fluoximesterona, fltamida, ácido folínico, FUDR[MR], fulvestrant, G-CSF, geftinib, gemcitabina, gemtuzumab, ozogamicina, Gemzar Gleevec[MR], Gliadel[MR] obleas, GM-CSF, goserelina, factor estimulante de colonia de granulocitos, factor estimulante de colonia de macrófagos, Halotestina[MR], Herceptina[MR], hexadrol, Hexalen[MR], hexametilmelamina, HMM; Hycamtin[MR], Hydrea[MR], Hydrocort Acetato[MR], hidrocortisona, fosfato de hidrocortisona de sodio, succinato de hidrocortisona de sodio, fosfato de hidrocortona, hidroxiurea, ibritumomab, ibritumomab, tiuxetan, Idamycin[MR], Idarrubicin Ifex[MR], IFN-alfa, ifosfamida, IL-11, IL-12, mesilato de imatinib, imidazol carboxamida, interferón alfa, interferón alfa 2b (conjugado de PEG), interleucina-2, interleucina-11, intrón A[MR] (interferón alfa-2b), Iressa[MR], irinotecano, isotretinoína, ixabepilona, Ixempra[MR], Kidrolasa[MR], Lanacort[MR], lapatinib, L-asparaginasa, LCR, lenalidomida, letrozol, leucovorina, leukerano, Leukine[MR], leuprolida, leurocristina, Leustatin[MR], Ara-C liposómica, Liquid Pred[MR], lomustina, L-PAM, L-sarcolisina, Lupron[MR], Lupron Depot[MR], Matulane[MR], maxidex, mecloretamina, clorhidrato de mecloretamina, Medralone[MR], Medrol[MR], Megace[MR], megestrol,

acetato de megestrol, melfalano, mercaptopurina, mesna, Mesnex[MR], metrotrexato, metotrexato de sodio, metilprednisolona, Meticorten[MR], mitomicina, mitomicina-C, mitoxantrona, M-Prednisol[MR], MTC, MTX, Mustargen[MR], mustina, Mutamycin[MR], myleran[MR], mylocel[MR], Mylotarg[MR], Navelbine[MR], nelarabina, Neosar[MR], Neulasta[MR], Neumega[MR], Neupogen[MR], Nexavar[MR], Nilandron[MR], Nilotinib, nilutamida, Nipent[MR], mostaza nitrogenada, Novaldex[MR], Novantrona[MR], Nplate, octeotride, acetato de octeotride, ofatumumab, Oncospar[MR], Oncovin[MR], Ontak[MR], Onxal[MR], oprelvekina, Orapred[MR], Orasone[MR], oxaliplatino, paclitaxel, paclitaxel unido a proteína, pamidronato, panitumumab, Panretin[MR], Paraplatin[MR], pazopanib, Pediapred[MR], PEG interferón, pegaspargasa, pegfilgrastim, PEG-INTRON[MR], PEG-L-asparaginasa, PEMETREXED, pentostatina, mostaza de fenilalanina, Platinol[MR], Platinol-AQ[MR], prednisolona, prednisona, Prelone[MR], procarbazina, PRIOCRIT[MR], Proleukin[MR], prolifeprospan 20 con implante de carmustina, Purinethol[MR], raloxifeno, Revlimid[MR], Rheumatrex[MR], Rituxan[MR], rituximab, Roferon A[MR] (interferón alfa-2a), romiplostim, Rubex[MR], clorhidrato de rubidomicina, Sandistatin[MR], Sandostatin LAR[MR], Sargramostim, Solu-Cortef[MR], Solu-Medrol[MR], Sorafenib, SPRYCEL[MR], STI-571, estreptozocina, SU11248, sunitinib, Sutent[MR], tamoxifeno, Tarceva[MR], Targretin[MR], Tasigna[MR], Taxol[MR], Taxotéro[MR], Temodar[MR], temozolomida, temsirolimus, tenipósido, TESPA, talidomida, Thalomid[MR],

TheraCys[MR], tioguanina, Thioguanine Tabloid[MR], tiofosfoamida, Thioplex[MR], tiotepa, TICE[MR], Toposar[MR], topotecano, toremifeno, Torisel[MR], tositumomab, trastuzumab, Treanda[MR], Tretinoina, Trexall[MR], trisenox[MR], TSPA, TYKERB[MR], VCR, Vectibix[MR], Velban[MR], Velcade[MR], VePesid[MR], Vesanoid[MR], Viadur[MR], Vidaza[MR], vinblastina, sulfato de vinblastina, Vincasar Pfs[MR], vincristina, vinorelbina, tartrato de vinorelbina, VLB, VM-26, vorinostat, votrient, VP-16, Vumon[MR], Xeloda[MR], Zanosar[MR], Zevalin[MR], Zinecard[MR], Zoladex[MR], ácido zoledrónico, zolinza, Zometa[MR], o combinaciones de cualquiera de los anteriores.

En ciertas modalidades, los compuestos de la presente invención se pueden administrar junto con una biguanida que se selecciona de metformina, fenformina o buformina a un paciente en necesidad del mismo. En ciertas modalidades, al paciente se le administra una combinación de un compuesto de la invención y una biguanida quien padece de cáncer, obesidad, enfermedad del hígado, diabetes o dos o más de los anteriores.

En ciertas modalidades, una combinación de 2 o más agentes terapéuticos se pueden administrar juntos con compuestos de la invención. En ciertas modalidades, una combinación de 3 o más agentes terapéuticos se pueden administrar con compuestos de la invención.

Otros ejemplos de agentes de inhibidores de esta invención también se pueden combinar incluyen, sin limitación:

vitaminas y suplementos nutricionales; vacunas contra el cáncer, tratamientos para neutropenia (por ejemplo G-CSF, filgrastrim, lenograstim), tratamientos para trombocitopenia (por ejemplo, transfusión sanguínea, eritropoyetina), inhibidores de PI3 cinasa (PI3K), inhibidores de MEK, activadores de AMPK, inhibidores de PCSK9, inhibidores de la proteasa de sitio 1 de SREBP, inhibidores de HMG CoA-reductasa, antieméticos (por ejemplo antagonistas del receptor 5-HT_3, antagonistas de dopamina, antagonistas del receptor NK1, antagonistas de receptor de histamina, cannabinoides, benzodiazepinas o anticolinérgicos), tratamientos para enfermedad de Alzheimer tales como Aricep^{MR} y Excelon^{MR}; tratamiento para enfermedad de Parkinson tal como L-DOPA/carbidopa, entacapona, ropinrole, pramipexole, bromocriptina, pergolida, trihexefendilo y amantadina; agentes para tratar esclerosis múltiple (MS, por sus siglas en inglés) tal como interferón beta (por ejemplo Avonex^{MR} y Rebif^{MR}), Copaxone^{MR} y mitoxantrona; tratamientos para asma tal como albuterol y Singulair^{MR}; agentes para tratar esquizofrenia tales como zyprexa, risperdal, seroquel y haloperidol; agentes antiinflamatorios tales como corticosteroides, bloqueadores de TNF, IL-1 RA, azatioprina, ciclofosfamida y sulfasalazina; agentes inmunomoduladores e inmunosupresores tales como ciclosporina, tacrolimus, rapamicina, micofenolato mofetilo, interferones, corticosteroides, ciclofofamida, azatioprina y

sulfasalazina; factores neutróficos tales como inhibidores de acetilcolinesterasa, inhibidores de MAO, interferones, anticonvulsivantes, bloqueadores de canal de iones, riluzol y agentes anti-Parkinsonianos; agentes para tratar enfermedades cardiovasculares tales como beta-bloqueadores, inhibidores de ACE, diuréticos, nitratos, bloqueadores de canal de calcio y estatinas, fibratos, inhibidores de absorción de colesterol, secuestrantes de ácido biliar y niacina; agentes para tratar enfermedad hepática tales como corticosteroides, colestiramina, interferonas y agentes anti virales; agentes para tratar trastornos de la sangre tales como corticosteroides, agentes anti-leucémicos y factores de crecimiento; agentes para tratar trastornos de inmunodeficiencia tal como gamma globulina; y agentes anti-diabéticos tales como biguanidas (metformina, fenformina, buformina), tiazolidinadionas (rosiglitazona, pioglitazona, troglitazona), sulfonilureas (tolbutamida, acetohexamida, tolazamida, clorpropamida, glipizida, gliburida, glimepirida, gliclazida), meglitinidas (repaglinida, nateglinida), inhibidores de alga-glucosidasa (miglitol, acarbosa), miméticos de incretina (exenatida, liraglutida, taspoglutida), análogos de péptido inhibidor gástrico, inhibidores de DPP-4 (vildagliptina, sitagliptina, saxagliptina, linagliptina, alogliptina), análogos de amilina (pramlintida) e insulina y análogos de insulina.

En ciertas modalidades, los compuestos de la presente invención o una composición farmacéuticamente aceptable de los mismos se administran en combinación con agentes antisentido, un anticuerpo monoclonal o policlonal o con una sustancia terapéutica ARNsi.

Aquellos agentes adicionales se pueden administrar por separado a partir de una composición que contenga compuesto de la invención, como parte de un régimen de dosificación múltiple. De manera alternativa, aquellos agentes pueden ser partes de una forma de dosificación única, se pueden mezclar junto con un compuesto de esta invención en una composición única. Si se administra como parte de un régimen de dosificación múltiple, dos o más agentes activos se pueden suministrar simultáneamente, de modo secuencial o dentro de un período de tiempo uno con respecto de otro, normalmente dentro de cinco horas entre sí.

Como se utiliza en la presente, el término "combinación", "combinado" y términos relacionados se refiere a la administración simultánea o secuencial de agentes terapéuticos de acuerdo con esta invención. Por ejemplo, un compuesto de la presente invención se puede administrar con otro agente terapéutico de manera simultánea o secuencial en formas de dosificación unitarias separadas o juntos en una forma de dosificación unitaria única. En consecuencia, la presente invención proporciona una forma de dosificación

unitaria única que comprende un compuesto de fórmula I, un agente terapéutico adicional y un portador, adyuvante o vehículo farmacéuticamente aceptable.

La cantidad de ambos, un compuesto de la invención y un agente terapéutico adicional (en aquellas composiciones las cuales comprenden un agente terapéutico adicional como se describe en lo anterior) que se pueden combinar con los materiales portadores para producir una forma de dosificación única variará dependiendo del hospedador tratado y el modo de administración particular. Preferiblemente, las composiciones de esta invención se pueden formular de manera que se pueda administrar una dosificación entre 0.01 - 100 mg/kg de peso corporal/día de un producto de la invención.

En aquellas composiciones las cuales comprenden un agente terapéutico adicional, ese agente terapéutico adicional y el compuesto de esta invención pueden actuar de modo sinergístico. Por lo tanto, la cantidad de agente terapéutico adicional en estas composiciones será menor que la que se requiere en un monotratamiento utilizando únicamente ese agente terapéutico. En estas composiciones se puede administrar una dosificación de entre 0.01 a 100 μg/kg de peso corporal/día de un agente terapéutico adicional.

La cantidad de agente terapéutico adicional presente en las composiciones de esta invención será no mayor que la cantidad que normalmente se administraría en una composición

que comprende a ese agente terapéutico como el único agente activo. Preferiblemente, la cantidad de agente terapéutico adicional en las composiciones descritas actualmente variará de aproximadamente 50% a 100% de la cantidad normalmente presente en una composición que comprende a ese agente como el único agente terapéuticamente activo.

La invención se relaciona adicionalmente con una composición agrícola que comprende por lo menos un compuesto de fórmula I como se define en lo anterior o una sal agrícolamente aceptable del mismo y un portador líquido o sólido. Los portadores adecuados así como auxiliares y compuestos activos adicionales los cuales también pueden estar contenidos en la composición de la invención se definen en lo siguiente.

Las "sales agrícolamente aceptables" adecuadas incluyen pero no se limitan a sales de aquellos cationes o las sales de adición de ácido de aquellos ácidos cuyos cationes y aniones, respectivamente, no tienen efecto adverso sobre la acción fungicida de los compuestos de fórmula I. De esta manera, los cationes adecuados son en particular los iones de metales alcalinos, preferiblemente de sodio y de potasio de los metales alcalinotérreos, preferiblemente calcio, magnesio y bario y de los metales de transición, preferiblemente manganeso, cobre, zinc y hierro y también el ión amonio el cual, si se desea, puede presentar uno a cuatro sustituyentes

alquilo de 1 a 4 átomos de carbono y/o un sustituyente fenilo o bencilo, preferiblemente diisopropilamonio, tetrametilamonio, tetrabutilamonio, trimetilbencilamonio. Las sales agrícolamente aceptables adicionales incluyen iones fosfonio, iones sulfonio, preferiblemente tri(alquil de 1 a 4 átomos de carbono)sulfonio e iones sulfoxonio, preferiblemente tri(alquil de 1 a 4 átomos de carbono)sulfoxonio. Los aniones de sales de adición de ácido útiles son principalmente cloruro, bromuro, fluoruro, sulfato ácido, sulfato, fosfato diácido, fosfato ácido, fosfato, nitrato, bicarbonato, carbonato, hexafluorosilicato, hexafluorofosfato, benzoato y también los aniones de ácidos alcanoicos de 1 a 4 átomos de carbono, preferiblemente formiato, acetato, propionato y butirato. Estas sales de adición de ácido agrícolamente aceptables se pueden formar al hacer reaccionar compuestos de fórmula I que presentan un grupo ionizable básico con un ácido del anión correspondiente, preferiblemente ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido fosfórico o ácido nítrico.

Los compuestos de fórmula I y las composiciones de acuerdo con la invención, respectivamente, son adecuados como fungicidas. Se distinguen por una eficacia sorprendente contra una amplia gama de hongos fitopatogénicos que incluyen hongos transportados por el suelo, los cuales derivan principalmente de las clases Plasmodiophoromycetes, Peronosporomycetes

(sinónimo de Oomycetes), Chytridiomycetes, Zygomycetes, Ascomycetes, Basidiomycetes y Deuteromycetes (sinónimo de hongos imperfectos). Algunos son sistemáticamente eficaces y pueden ser utilizados en la protección de cosechas como fungicidas foliares, fungicidas para apósito de semillas y fungicidas para el suelo. Además, son adecuados para controlar hongos dañinos los cuales se presentan, por ejemplo, en la madera o las raíces de las plantas.

En algunas modalidades, los compuestos de fórmula I en las composiciones de acuerdo con la invención son particularmente importantes en el control de hongos fitopatogénicos sobre diversas plantas cultivadas tales como cereales, por ejemplo trigo, centeno, cebada, tritical, avena o arroz; remolachas; por ejemplo remolacha de azúcar o remolacha fodder; frutos tales como manzanas, frutos con nueces o frutos suaves, por ejemplo manzanas, peras, ciruelas, duraznos, almendras, cerezas, fresas, arándanos, bayas negras o gooseberries; plantas leguminosas tales como lentejas, chícharos, alfafa o frijol de soya; plantas oleosas tales como colza, mostaza, oliva, girasol, coco, granos de cacao, plantas de aceites de ricino, palmas oleosas, nueces molidas o frijoles de soya, curcubitáceas tales como pepinillos, pepinos o melones; plantas fibrosas tales como algodón, lino, cáñamo o yute; frutos cítricos tales como naranjas, limones, toronjas o mandarinas; vegetales tales como espinacas, lechugas,

espárragos, repollos, zanahorias, cebollas, tomates, papas curcubitáceas o prapica; plantas lauraceosas tales como aguacate, canela o alcanfor; plantas energéticas y de materia prima tales como maíz, frijol de soya, colza, caña de azúcar o palma de aceite; maíz; tabaco; nueces; café; té; plátanos; viñedos (uvas de mesa y uvas de jugo y uvas de vino); hop; turf; plantas rubiáceas naturales o plantas de ornato y del bosque tales como flores, arbustos, árboles con hojas amplias o pereniforias; por ejemplo coníferas o sobre material de propagación de plantas tales como semillas y el material de cosecha de estas plantas.

En algunas modalidades, los compuestos de fórmula I y composiciones de los mismos, respectivamente, se utilizan para controlar una multitud de hongos en cosechas de campos tales como papas, azúcar, remolachas, tabaco, trigo, centeno, cebada, avena, arroz, maíz, algodón, frijol de soya, colza, legumbres, girasoles, café o caña de azúcar; frutos; viñedos; plantas de ornato o vegetales tales como pepinos, tomates, frijoles o calabazas.

El término “material de propagación vegetal” debe entenderse que indica todas las partes generativas de una planta tales como semillas y material vegetal vegetativo tales cortes y tubérculos (por ejemplo papas), los cuales se pueden utilizar para la multiplicación de la planta. Estos incluyen semillas, raíces, frutos, tubérculos, bulbos, rizomas,

retoños, brotes y otras partes de las plantas que incluyen plántulas y plantas pequeñas las cuales van a ser transplantadas después de germinación o después de surgimiento del suelo. Estas plantas jóvenes también pueden ser protegidas antes del transplante por un tratamiento total o parcial por inmersión o vertido.

En algunas modalidades, el tratamiento de materiales de propagación de plantas con compuestos de la fórmula I y composiciones de las mismas, respectivamente, se utilizan para controlar una multitud de hongos sobre cereales tales como trigo, centeno, cebada y avena; arroz; maíz, algodón y frijol de soya.

El término “plantas cultivadas” debe entenderse que incluye plantas las cuales se han modificado por crianza, mutagénesis o manipulación genética que incluye pero que no se limita a productos biotecnológicos agrícolas en el mercado o en desarrollo. Las plantas modificadas genéticamente son plantas las cuales son material genético que va a ser modificado de manera tal por el uso de técnicas de ADN recombinante que bajo circunstancias naturales no pueden obtenerse fácilmente por crianza cruzada, mutaciones o recombinación natural. Típicamente, uno o más genes han sido integrados en el material genético de una planta modificada genéticamente con el fin de mejorar ciertas propiedades de la planta. Estas modificaciones genéticas también incluyen pero

no se limitan a modificaciones post-transduccionales dirigidas de una o varias proteínas, oligo- o polipéptidos, por ejemplo por glucosilación o adiciones de polímero tales como porciones preniladas, acetiladas o farnesiladas o porciones PEG.

Las plantas que han sido modificadas por crianza, mutagénesis o manipulación genética, por ejemplo, se han vuelto tolerantes a aplicaciones de clases específicas de herbicidas tales como inhibidores de hidrofenilpiruvato dioxigenasa (HPPD); inhibidores de acetolactato sintasa (ALS) tales como sulfonilureas (véase, por ejemplo, US 6,222,100, WO 01/82685, WO 00/26390, WO 97/41218, WO 98/02526, WO 98/02527, WO 04/106529, WO 05/20673, WO 03/14357, WO 03/13225, WO 03/14356, WO 04/16073) o imida- zolinonas (véase, por ejemplo, US 6,222,100, WO 01/82685, WO 00/26390, WO 97/41218, WO 98/02526, WO 98/02527, WO 04/106529, WO 05/20673, WO 03/14357, WO 03/13225, WO 03/14356, WO 04/16073); inhibidores de enolpiruvilshikimato-3-fosfato sintasa (EPSPS) tales como glifosato (véase, por ejemplo, WO 92/00377); inhibidores de glutamina sintetasa (GS) tales como glufosinato (véase, por ejemplo, EP-A 242 236, EP-A 242 246) o herbicidas de oxinilo (véase por ejemplo US 5,559,024) como un resultado de métodos convencionales de crianza o manipulación genética. Varias plantas cultivadas se han vuelto tolerantes a herbicidas por métodos convencionales de crianza (mutagénesis) por ejemplo la colza de verano Clearfield^{MR} (Canola, BASF, SE, Alemania) que

es tolerante a imidazolinonas, por ejemplo imazamox. Se han utilizado métodos de manipulación genética para volver a las plantas cultivadas tales como frijol de soya, algodón, maíz, remolachas y colza tolerantes a herbicidas tales como glifosato o glufosinato, algunos de los cuales están disponibles comercialmente bajo los nombres comerciales RoundupReady^{MR} (tolerante a glifosato, Monsanto, Estados Unidos) y LibertyLink^{MR} (tolerante a glufosinato, Bayer CropScience, Alemania).

Además, las plantas también están cubiertas por el uso de técnicas de ADN recombinantes que son capaces de sintetizar una o más proteínas insecticidas, especialmente aquellas conocidas de las bacterias de los géneros Bacillus particularmente de *Bacillus thuringiensis*, tal como δ-endotoxinas, por ejemplo CrylA(b), CrylA(c), CrylF, CrylF(a2), CryllA(b), CrylllA CrylllB(bi) o Cryθc; proteínas insecticidas vegetativas (VIP, por sus siglas en inglés), por ejemplo VIP1, VIP2, VIP3 o VIP3A; proteínas insecticidas de nemátodos colonizadores de bacterias, por ejemplo Photorhabdus spp. o Xenor-handus spp; toxinas producidas por animales tales como toxinas de escorpión, toxinas de arácnidos, toxinas de avispas u otras neurotoxinas específicas de insecto; toxinas producidas por hongos, tales como toxina de Streptomycetes, lectinas de plantas tales como lectinas de chícharo o cebada; aglutininas; inhibidores de proteinasa tales como inhibidores

de tripsina, inhibidores de serina proteasa, inhibidores de patatina, cistatina o pa-paína; proteínas inactivadas de ribosoma (RIP) tales como ricina, maíz-RIP, abrina, lufina, saporina o briodina; enzimas del metabolismo de esteroides tal como 3-hidroxiesteroide oxidasa, ecdisteroide-IDP-glucosil-transferasa, colesterol oxidasas, inhibidores de ecdisona o HMG-CoA-reductasa; bloqueadores de canal de iones tales como bloqueadores de canales de sodio o calcio; esterasa de hormona juvenil; receptores de hormona diurética (receptores de helicocinina); estilbeno sintasa, bibencil sintasa, quitinasas o glucanasas. En el contexto de la presente invención, estas proteínas insecticidas o toxinas se debe entender que expresamente también son pre-toxinas, proteínas híbridas, truncadas o proteínas modificadas de alguna otra manera. Las proteínas híbridas se caracterizan por una combinación nueva de dominios de proteína (véase, por ejemplo, WO 02/015701). Los ejemplos adicionales de estas toxinas o de plantas modificadas genéticamente capaces de sintetizar estas toxinas se describen, por ejemplo, en EP-A 374 753, WO 93/007578, WO 95/34656, EP-A 427 529, EP-A 451 878, WO 03/18810 y WO 03/52073. Los métodos para producir estas plantas modificadas genéticamente generalmente se conocen por las personas expertas en el ámbito y se describen, por ejemplo, en las publicaciones mencionadas antes. Estas proteínas insecticidas contenidas en plantas modificadas genéticamente imparten a las

plantas productoras de estas proteínas tolerancia a plagas dañinas de todos los grupos taxonómicos y artrópodos, especialmente escarabajos (Coleoptera), insectos con dos alas (Diptera) y polillas (Lepidoptera) y nemátodos (Nematoda). Las plantas modificadas genéticamente capaces de sintetizar una o más proteínas insecticidas se describen, por ejemplo, en las publicaciones mencionadas antes y algunas de ellas están disponibles comercialmente tales como YieldGard^{MR} (cultivos de maíz productores de toxina CryiAb), YieldGard^{MR} Plus (cultivos de maíz que producen toxinas Cry1 Ab y Cry3Bb1), Starlink^{MR} (cultivos de maíz que producen la toxina Cry9c), Her-culex^{MR} RW (cultivos de maíz que producen Cry34Ab1, Cry35Ab1 y la enzima fosfi-notricin-N-acetiltransferasa [PAT]); NuCOTN^{MR} 33B (cultivos de algodón que producen la toxina Cry1 Ac), Bollgard^{MR} I (cultivos de algodón que producen la toxina CryiAc), Bollgard^{MR} II (cultivos de algodón que producen las toxinas CryiAc y Cry2Ab2); VIPCOT^{MR} (cultivos de algodón que producen la toxina VIP); NewLeaf^{MR} (cultivos de papa que producen la toxina Cry3A); Bt-Xtra^{MR}, NatureGard^{MR}, KnockOut^{MR}, BiteGard^{MR}, Protecta^{MR}, Bt 1 1 (por ejemplo, Agrisure^{MR} CB) y Bt176 de Syngenta Seeds SAS, Francia (cultivos de maíz productores de la toxina CryiAb y la enzima PAT), MIR604 de Syngenta Seeds SAS, Francia (cultivos de maíz que producen una versión modificada de la toxina Cry3A, véase WO 03/018810), MON 863 de Monsanto Europe S.A., Bélgica (cultivos de maíz

productores de la toxina Cry3Bb1), IPC 531 de Monsanto Europe S.A., Bélgica (cultivo de algodón productores de una versión modificada de la toxina CryiAc) y 1507 de Pioneer Overseas Corporation, Bélgica (cultivos de maíz productores de la toxina Cry1 F y la enzima PAT).

Además, las plantas también están cubiertas en la medida en que, mediante el uso de técnicas de ADN recombinantes, sean capaces de sintetizar una o más proteínas para incrementar la resistencia o tolerancia de estas plantas a patógenos bacterianos, virales o micóticos. Los ejemplos de estas proteínas son las denominadas "proteínas relacionadas con patogénesis (proteínas PR, véase, por ejemplo EP-A 392225), genes de resistencia a enfermedades en plantas (por ejemplo, cultivos de papa, los cuales expresan genes de resistencia que actúan contra *Phytophthora infestans* derivada de la papa silvestre Mexicana Solanum bulbocastanum) o T4-lisozima (por ejemplo, cultivos de papa capaces de sintetizar estas proteínas con resistencia aumentada contra bacterias tal como *Erwinia amylvora*). Los métodos para producir estas plantas modificadas genéticamente generalmente se conocen por las personas expertas en el ámbito y se describen, por ejemplo, en las publicaciones mencionadas en lo anterior.

Además, las plantas también están cubiertas en la medida en que, mediante el uso de técnicas de ADN

recombinante, son capaces de sintetizar una o más proteínas para incrementar la productividad (por ejemplo producción de biomasa, rendimiento de grano, contenido de almidón, contenido de aceite o contenido de proteína), tolerancia a sequía, salinidad u otros factores ambientales limitantes del crecimiento o tolerancia a plaga y patógenos micóticos, bacterianos o virales de estas plantas.

Además, las plantas también están cubiertas en la medida en que, mediante el uso de técnicas de ADN recombinantes contengan una cantidad modificada de sustancias de contenido o sustancias de contenido nuevas, específicamente para mejorar la nutrición humana o animal, por ejemplo cosecha de aceite que producen ácidos grasos omega-3 de cadena larga que promueve la salud o ácidos grasos omega-9 insaturados (por ejemplo colza Nexera^{MR}, DOW Agro Sciences, Canadá).

Además, también están abarcadas las plantas que, mediante el uso de técnicas de ADN recombinante, contienen una cantidad modificada de sustancias de contenido o sustancias de contenido nuevas, específicamente para mejorar la producción de materia prima, por ejemplo papas que producen cantidades aumentadas de amilopectina (por ejemplo papa Amflora^{MR}, BASF SE; Alemania).

Los compuestos de fórmula I y composiciones de los mismos, respectivamente, son particularmente adecuados para controlar las siguientes enfermedades de plantas:

Albugo spp. (rolla blanca) en plantas de ornato, vegetales (por ejemplo A. Candida) y girasoles (por ejemplo A. tragoponis); *Altemaria spp*. (manchas en las hojas de alternaria) sobre vegetales, colza {*A. brassicola* o *brassicae*), remolachas de azúcar (*A. tenuis*), frutos, arroz, frijol de soya, papas (por ejemplo *A. solani* o *A. alternata*), tomates (por ejemplo, *A. solani* o *A. alternata*) y trigo; *Aphanomyces spp*. sobre remolachas de azúcar y vegetales; *Ascochyta spp*. sobre cereales y vegetales, por ejemplo *A. tritici* (antracnosa) o trigo y *A. hordei* en cebada; *Bipolaris* y *Drechslera spp*. (teleomorfo: Cochliobolus spp.), por ejemplo plaga de hojas sureñas (*D. maydis*) o plaga de hojas norteñas (β-*zeicola*) sobre maíz, por ejemplo pústula de mancha (β. *sorokiniana*) sobre cereales y, por ejemplo, *B. oryzae* en arroz y césped; Blumeria (anteriormente *Erysiphe*), graminis (mildew polvoso) sobre cereales (por ejemplo, sobre trigo o cebada); *Botrytis cinerea* (teleomorfo: Botryotinia fuckeliana: moho gris) sobre las frutas y bayas (por ejemplo fresas), vegetales (por ejemplo lechugas, zanahorias, apio y repollo), colza, flores, viñedos, plantas del bosque y trigo; *Bremia lactucae* (mildew velloso) sobre lechuga; *Ceratocystis* (sinónimo *Ophiostoma*) spp. (podredumbre o marchitamiento) en árboles de hojas amplias y pereniforeas, por ejemplo *C. ulmi* (enfermedad de Olmo Holandés) sobre olmos; *Cercospora spp*. (manchas en hojas de *Cercospora*) sobre maíz (por ejemplo manchas de hojas

grises: *C. zeaemaydis*), arroz, remolachas de azúcar (por ejemplo *C. beticola*), caña de azúcar, vegetales, café, frijoles de soya (por ejemplo *C. sojina* o *C. kikuchii*) y arroz; *Cladosporium spp*. en tomates (por ejemplo, *C. fulvum*: moho de las hojas) y cereales, por ejemplo *C. herbarum* (oreja negra) en trigo; *Claviceps purpurea* (ergot) en cereales; *Cochliobolus* (anamorfo: *Helminthosporium* de bipolaris) spp. (manchas en las hojas) sobre maíz (*C. carbonum*), cereales (por ejemplo *C. sativus*, anamorfo: *B. sorokiniana*) y arroz (por ejemplo *C. miyabeanus*, anamorfo: *H. oryzae*); *Colletotrichum* (teleomorfo: *Glomerella*) spp. (anthracnosa) sobre algodón (por ejemplo *C. gossypii*), maíz (por ejemplo *C. graminicola*: podredumbre del talla por anthracnosa), frutos suaves, papas (por ejemplo *C. coccodes*: punto negro), frijoles (por ejemplo *C. lindemuthianum*) y frijoles de soya (por ejemplo *C. truncatum* o *C. gloeosporioides*); *Corticium spp*. por ejemplo *C. sasakii* (plaga de las vainas) sobre arroz; *Corynespora cassiicola* (manchas en las hojas) sobre frijoles de soya y plantas de ornato; *Cycloconium spp.* por ejemplo *C. oleaginum* en árboles de oliva; *Cylindrocarpon spp.* (por ejemplo, llaga del árbol de la fruta o marchitamiento de viñedo joven, teleomorfo: *Nectria* o *Neonectria spp.*) sobre árboles frutales, viñedos (por ejemplo *C. liriodendri*, teleomorfo: *Neonectria liriodendri*, enfermedad de patas negras) y plantas de ornato; *Dematophora* (teleomorfo: *Rosellinia*) necatrix (podredumbre de

raíz y tallos) en frijoles de soya, *Diaporthe spp.*, por ejemplo D. faseolorum (podredumbre húmeda) sobre frijoles de soya; *Drechslera* (sinónimo *Helminthosporium*, teleomorfo: *Pyrenophora*) spp. sobre maíz, cereales tales como cebada (por ejemplo, *D. teres*, pústula de red) y trigo (por ejemplo *D. tritici-repentis*: punto canela); arroz y césped; Esca (acronecrosis, apoplejía) en viñas, causado por *Formitiporia* (sinónimo *Phellinus*) punctata, *F. mediterranea*, *Phaeomoniella chlamydospora* (anteriormente *Phaeo- acremonium chlamydosporum*), *Phaeoacremonium aleophilum* y/o *Botryosphaeria obtusa*; *Elsinoe spp*. en frutos de pomo (*E. pyri*), frutos suaves (*E. veneta:* anthracnosa) y viñas (*E ampelina*: anthracnosa); *Entyloma oryzac* (tizón de las hojas) sobre arroz; *Epicoccum spp*. (moho negro) en trigo; *Erysiphe spp*. (mildew polvoso) sobre remolachas de azúcar (*E. betae*), vegetales (por ejemplo *E. pisi*), tales como curcubiteas (por ejemplo *E. cichoracearum*), repollos, colza (por ejemplo *E. cruciferarum*); *Eutypa lata* (llaga o acronecrósis Eutypa, anamorfo: *Cytosporina lata*, sinónimo *Libertella blepharis*) sobre árboles frutales, viñas y madera de ornato; *Exserohilum* (sinónimno *Helminthosporium*) spp. sobre maíz (por ejemplo *E. turcicum*); *Fusarium* (teleomorfo: *Gibberella*) spp. (marchitamiento, podredumbre de raíz o tallo) sobre diversas plantas tal como *F. graminearum* o *F. culmorum* (marchitamiento de raíz, roña o aleheña de cabeza) sobre cereales (por ejemplo

trigo o cebada), *F. oxysporum* en tomates, *F. solani* en frijoles de soya y *F. verticillioides* sobre maíz; *Gaeumannomyces graminis* (pietin) en cereales (por ejemplo, trigo o cebada) y maíz; *Gibberella spp.* en cereales (por ejemplo *G. zeae*) y arroz (por ejemplo *G. fujikuroi*: enfermedad de Bakanae); *Glomerella cingulata* en viñas, frutos de manzano y otras plantas y *G. gossypii* en algodón; complejos de tinción de granos en arroz; *Guignardia bidwellii* (podredumbre negra) en viñas; *Gymnosporangium spp.* en plantas rosáceas y juníperos, por ejemplo *G. sabinae* (roya) en peras; *Helminthosporium spp.* (sinónimos *Drechslera*, teleomorfo: *Cochliobolus*) en maíz, cereales y arroz; *Hemileia spp.*, por ejemplo *H. vastatrix* (roya de las hojas de café) en café; *Isariopsis clavispora* (sinónimo *Cladosporium vitis*) en viñas; *Macrophomina phaseolina* (sinónimo, *phaseoli*) (podredumbre de raíz y tallo) en frijoles de soya y algodón; *Microdochium* (sinónimo *Fusarium*) *nivale* (moho de nieve rosa) en cereales (por ejemplo trigo o cebada); *Microsphaera diffusa* (mildew polvoso) en frijoles de soya; *Monilinia spp.*, por ejemplo *M. laxa, M. fructicola* y *M. fructigena* (aleheña de floración y rama, podredumbre café) en frutos duros y otras plantas rosáceas; *Mycosphaerella spp.* en cereales, plátanos, frutos suaves y nueces molidas, tales como, por ejemplo, *M. graminicola* (anamorfo: *Septoria tritici,* pústula de *Septoria*) en trigo o *M. fijiensis* (enfermedad de Sigatoka

negra) en plátanos; *Peronospora spp*. (mildew velloso) en repollo (por ejemplo *P. brassicae*), colza (por ejemplo *P. parasitica*), cebollas (por ejemplo *P. destructor*), tabaco (*P. tabacina*) y frijoles de soya (por ejemplo, *P. manshurica*); *Phakopsora pachyrhizi* y *P. meibomiae* (roya del frijol de soya) en frijoles de soya; *Phialophora spp.* por ejemplo en viñas (por ejemplo *P. tracheiphila* y *P. tetraspora*) y frijoles de soya (por ejemplo *P. gregata*: podredumbre del tallo); *Phoma lingam* (podredumbre de raíz y tallo) en colza y repollo y *P. betae* (podredumbre de raíz, puntos en las hojas y podredumbre húmeda) en remolachas de azúcar; *Phomopsis spp*. en girasoles, viñas (por ejemplo *P. viticola*: manchas de caña y hoja) y frijoles de soya (por ejemplo podredumbre de tallo: *P. phaseoli*, teleomorfo: *Diaporthe phaseolorum*); *Physoderma maydis* (manchas café) en maíz; *Phytophthora spp.* (marchitamiento, raíz, hoja, fruto y raíz del tallo) en diversas plantas tales como paprika y curcubitáceas (por ejemplo *P. capsici*),frijoles de soya (por ejemplo *P. megasperma,* sinónimo *P. sojae*), papas y tomates (por ejemplo, *P. infestans*: aleheña tardía) y árboles de hojas amplias (por ejemplo *P. ramorum*: muerte súbita de roble); *Plasmodiophora brassicae* (raíz de barra) sobre repollo, colza, rábano y otras plantas; *Plasmopara* spp., por ejemplo *P. viticola* (mildew velloso de viñedo de uva) sobre viñas y P. halstediiou girasoles; *Podosphaera spp*. (mildew polvoso)

sobre plantas rosáceas, lúpulo, manzanas y frutos suaves, por ejemplo *P. leucotricha* en manzanas; *Polymyxa spp.*, por ejemplo en cereales tales como cebada y trigo (*P. graminis*) y remolachas de azúcar (*P. betae*) y enfermedades virales transmitidas por las mismas; *Pseudocercosporella herpotrichoides* (punto de ojo, teleomorfo: *Tapesia yallundae*) sobre cereales, por ejemplo trigo o cebada; *Pseudoperonospora* (mildew polvoso) sobre diversas plantas, por ejemplo *P. cubensis* en cucurbitáceas o *P. humili* en lúpulo; *Pseudopezicula tracheiphila* (enfermedad de fuego rojo o rotbrenner', anamorfo: *Phialo- phora*) en viñas; *Puccinia spp.* (roya) sobre diversas plantas, por ejemplo *P. triticina* (roya café o de hojas), *P. striiformis* (veta o roya amarilla), *P. hordei* (roya enana), *P. graminis* (roya de tallos o negra) o *P. recondita* (roya café o de hojas) sobre cereales, tales como, por ejemplo, trigo, cebada o centeno y espárragos (por ejemplo, *P. asparagi*); *Pyrenophora* (anamorfo: *Drechslera*) *tritici- repentis* (mancha canela) sobre trigo o *P. feres* (pústula de red) en cebada; *Pyricularia spp.*, por ejemplo *P. oryzae* (teleomorfo: *Magnaporthe grisea*, añuflo de arroz) sobre arroz y *P. grisea* en césped y cereales; *Pythium spp.* (podredumbre húmeda) en céspedes, arroz, maíz, trigo, algodón, colza, girasoles, frijoles de soya, remolachas de azúcar, vegetales y diversas otras plantas (por ejemplo *P. ultimum* o *P. aphanidermatum*); *Ramularia spp.*, por ejemplo *R. collo-cygni*

(puntos de hojas de Ramularia, puntos de hojas fisiológicos) en cebada y *R. beticola* en remolachas de azúcar; *Rhizoctonia spp.* en algodón, arroz, papas, césped, maíz, colza, papas, remolachas de azúcar, vegetales y diversas otras plantas, por ejemplo *R. solani* (podredumbre de raíz y tallo) en frijoles de soya, *R. solani* (aleheña de vaina) en arroz o *R. cerealis* (aleheña de primavera de *Rhizoctonia*) sobre trigo o cebada; *Rhizopus stolonifer* (moho negro, podredumbre suave) fresas, zanahorias, repollo, viñas y tomates; *Rhynchosporium secalis* (escaldadura) sobre cebada, centeno y triticale; *Sarocladium oryzae* y *S. attenuatum* (podredumbre de vaina) en arroz; *Sclerotinia spp.* (podredumbre de tallo o moho blanco) sobre vegetales y cosechas de campo tales como colza, girasoles (por ejemplo, *S. sclerotiorum*) y frijoles de soya (por ejemplo *S. rolfsii* o *S. sclerotiorum*); *Septoria spp.* en diversas plantas, por ejemplo *S. glycines* (manchas café) sobre frijoles de soya, *S. tritici* (pústula de *Septoria*) sobre trigo y S. (sinónimo *Stagonospora*) *nodorum* (pústula de *Stagonospora*) sobre cereales; *Uncinula* (sinónimo *Erysiphe*) *necator* (mildew polvoso, anamorfo: *Oidium tuckeri*) en viñas; *Setospaeria spp.* (aleheña de hoja) sobre maíz (por ejemplo *S. turcicum*, sinónimo *Helminthosporium turcicum*) y césped; *Sphacelotheca spp.* (tizón) en maíz, (por ejemplo *S. miliaria*: tizón de cabeza), sorgo y caña de azúcar; *Sphaerotheca fuliginea* (mildew polvoso) sobre cucurbitáceas; *Spongospora subterranea*

(roña polvosa) en papas y de esta manera se transmiten enfermedades virales; *Stagonospora spp.* en cereales, por ejemplo *S. nodorum* (pústula de *Stagonospora*, teleomorfo: *Leptosphaeria* [sinónimo *Phaeosphaeria*] *nodorum*) sobre trigo; *Synchytrium endobioticum* sobre papas (enfermedad de las verrugas de papa); *Taphrina spp.*, por ejemplo *T. deformans* (enfermedad de rizado de hojas) sobre duraznos y *T. pruni* (bolsa de ciruelas) en ciruelas; *Thielaviopsis spp.* (podredumbre de raíz negra) en tabaco, frutos de manzana, vegetales, frijoles de soya y algodón, por ejemplo *T. basicola* (sinónimo *Chalara elegans*); *Tilletia spp.* (tizón común o tizón maloliento sobre cereales, tales como, por ejemplo *T. tritici* (sinónimo *T. caries*, tizón de trigo) y *T. controversa* (tizón enano) sobre trigo; *Typhula incamata* (moho de nieve gris) sobre cebada o trigo; *Urocystis spp.*, por ejemplo *U. occulta* (tizón de tallo) sobre cebada; *Uromyces spp.* (roya) sobre vegetales, tales como frijoles (por ejemplo *U. appendiculatus*, sinónimo *U. phaseoli*) y remolachas de azúcar (por ejemplo *U. betae*); *Ustilago spp.* (tizón suelto) sobre cereales (por ejemplo *U. nuda* y *U. avaenae*), maíz (por ejemplo, *U. maydis*: tizón de maíz) y caña de azúcar; *Venturia spp.* (roña) en manzanas (por ejemplo *V. inaequalis*) y peras; y *Verticillium spp.* (marchitamiento) sobre diversas plantas, tales como frutos y plantas de ornato, viñas, frutos suaves, vegetales y cosechas de campo, por ejemplo *V. dahliae* en fresas, colza,

papas y tomates.

Los compuestos de fórmula I y composiciones de los mismos, respectivamente, también son adecuados para controlar hongos dañinos en la protección de productos almacenados o cosechas y en la protección de materiales. El término "protección de materiales" debe entenderse que indica la protección de materia técnica y no viva, tales como adhesivos, pegamentos, madera, papel y cartón, materiales textiles, cuero, dispersiones de pintura, plásticos, lubricantes de colado, fibras de telas, contra infestación y destrucción de microorganismos dañinos tales como hongos y bacterias. Respecto a la protección de madera y otros materiales, se debe poner atención particular a los siguientes hongos dañinos: *Ascomycetes* tales como *Ophiostoma spp., Ceratocystis spp., Aureobasidium pullulans, Sclerophoma spp., Chaetomium spp., Humicola spp., Petriella spp., Trichurus spp.; Basidiomycetes* tales como *Coniophora spp., Coriolus spp., Gloeophyllum spp., Lentinus spp., Pleurotus spp., Poria spp., Serpula spp.* y *Tyromyces spp., Deuteromycetes tales como Aspergillus spp., Cladosporium spp., Penicillium spp., Trichorma spp., Altemaria spp., Paecilomyces spp.* y *Zygomycetes* tales como *Mucor spp.*, y además en la protección de productos almacenados y cosechas los siguentes hongos de levadura son dignos de anotarse: *Candida spp.* y *Saccharomyces cerevisae*.

Los compuestos de fórmula I y composiciones de los

mismos, respectivamente, se pueden utilizar para mejorar la salud de una planta. La invención también se relaciona con un método para mejorar la salud de una planta por tratamiento de una planta, su material de propagación y/o el locus en donde la planta está creciendo o va a crecer, con una cantidad eficaz de compuestos de fórmula I o composiciones de los mismos, respectivamente.

El término "salud de una planta" debe entenderse que indica una condición de la planta y/o sus productos los cuales se determinan por varios indicadores, solos o en combinación entre sí tal como rendimiento (por ejemplo, biomasa aumentada y/o contenido aumentado de ingredientes valiosos), vigor de la planta (por ejemplo crecimiento mejorado de la planta y/u hojas más verdes ("efecto enverdecedor")), calidad (por ejemplo, contenido mejorado o composición de ciertos ingredientes) y tolerancia a estrés abiótico y/o biótico. Los indicadores identificados en lo anterior para la condición de salud de una planta se pueden ser interdependientes o pueden resultar unos de otros.

Los compuestos de fórmula I se pueden presentar en diferentes modificaciones de cristal cuya actividad biológica puede diferir. De igual manera son materia objeto de la presente invención.

Los compuestos de fórmula I se utilizan como tales o en forma de composiciones para tratar los hongos o las

plantas, materiales de propagación de plantas tales como semillas, suelo, superficies, materiales o habitaciones que se van a proteger de ataque por hongos con una cantidad fungicida eficaz de las sustancias activas. La aplicación se puede llevar a cabo antes o después de la infección de las plantas, materiales de propagación de las plantas tales como semillas, suelo, superficies, materiales o habitaciones por el hongo.

Los materiales de propagación de las plantas se pueden tratar con compuestos de fórmula I como tales o una composición que comprenda por lo menos un compuesto de fórmula I profilácticamente ya sea en o antes de la plantación o del transplante.

La invención también se relaciona con composiciones agroquímicas que comprenden un disolvente o portador sólido y por lo menos un compuesto de fórmula I y con el uso para controlar hongos dañinos.

Una composición agroquímica comprende una cantidad fungicida eficaz de un compuesto I y/o II. El término “cantidad eficaz” indica una cantidad de la composición o del compuesto de fórmula I, en la cual es suficiente para controlar hongos dañinos en plantas cultivadas o en protección de materiales el cual no resulta en un daño sustancial a las plantas tratadas. Esta cantidad puede variar en un intervalo amplio y depende de diversos factores tales como la especie micótica que se va a controlar, la planta o material cutivado

o tratado, las condiciones climáticas y el compuesto específico de fórmula I utilizado.

Los compuestos de fórmula I y sales de los mismos se pueden convertir en tipos habituales de composiciones agroquímicas, por ejemplo, soluciones, emulsiones, suspensiones, polvos ligeros, polvos gruesos, pastas y gránulos. El tipo de composición depende del propósito destinado particular; en cada caso debe asegurar una distribución fina y uniforme del compuesto de acuerdo con la invención.

Los ejemplos para tipos de composición son suspensiones (SC, OD, FS), concentrados emulsificables (EC), emulsiones (EW, EO, ES), pastas, pastillas, polvos o polvos ligeros humectables (WP, SP, SS, WS, DP, DS) o gránulos (GR, FG, GG, MG), los cuales pueden ser hidrosolubles o humedecibles así como formulaciones en gel para el tratamiento de materiales de propagación de plantas tales como semillas (GF).

Habitualmente los tipos de composición (por ejemplo SC, OD, FS, EC, WG, SG, WP, SP, SS, WS, GF) se utilizan diluidas. Los tipos de composiciones tales como DP, DS, GR, FG, GG y MG habitualmente se utilizan sin diluir.

Las composiciones se preparan de una manera conocida (véase, por ejemplo US 3,060,084, EP-A 707 445 (para concentrados líquidos), Browning: "Agglomeration", Chemical

Engineering, 4 de diciembre de 1967, 147-48, Perry's Chemical Engineer's Handbook, cuarta edición, McGraw-Hill, New York, 1963, páginas 8 a 57 y siguientes, WO 91/13546, US 4,172,714, US 4,144,050, US 3,920,442, US 5,180,587, US 5,232,701 , US 5,208,030, GB 2,095,558, US 3,299,566, Klingman: Weed Control as a Science (J. Wiley & Sons, New York, 1961), Hance et al.: Weed Control Handbook (8th Ed., Blackwell Scientific, Oxford, 1989) and Mollet, H. and Grubemann, A.: Formulation technology (Wiley VCH Verlag, Weinheim, 2001).

Las composiciones agroquímicas también comprenden sustancias auxiliares las cuales son habituales en composiciones agroquímicas. Las sustancias auxiliares utilizadas dependen de la forma de aplicación particular y la sustancia activa, respectivamente.

Los ejemplos para sustancias auxiliares adecuadas son disolventes, portadores sólidos, dispersantes o emulsificantes (tales como solubilizantes adicionales, coloides protectores, tensioactivos y agentes de adhesión), espesantes orgánicos e inorgánicos, bactericidas, agentes anticongelamiento, agentes antiespumantes, si es apropiado, colorantes y mejoradores de adherencia o aglutinantes (por ejemplo para formulaciones de tratamiento de semillas). Los disolventes adecuados son agua, disolventes orgánicos tales como fracciones de aceite mineral o con un punto de ebullición medio a alto, tales como queroseno o petróleo diesel, además

petróleos de alquitrán de carbón y petróleos de origen vegetal o animal, hidrocarburos alifáticos, cíclicos y aromáticos, por ejemplo, tolueno, xileno, parafina, tetrahidronaftaleno, naftalenos alquilados o sus derivados, alcoholes tales como metanol, etanol, propanol, butanol y ciclohexanol, glicoles, cetonas tales como ciclohexanona y gamma-butirolactona, dimetilamidas de ácido graso, ácidos grasos y ésteres de ácido graso y disolventes fuertemente polares, por ejemplo aminas tales como N-metilpirrolidona.

Los portadores sólidos son tierras minerales tales como silicatos, geles de sílice, talco, caolines, carbonato cálcico, cal viva, greda, arcilla carcáreo ferruginosa, loess, arcillas, dolomita, tierra de diatomáceas, sulfato de calcio, sulfato de magnesio, óxido de magnesio, materiales sintéticos molidos, fertilizantes tales como, por ejemplo, sulfato de amonio, fosfato de amonio, nitrato de amonio, ureas y productos de origen vegetal tales como harina de cereal, harina de corteza de árbol, harina de madera y harina de cáscaras de nuez, polvos de celulosa y otros portadores sólidos.

Los tensioactivos adecuados (adyuvantes, edulcorantes, mejoradores de adherencia, dispersantes o emulsificantes) son sales de metal alcalino, metal alcalinotérreo y de amonio de ácidos sulfónicos aromáticos tales como ácido ligninsulfónico (tipos Borresperse^{MR},

Borregard, Noruega) ácido fenolsulfónico, ácido naftalensulfónico (tipos Morwet[MR], Akzo Nobel, Estados Unidos), ácido dibutilnaftalensulfónico (tipos Nekal[MR], BASF, Alemania), y ácidos grasos, sulfonatos de alquilo, arilsufonatos de alquilo, sulfatos de alquilo, sulfatos de lauriléter, sulfatos de alcohol graso y hexa-, hepta- y octadecanolatos sulfatados, glicoléteres de alcohol graso sulfatados, además condensados de naftaleno o ácido naftalensulfónico con fenol y formaldehído, polioxietilen octilfeniléter, isoctilfenol etoxilado, octilfenol nonilfenol, éteres de alquilfenilpoliglicol, tributilfenilpoliglicoléter, tristearil-fenilpoliglicoléter, alcoholes de alquilarilpoliéter, alcohol y condensados de alcohol graso/óxido de etileno, aceite de ricino etoxilado, alquiléteres de polioxietileno, polioxipropileno etoxilado, alcohol laurílico poliglicoléter acetal, ésteres de sorbitol, licores de desecho de lignina-sulfito y proteínas, proteínas desnaturalizadas, polisacáridos (por ejemplo, metilcelulosa), almidones modificados hidrofóbicamente, alcoholes polivinílicos (tipos Mowiol[MR], Clariant, Suiza), policarboxilatos (tipos Sokolan[MR], BASF, Alemania), polialcoxilatos, polivinil-aminas (tipos Lupasol[MR], BASF, Alemania), polivinilpirrolidona y los copolímeros de los mismos.

Los ejemplos de mejoradores de adherencia (es decir,

compuestos que imparten una fluidez modificada a las composiciones, es decir, alta viscosidad bajo condiciones estáticas y baja viscosidad durante la agitación) son polisacáridos y arcillas orgánicas y anorgánicas tales como goma de xantano (Kelzan^{MR}, CP Kelco, U.S.A.), Rhodopol^{MR} 23 (Rhodia, Francia), Veegum^{MR} (RT. Vanderbilt, U.S.A.) o Attaclay^{MR} (Engelhard Corp., NJ, USA).

Los bactericidas se pueden agregar para la conservación y estabilización de la composición. Los ejemplos de bactericidas adecuados son aquellos basados en diclorofeno y alcohol bencílico hemiformal (Proxel^{MR} de ICI o Acticide^{MR} de RS de Thor Chemie y Kathon^{MR} MK de Rohm & Haas) y derivados de isotiazolinona tales como alquilisotiazolinonas y bencisotiazolinonas (Acticide^{MR} MBS de Thor Chemie).

Los ejemplos de agentes anticongelates adecuados son etilenglicol, propilenglicol, urea y glicerina.

Los ejemplos de agentes antiespumantes son emulsiones de silicona (tales como Silikon^{MR} SRE, Wacker, Alemania o Rhodorsil^{MR}, Rhodia, Francia), Alcoholes de cadena larga, ácidos grasos, sales de ácidos grasos, compuestos fluoro orgánicos y mezclas de los mismos.

Los colorantes adecuados son pigmentos de baja hidrosolubilidad y tintes solubles en agua. Los ejemplos que se pueden mencionar y las designaciones rodamina B, C. I. rojo pigmentado 112, C. I. rojo solvente 1, azul pigmento 15:4,

azul pigmento 15:3, azul pigmento 15:2, azul pigmento 15:1, azul pigmento 80, amarillo pigmento 1, amarillo pigmento 13, rojo pigmento 112, rojo pigmento 48.2, rojo pigmento 48.1, rojo pigmento 57.1, rojo pigmento 53:1, naranja pigmento 43, naranja pigmento 34, naranja pigmento 5, verde pigmento 36, verde pigmento 7, blanco pigmento 6, café pigmento 25, violeta básico 10, violeta básico 49, rojo ácido 51, rojo ácido 52, rojo ácido 14, azul ácido 9, amarillo ácido 23, rojo básico 10, rojo básico 108.

Los ejemplos de mejoradores de adherencia o aglutinantes son polivinilpirrolidonas, acetatos de polivinilo, alcoholes polivinílicos y éteres de celulosa (Tylose^{MR}, Shin-Etsu, Japón).

Los polvos, materiales para dispersión y polvos finos se pueden preparar por mezclado o molido de modo concomitante de los compuestos de fórmula I y, si es apropiado, sustancias activas adicionales con por lo menos un portador sólido.

Se pueden preparar gránulos, por ejemplo gránulos recubiertos, gránulos impregnados y gránulos homogéneos por unión de las sustancias activas a portadores sólidos. Los ejemplos de portadores sólidos son tierras minerales tales como geles de sílice, silicatos, talco, caolín, attaclay, carbonato cálcico, cal viva, greda, arcilla calcáreo ferruginosa, loes, arcilla, dolomita, tierra de diatomáceas,

sulfato de calcio, sulfato de magnesio, óxido de magnesio, materiales sintéticos molidos, fertilizantes tales como por ejemplo, sulfato de amonio, fosfato de amonio, nitrato de amonio, ureas y productos de origen vegetal tales como cereal, harina, harina de corteza de árbol, harina de madera y harina de cáscara de nueces, polvo de celulosa y otros portadores sólidos.

Los ejemplos para tipos de composición incluyen, pero no se limitan a: 1. Tipos de composición para dilución con agua, i) concentrados hidrosolubles (SL, LS): 10 partes en peso de un compuesto de fórmula I de acuerdo con la invención se disuelven en 90 partes en peso de agua o en un solvente hidrosoluble. Como una alternativa se agregan agentes humectantes u otros auxiliares. La sustancia activa se disuelve ante dilución con agua. De esta manera, se obtiene una composición que tiene un contenido de 10% en peso de sustancia activa. ii) concentrados dispersables (DC): 20 partes en peso de compuesto de fórmula I de acuerdo con la invención se disuelven en 70 partes en peso de ciclo hexanona con adición de 10 partes en peso de un dispersante, por ejemplo, polivinilpirrolidona. La dilución con agua proporciona una dispersión. El contenido de sustancia activa es 20% en peso, iii) concentrados emulsificables (EC): 15 partes en peso de un compuesto de fórmula I de acuerdo con la invención se disuelven en 75 parte sen peso de xileno con

adición de dodecilbencensulfonato de calcio y etoxilato de aceite de ricino (en cada caso, 5 partes en peso). La dilución con agua proporciona una emulsión. La composición tiene un contenido de sustancia activa de 15% en peso. iv) emulsiones (EW, EO, ES): 25 partes en peso de un compuesto de fórmula I de acuerdo con la invención se disuelven en 35 partes en peso de xileno con la adición de dodecilbencensulfonato de calcio y etoxilato de aceite de ricino (en cada caso, 5 partes en peso). Esta mezcla se introduce en 30 partes en peso de agua por medio de una máquina emulsificante (Ultraturrax) y se elabora hasta una emulsión homogénea. La dilución con agua proporciona una emulsión. La composición tiene un contenido de sustancia activa de 25% en peso. v) Suspensiones (SC, OD, FS): En un molino de bolas agitado, 20 partes en peso de un compuesto de fórmula I de acuerdo con la invención se trituran con adición de 10 partes en peso de dispersantes y agentes humectantes y 70 partes en peso de agua o un disolvente orgánico para proporcionar una suspensión de sustancia activa fina. La dilución con agua proporciona una suspensión estable de la sustancia activa. El contenido de sustancia activa en la composición es 20% en peso. vi) Gránulos dispersables en agua y gránulos hidrosolubles, (WG, SG) 50 partes en peso de un compuesto de fórmula I de acuerdo con la invención se muelen finamente con adición de 50 partes en peso de dispersantes de agentes humectantes y se preparan como gránulos dispersables

en agua o hidrosolubles por medio de dispositivos técnicos (pr ejemplo, extrusión, torre de aspersión, lecho fluidizado). La dilución con agua proporciona una dispersión o solución estable de la sustancia activa. La composición tiene un contenido de sustancia activa de 50% en peso. vii) Polvos dispersables en agua y polvos hidrosolubles (WP, SP, SS, WS): 75 partes en peso de un compuesto de fórmula I de acuerdo con la invención se muelen en un molino de rotor-estator con adición de 25 partes en peso de dispersantes, agentes humectantes y gel de sílice. La dilución con agua proporciona una dispersión o solución estable de la sustancia activa. El contenido de sustancia activa de la composición es 75% en peso. viii) Gel (GF): En un molino de bolas agitado, 20 partes en peso de un compuesto de fórmula I de acuerdo con la invención se tritura con adición de 10 partes en peso de dispersantes, 1 parte en peso de agentes gelificantes wetters y 70 partes en peso de agua o de un disolvente orgánico para proporcionar una suspensión fina de la sustancia activa. La dilución con agua proporciona una suspensión estable de la sustancia activa por lo que se obtiene una composición con 20% (peso/peso) de la sustancia activa.

2. Tipos de composición para ser aplicados sin diluir: ix) Polvos que se pueden volver polvos finos (DP, DS): 5 partes en peso de un compuesto de fórmula I de acuerdo con la invención se muelen finamente y se mezclan perfectamente

con 95 partes en peso de caolín dividido finamente. Esto proporciona una composición que se puede volver un polvo muy fino que tiene un contenido de sustancia activa de 5% en peso.

x) Gránulos (GR, FG, GG, MG): 0.5 partes en peso de un compuesto de fórmula I de acuerdo con la invención se muelen finamente y se asocian con 99.5 partes en peso de portadores. Los métodos actuales son extrusión, secado por aspersión del lecho fluidizado. Esto proporciona gránulos que van a ser aplicados sin diluir que tienen un contenido de sustancia activa de 0.5% en peso. xi) Soluciones ULV (UL): 10 partes en peso de un compuesto de fórmula I de acuerdo con la invención se disuelven en 90 partes en peso de un disolvente orgánico, por ejemplo xileno. Esto proporciona una composición para ser aplicada sin diluir que tiene un contenido de sustancia activa de 10% en peso.

Las composiciones agroquímicas generalmente comprenden entre 0.01 y 95%, de manera preferible entre 0.1 y 90%, de manera más preferible entre 0.5 y 90% en peso de la sustancia activa. Las sustancias activas se utilizan con una pureza de 90% a 100%, de manera preferible de 95% a 100% (de acuerdo con el espectro RMN).

Los concentrados hidrosolubles (LS), concentrados fluibles (FS), polvos para tratamiento en seco (DS), polvos dispersables en agua para tratamiento en suspensión (WS), polvos hidrosolubles (SS), emulsiones (ES), concentrados

emulsificables (EC) y geles (GF) habitualmente se utilizan para propósitos de tratamiento de materiales de propagación de plantas, particularmente semillas. Estas composiciones se pueden aplicar a materiales de propagación de plantas, particularmente semillas, diluidos o sin diluir. Las composiciones en cuestión proporcionan, después de una dilución de dos a diez veces, concentraciones de sustancia activa desde 0.01 hasta 60% en peso, preferiblemente desde 0.1 hasta 40% en peso en preparaciones listas para usarse. La aplicación se puede llevar a cabo antes o durante la siembra. Los métodos para aplicación o tratamiento de compuestos y composiciones agroquímicas de los mismos, respectivamente, sobre el material de propagación de plantas, especialmente semillas, se conocen en el ámbito e incluyen apresto, recubrimiento, peletizado, generación de polvo, remojado y métodos de aplicación en surco del material de propagación. En una modalidad preferida, los compuestos o composiciones de la misma, respectivamente, se aplican sobre el material de propagación de la planta por un método tal como germinación no se introducen, por ejemplo, por apresto de semilla, peletizado, recubrimiento y formación de polvo fino.

En una modalidad preferida, se utiliza una composición de tipo de suspensión (FS) para tratamiento de semillas. Típicamente, una composición FS puede comprender 1-800 g/l de sustancia activa, 1-200 g/l de tensioactivo o 0 a

200 g/l de agente anticongelante, 0 a 400 g/l de aglutinante, 0 a 200 g/l de pigmento y hasta 1 litro de un disolvente, preferiblemente agua.

Las sustancias activas se pueden utilizar como tales o en forma de sus composiciones, por ejemplo, en forma de soluciones rociables directamente, polvos, suspensiones, dispersiones, emulsiones, dispersiones, pastas, productos que se pueden volver polvo fino, materiales para dispersión o gránulos por medio de aspersión, atomización, generación de polvo fino, diseminación, cepillado, inmersión o vertido. Las formas de aplicación dependen completamente de los propósitos destinados; se pretende asegurar en cada caso la distribución más fina posible de las sustancias activas de acuerdo con la invención. Las formas de aplicación acuosa se pueden preparar a partir de concentrados de emulsión, pastas o polvos humedecibles (polvos susceptibles de ser dispersados, dispersiones de aceite) mediante adición de agua. Para preparar emulsiones, las pastas o dispersiones oleosas, las sustancias como tales o disueltas en un aceite o disolvente se pueden homogeneizar en agua por medio de un humidificador, mejorador de adherencia, dispersante o emulsificante. De manera alternativa, es posible preparar concentrados constituidos de sustancia activa, humidificador, mejorador de adherencia, dispersante o emulsificante y, si es apropiado, disolvente o aceite y estos concentrados son adecuados para

dilución con agua.

Las concentraciones de sustancia activa en preparaciones listas para usarse puede variar dentro de intervalos relativamente amplios. En general, se les encuentra desde 0.0001 hasta 10%, de manera preferible 0.001 a 1% en peso de sustancia activa.

Las sustancias activas también se pueden utilizar con éxito en procesos de volumen ultrabajo (ULV, por sus siglas en inglés), es posible aplicar composiciones que comprenden más de 95% por ciento en peso de la sustancia activa, o incluso aplicar la sustancia activa sin aditivos.

Cuando se utiliza en protección de una planta, las cantidades de sustancias activas aplicadas son, dependiendo de la clase del efecto deseado, de 0.001 a 2 kg por ha, de manera preferible de 0.005 a 2 kg por ha, de manera más preferible de 0.005 a 0.9 kg por ha, en particular de 0.1 a 0.75 kg por ha.

En el tratamiento de materiales de propagación de planta tales como semillas, por ejemplo, por aplicación de un polvo fino, recubrimiento o drenado de las semillas, las cantidades de sustancia activa son de 0.1 a 1000 g, de manera preferible de 1 a 1000 g, de modo más preferible de 1 a 100 g y de manera mucho más preferible de 5 a 100 g por 100 kilogramos de material de propagación de planta (preferiblemente semilla) es lo que se requiere de manera general.

Cuando se utiliza en la protección de materiales o productos almacenados, la cantidad de sustancia activa aplicada depende de la clase de área de aplicación y sobre el efecto deseado. Las cantidades aplicadas habitualmente en la protección de materiales son, por ejemplo, 0.001 g a 2 kg, preferiblemente 0.005 a 1 kg de sustancia activa por metro cúbico de material tratado.

Diversos tipos de aceites, humectantes, adyuvantes, herbicidas, bactericidas, otros fungicidas y/o plaguicidas se pueden agregar a las sustancias activas o las composiciones que los comprenden, si es apropiado no hasta inmediatamente antes de su uso (mezcla de tanque). Estos agentes se pueden mezclar con las composiciones de acuerdo con la invención en una relación en peso de 1:100 a 100:1, preferiblemente 1:10 a 10:1.

Los adyuvantes los cuales se pueden utilizar son en particular polisiloxanos modificados orgánicos tales como Break Thru S 240^{MR}; alcoxilatos de alcohol tal como Atplus 245^{MR}, Atplus MBA 1303^{MR}, Plurafac LF 300^{MR} y Lutensol ON 30^{MR}; polímeros de bloque de EO/PO, por ejemplo Pluronic RPE 2035^{MR} y Genapol B^{MR}; etoxilatos de alcohol tal como Lutensol XP 80^{MR}; y dioctil sulfosuccinato de sodio tal como Leophen RA^{MR}.

Las composiciones de acuerdo con la invención pueden, en forma de uso como fungicidas, también estar presentes junto con otras sustancias activas, por ejemplo con

herbicidas, insecticidas, reguladores de crecimiento, fungicidas o también con fertilizantes o con premezclas o, si es apropiado, no sino hasta inmediatamente antes de su uso (mezcla de tanque).

El mezclado de los compuestos de fórmula I o las composiciones que las comprenden en la forma de uso como fungicidas con otros fungicidas en muchos casos resulta en una expansión del espectro de actividad fungicida que se obtiene o en la prevención de desarrollo de resistencia a fungicidas. Además, en muchos casos, se obtienen efectos sinergísticos.

La siguiente lista de sustancias activas junto con las cuales los compuestos de acuerdo con la invención se pueden utilizar se pretende que ilustre las posibles combinaciones pero no las limita:

A) estrobilurinas azoxistrobina, dimoxistrobina, enestroburina, fluoxastrobina, kresoxim-metilo, metominostrobina, orisastrobina, picosistrobina, piraclostrobina, piribencarb, trifloxistrobina, 2-(2-(6-(3-cloro-2-metil-fenoxi)-5-fluoro-pirimidin-4-iloxi)-fenil)-2-metoxiimino-N-metil-acetamida, éster metílico del ácido 3-metoxi-2-(2-(N-(4-metoxi-fenil)-ciclopropan-carboximidoilsulfanilmetil)-fenil)-acrílico, (2-cloro-5-[1-(3-metilbenciloxiimino)etil]-bencil)carbamato y 2-(2-(3-(2,6-diclorofenil)-1-metil-alilidenoaminooximetil)-fenil)-2-metoxiimino-N-metil-acetamida;

B) carboxamidas y carboxanilidas: benalaxilo, benalaxil-M- benodanil, bixafeno, boscalida, carboxina, fenfuram, fenhexamid, flutolanilo, furametpir, isopirazam, isotianilo, quiralaxilo, me-pronil, metalaxil, metalaxil-M (mefenoxam), ofurace, oxadixil, oxicarboxina, pentiopirad, sedaxano, tecloftalam, tifluzamida, tiadinil, 2-amino-4-metil-tiazol-5-carboxanilida, 2-cloro-N-(1,1,3-trimetil-indan-4-il)-nicotinamida, N-(3',4',5'-trifluorobifenil-2-il)-3-difluorometil-1-metil-1H-pirazol-4-carboxamida, N-(4'-trifluorometiltiobifenil-2-il)-3-difluorometil-1-metil-1H-pirazol-4-carboxamida, N-(2-(1,3-dimetil-butil)-fenil)-1,3-dimetil-5-fluoro-1H-pirazol-4-carboxamida y N-(2-(1,3,3-trimetil-butil)-fenil)-1,3-dimetil-5-fluoro-1H-pirazol-4-carboxamida; morfólidos carboxílicos; dimetomorf, flumorf, pirimorf, amidas de ácido benzoico: flumetover, fluopicolida, fluopiram, zoxamida, N-(3-etil-3,5,5-trimetil-ciclohexil)-3-formilamino-2-hidroxi-benzamida; otras carboxamidas; carpropamida, diciclomet, mandiproamida, oxitetraciclina, siltiofarm y amida del ácido N-(6-metoxi-piridin-3-il)-ciclopropancarboxílico;

C) azoles y triazoles: azaconazol, bitertanol, bromuconazol, ciproconazol, difenoconazol, diniconazol, diniconazol-M, epoxiconazol, fenbuconazol, fluquinconazol, flusilazol, flutriafol, hexaconazol, imibenconazol, ipconazol, metconazol, miclobutanilo, oxpoconazol, paclobutrazol,

penconazol, propiconazol, protioconazol, semiconazol, tebuconazol, tetraconazol, triadimefon, triadimenol, triticonazol, uniconazol, 1-(4-cloro-fenil)-2-[(1,2,4]triazol-1-il)-cicloheptanol; imidazoles: ciazofamida, imazalilo, pefurazoato, procloraz, triflumizol; bencimidazoles: benomil, carbendazim, fuberidazol, tiabendazol; otros: etaboxam, etridiazol, himexazol y 2-(4-cloro-fenil)-N-[4-(3,4-dimetoxi-fenil)-isoxazol-5-il]-2-prop-2-iniloxi-acetamida;

D) compuestos heterocíclicos piridinas: fluazinam, pirifenox, 3-[5-(4-clorofenil)-2,3-dimetil-isoxazolidin-3-il]-piridina, 3-[5-(4-metil-fenil)-2,3-dimetil-isoxazolidin-3-il]-piridina, 2,3,5,6-tetra-cloro-4-metansulfonil-piridina, 3,4,5-tricloropiridin-2,6-dicarbonitrilo, N-(1-(5-bromo-3-cloro-piridin-2-il)-etil)-2,4-dicloronicotinamida, N-[(5-bromo-3-cloro-piridin-2-il)-metil]-2,4-dicloro-nicotinamida, pirimidinas; bupirimato, ciprodinil, diflumetorim, fenarimol, ferimzona, mepanipirim, nitrapirim, nuarimol, pirimetanil; piperazinas; triforina, pirroles; fenpiclonil, fludioxonil; morfolinas; aldimorf, dodemorf, dodemorf-acetato, fenpropimorf, tridemorf; piperidinas: fenpropidina;; dicarboxamidas: fluoroimida, iprodiona, procimidona, vinclozolina; heterociclos de 5 miembros no aromáticos: famoxadona, fenamidona, flutianilo, octilinona, probenazol, éster S-alílico del ácido 5-amino-2-isopropopil-3-oxo-4-orto-tolil-2,3-dihidro-pirazol-1-carbotioico; otros: acibenzolar-S-

metilo, amisulbrom, anilazina, blasticidina-S, captafol, captano, quinometionat, dazomet, debacarb, diclomezina, difenzoquat, difenzoquat-metilsulfato, fenoxanil, Folpet, ácido oxolínico, piperalina, proquinazida, piroquilon, quinoxifeno, triazóxido, triciclazol, 2-butoxi-6-yodo-3-propilcromen-4-ona, 5-cloro-1-(4,6-dimetoxi-pirimidin-2-il)-2-metil-1H-bencimidazol, 5-cloro-7-(4-metilpiperidin-1-il)-6-(2,4,6-trifluorofenil)-[1,2,4]triazolo[1,5-a]pirimidina y 5-etil-6-octil-[1,2,4]tirazolo[1,5-a]pirimidin-7-ilamina;

E) carbamatos tio- y ditiocarbamatos: ferbam, mancozeb, maneb, metam, metasulfocarb, metiram, propineb, tiram, zineb, ziram; carbamatos: bentiavalicarb, dietofencarb, iprovalicarb, propamocarb, clorhidrato de propamo-carborundum, valifenal y éster 4-fluorofenílico del ácido N-(1-(1-(4-cianofenil)etansulfonil)-but-2-il)carbámico;

F) otras sustancias activas – gaunidinas: guanidina, dodina, base libre de dodina, guazatina, guazatina-acetato, iminoctadina, iminoctadina-triacetato, iminoctadina-tris(albesilato); antibióticos: kasugamicina, clorhidrato-hidrato de kasugamicina, estreptomicina, polioxina, validamicina A; derivados de nitrofenilo; binapacrilo, dinobuton, dinocap, nitrtal-isopropilo, tecnazen compuestos organometálicos: sales de fentina como fentin acetato, cloruro de fentina o hidróxido de fentina; compuestos heterociclilo que contienen azufre: ditianon, isoprotiolano; compuestos de

organofósforo: edifenfos, fosetil, fosetil-aluminio, iprobenfos, ácidos fosforosos y sus sales, pirazofos, tolclofos-metilo; compuestos de organocloro: clorotalonilo, diclofluanida, diclorofeno, flusulfamida, hexaclorobenceno, pencicuron, pentaclorofenol y sus sales, ftalida, quintoceno, tiofanato-metilo, tolilfluanida, N-(4-cloro-2-nitrofenil)-N-etil-4-metil-bencensulfonamida; sustancias activas inorgánicas; mezcla de Bordeaux, acetato de cobre, hidróxido de cobre, oxicloruro de cobre, sulfato de cobre básico, azufre, bifenilo, bronopol, ciflufenamida, cimoxanilo, difenilamina, metrafenona, mildiomicina, oxina-cobre, prohexadiona-calcio, espiroxamina, tolilfluanida, N-(ciclopropilmetoxiimino-(6-difluoro-metoxi-2,3-difluorofenil)-metil)-2-fenilacetamida, N'-(4-(4-cloro-3-trifluorometil-fenoxi)-2,5-dimetil-fenil)-N-etil-N-metilformamidina, N'-(4-(4-fluoro-3-trifluorometil-fenoxi)-2,5-dimetil-fenil)-N-etil-N-metil-formamidina, N'-(2-metil-5-trifluorometil-4-(3-trimetilsilanil-propoxi)-fenil)-N-etil-N-metilformamidina, N'-(5-difluorometil-2-metil-4-(3-trimetilsilanil-propoxi)-fenil)-N-etil-N-metilformamidina, metil-(1,2,3,4-tetrahidro-naftalen-1-il)-amida del ácido 2-{1-[2-(5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-trifluorometil-pirazol-1-il)-acetil]-piperidin-4-il}-tiazol-4-carboxílico, metil-(R)-1,2,3,4-tetrahidro-naftalen-1-il-amida del ácido 2-{1-[2-(5-metil-S-trifluorometil-pirazol-i-iO-acetil-piperidin-ilJ-tiazol-

carboxílico, éster 6-terbutil-8-fluoro-2,3-dimetilquinolin-4-ílico del ácido acético y éster 6-terbutil-8-fluoro-2,3-dimetil-quinolin-4-ílico del ácido metoxiacético;

G) reguladores del crecimiento, ácido absísico, amidoclor, ancimidol, 6-bencilaminopurina, brasinolida, butralina, clormequat (cloruro de clormecuat), cloruro de colina, ciclanilida, daminozida, diquegulac, dimetipina, 2,6-dimetilpuridina, etefon, flumetralina, flurprimidol, flutiacet, forclorfenuron, ácido giberélico, inabenfida, ácido indol-3-acético, hidrazida maleica, mefluidida, mepicuat (cloruro de mepicuat), ácido naftalenacético, N-6-benciladenina, paclobutrazol, prohexadiona (prohexadiona-calcio), prohidrojasmona, tidiazuron, triapentenol, fosforotritioato de tributilo, ácido 2,3,5-tri-yodobenzoico, trinexapac-etilo y uniconazol;

H) herbicidas acetamidas: acetoclor, alaclor, butaclor, dimetaclor, dimetenamida, flufen-acet, mefenacet, metolaclor, metazaclor, napropamida, naproanilida, petoxamida, pretilaclor, propaclor, tenilclor; derivados de aminoácidos; bilanafos, glifosato, glufosinato, sulfosato; ariloxifenoxipropionatos: clodinafop, cialofop-butilo, fenoxaprop, fluazifop, haloxifop, metamifop, propaquizafop, quizalofop, quizalofop-P-terfurilo; Bipiridilos: diquat, paraquat; (tio)carbamatos: asulam, butilato, carbetamida, desmedifam, dimepiperato, eptam (EPTC), esprocarb, molinato,

orbencarb, fenmedifam, prosulfocarb, piributicarb, tiobencarb, trialato; ciclohexanodionas: butroxidim, cletodim, cicloxidim, profoxidim, setoxidim, tepraloxidim, tralcoxidim; -dinitroanilinas; benfluralina, etalfluralina, orizalina pendimetalina, prodiamina, trifluralina; éteres de difenilo: acifluorfeno, aclonifeno, bifenox, diclofop, etoxifeno, fomesafeno, lactofeno, oxifluorfeno; hidroxibenzonitrilos: bomoxinilo, diclobenilo, ioxinilo; -imidazolinonas: imazametabenz, imazamox, imazapic, imazapir, imazaquin, imazetapir; ácidos fenoxiacéticos: clormeprop, ácido 2,4-diclorofenoxiacético (2,4-D), 2,4-DB, diclorprop, MCPA, MCPA-tioetilo, MCPB, Mecoprop; pirazinas; cloridazon, flufenpir-etilo, flutiacet, norfluorazona, piridato, piridinas: aminopiralida, clopiralida, diflufenican, ditiopir, fluridona, fluroxipir, picloram, picolinafeno, tiazopir; sulfonilureas; amidosulfuron, azimsulfuron, bensulfuron, clorimuron-etilo, clorsulfuron, cinosulfuron, ciclosulfamuron, etoxisulfuron, flazasulfuron, flucetosulfuron, flupirsulfuron, foramsulfuron, halosulfuron, imazosulfuron, yodosulfuron, mesosulfuron, metsulfuron-metilo, nicosulfuron, oxasulfuron, primisulforon, prosulfuron, pirazosulfulron, rimsulfuron, sulfometuron, sulfosulfuron, tifensulfuron, triasulsufuron, tribenuron, trifloxisulfuron, triflusulfuron, tritosulfuron, 1-((2-cloro-6-propil-imidazo[1,2-b]piridazin-3-il)sulfonil)-3-(4,6-dimetoxi-pirimidin-2-il)urea; triazinas: ametrin, atrazina,

cianazina, dimetametrin, etioxin, hexazinona, metamitron, metribuzina, prometrin, simazina, terbutilazina, terbutrin, triaziflam; ureas: clorotoluron, daimuron, diuron, flometuron, isoproturon, linuron, metabenzotiazuron, tebutiuron; otros inhibidores de acetolactato sintasa: bispiribac-sodio, cloransulam-metilo, diclosulam, florasulam, flucarbazona, flumetsulam, metosulam, orto-sulfamuron, penoxsulam, propoxicarbazona, piribambenz-propilo, piribenzoxim, piriftalida, piriminobac-metilo, pirimisulfano, piritiobac, piroxasulfona, piroxsulam; otros: amicarbazona, aminotriazol, anilofos, beflubutamida, benazolina, bencar-bazona, benfluresato, benzofenap, bentazona, benzobiciclon, bromacilo, bromo-butida, butafenacilo, butamifos, cafenstrol, carfentrazona, cinidon-etilo, clortal, cinmetilina, clomazona, cumiluron, ciprosulfamida, dicamba, difenzocuat, difluofenzopir, Drechslera monoceras, endotal, etofumesato, etobenzanida, fen-trazamida, flumiclorac-pentilo, flumioxazina, flupoxam, flurocloridona, flurtamona, indanofano, isoxabeno, isoxaflutol, lenacil, propanil, propizamida, quinclorac, quinmerac, mesotriona, ácido metil arsónico, naptalam, oxadiargilo, oxadiazona, oxaziclomefona, pentoxazona, pinoxaden, piraclonilo, piraflufen-etilo, pirasulfotol, pirazoxifeno, pirazolinato, quinoclamina, saflufenacilo, sulcotriona, sulfentrazona, terbacilo, tefuriltriona, tembotriona, tiencarbazona, topramezona, 4-

hidroxi-3-[2-(2-metoxi-etoximetil)-6-trifluorometil-piridin-3-carbonil]-biclo[3.2.1]oct-3-en-2-ona, éster etílico del ácido (3-[2-cloro-4-fluoro-5-(3-metil-2,6-dioxo-4-trifluorometil-3,6-dihidro-2H-pirimidin-1-il)-fenoxi]-piridin-2-iloxi)-acético, éster metílico del ácido 6-amino-5-cloro-2-ciclopropil-pirimidin-4-carboxílico, 6-cloro-3-(2-ciclopropil-6-metil-fenoxi)piridazin-4-ol, 4-amino-3-cloro-6-(4-clorofenil)-5-fluoropiridin-2-carboxílico, éster metílico del ácido 4-amino-3-cloro-6-(4-cloro-2-fluoro-3-metoxi-fenil)-piridin-2-carboxílico, y éster metílico del ácido 4-amino-3-cloro-6-(4-cloro-3-dimetilamino-2-fluorofenil)-piridin-2-carboxílico;

I) insecticidas – organo(tio)fosfatos: acefato, azametifos, azinfos-metilo, clorpirifos; clorpirifos-metilo, clorfenvinfos, diazinon, diclorvos, dicrotofos, dimetoato, disulfoton, etion, fenitrotion, fention, isoxation, malation, metamidofos, metadition metil-paration, mevinfos, monocrotofos, oxidemeton-metilo, paraoxon, paration, fentoato, fosalona, fosmet, fosfamidon, forato, foxima, pirimifos-metilo, profenofos, protiofos, sulfopros, tetra-clorbinfos, terbufos, triazofos, triclorfon; carbamatos: alanicarb, aldicarb, bendiocarb, benfuracarb, carbarilo, carbofurano, carbosulfano, fenoxicarb, furatiocarb, metiocarb, metomil, oxamil, pirimicarb, propoxur, tiodicarb, triazamato; piretroides: aletrin, bifentrin, ciflutrin, cihalotrin,

cifenotrin, cipermetrin, alfa-cipermetrin, beta-cipermetrin, zeta-cipermetrin, deltametrin, esfenvalerato, etofenprox, fenpropatrina, fenvalerato, imiprotrina, lambda-cihalotrin, permetrin, praletrin, piretrin I y II, resmetrin, silafluofeno, tau-fluvalinato, teflutrin, tetrametrin, tralometrin, transflutrin, proflutrin, dimeflutrin; reguladores del crecimiento de insectos: a) inhibidores de síntesis de quitina; benzoilureas: clorfluazuron, ciramazina, diflubenzuron, flucicloxuron, flufenoxuron, hexaflumuron, lufenuron, novaluron, teflubenzuron, triflumuron; buprofezina, diofenolano, hexitiazox, etoxazol, clofentazina; b) antagonistas de ecdisona: halofenozida, metoxifenozida, tebufenozida, azadiractina; c) juvenoides: piriproxifeno, metopreno, fenoxicarb; d) inhibidores de biosíntesis de lípidos: espirodiclofeno, espiromesifeno, espirotetramat; compuestos agonistas/antagonistas de receptor nicotínico: clotianidina, dinotefurano, imidacloprid, tiametoxam, nitenpiram, acetamiprid, tiacloprid, 1-(2-cloro-tiazol-5-ilmetil)(-2-nitrimino-3,5-dimetil-[1,3,5]triazinano; compuestos antagonistas de GABA: endosulfano, etiprol, fipronil, vaniliprol, pirafluprol, piriprol, amida del ácido 5-amino-1-(2,6-dicloro-4-metil-fenil)-4-sulfinamoil-1H-pirazol-3-carbotioico; insecticidas de lactona macrocíclicos: abamectina, emamectina, milbemectina, lepimectina, espinosad, espinetoram; acaricidas del inhibidor I de transporte de

electrón mitocondrial (METI): fenazaquin, piridabeno, tebufenpirad, tolfenpirad, flufenerim; compuestos METI II y III: acequinocilo fluaciprim, hidrametilnon; desacopladores: clorfenapir; - inhibidores de fosforilación oxidativa; cihexatina, diafentiuron, óxido de fenbutatina, propargita; compuestos interruptores de moulting: criomazina; inhibidores de función de oxidasa mixtos: butóxido de piperonilo; bloqueadores de canal de sodio: indoxacarb, metaflumizona; - otros: benclotiaz, bifenazato, cartap, flonicamida, piridalilo, pirmetrozina, azufre, tiociclam, flubendiamida, clorantraniliprol, ciazipir (HGW86), cienopirafeno, flupirazofos, ciflumetofeno, amidoflumet, imiciafos, bistrifluron y pirifluquinazona.

La presente invención se relaciona adicionalmente con composiciones agroquímicas que comprenden una mezcla de por lo menos un compuesto de fórmula I (componente I) y por lo menos una sustancia activa adicional útil para protección de plantas, por ejemplo que se selecciona de los grupos A) a I) (componente 2), en particular un fungicida adicional, por ejemplo uno o más fungicidas de los grupos A) a F), como se describe en lo anterior y, si se desea, un disolvente adecuado o un portador sólido. Estas mezclas son de interés particular puesto que muchas de ellas en la misma tasa de aplicación muestran eficiencias más grandes contra hongos dañinos. Además, el combatir hongos dañinos con una mezcla de

compuestos de fórmula I y por lo menos un fungicida de los grupos A) a F), como se describe en lo anterior es más eficiente que combatir estos hongos con compuestos individuales de fórmula I o fungicidas individuales de los grupos A) a F). Al aplicar compuestos de fórmula I junto con por lo menos una sustancia activa de los grupos A) a I) se puede obtener un efecto sinergístico, es decir, se obtiene más de una simple adición de efectos individuales (mezclas sinergísticas).

De acuerdo con esta invención, la aplicación de los compuestos de fórmula I junto con por lo menos una sustancia activa adicional debe entenderse que indica que por lo menos un compuesto de fórmula I y por lo menos una sustancia activa adicional se presentan simultáneamente en el sitio de acción (es decir, los hongos dañinos que van a ser controlados o sus hábitat tales como plantas infectadas, materiales de propagación vegetal, particularmente semillas, superficies, materiales o el suelo así como las plantas, materiales de propagación de plantas, particularmente semillas, suelo, superficies, materiales o habitaciones que van a ser protegidas de ataque por hongo (en una cantidad fungicida eficaz). Esto se puede obtener al aplicar los compuestos de la fórmula I y por lo menos una sustancia activa adicional, simultáneamente, ya sea de modo conjunto (por ejemplo, como una mezcla en el tanque) o por separado, o en sucesión, en

donde el intervalo de tiempo entre las aplicaciones individuales se selecciona para asegurar que la sustancia activa aplicada aún se encuentre en el sitio de acción en cantidad suficiente en el momento de aplicación de una o varias sustancias activas adicionales. El orden de aplicación no es esencial para el funcionamiento de la presente invención.

En mezclas binarias, es decir, composiciones de acuerdo con la invención que comprenden un compuesto I (componente 1) y una sustancia activa adicional (componente 2), por ejemplo una sustancia activa de los grupos A) a I), la relación en peso del componente 1 y del componente 2 generalmente depende de las propiedades de las sustancias activas utilizadas, habitualmente están en el intervalo de 1:100 a 100:1, de manera regular en el intervalo de 1:50 a 50:1, preferiblemente en el intervalo de 1:20 a 20:1, de manera más preferible en el intervalo de 1:10 a 10:1 y en particular en el intervalo de 1:3 a 3:1.

En mezclas terciarias, es decir, composiciones de acuerdo con la invención que comprenden un compuesto I (componente 1) y una primera sustancia activa adicional (componente 2) y una segunda sustancia activa adicional (componente 3), por ejemplo, dos sustancias activas de los grupos A) a I), la relación en peso del componente 1 y del componente 2 depende de las propiedades de las sustancias

activas utilizadas, preferiblemente está en el intervalo de 1:50 a 50:1, y particularmente en el intervalo de 1:10 a 10:1, y la relación en peso del componente 1 y del componente 3 preferiblemente está en el intervalo de 1:50 a 50:1, y particularmente en el intervalo de 1:10 a 10:1.

Los componentes pueden ser utilizados individualmente o de antemano de modo parcial o completo mezclados entre sí para preparar la composición de acuerdo con la invención. También es posible que sean empacados y utilizados adicionalmente como composición de combinación tal como un kit de partes.

En una modalidad de la invención, los kits pueden incluir uno o más, incluyendo la totalidad de los componentes que se pueden utilizar para preparar una composición agroquímica objetivo. Por ejemplo, los kits pueden incluir uno o más componentes fungicidas y/o un componente adyuvante y/o un componente insecticida y/o un componente regulador de crecimiento y/o un herbicida. Uno o más de los componentes pueden combinarse de antemano juntos o se pueden preformular. En aquellas modalidades, en donde más de dos componentes se proporcionan en un kit, los componentes se pueden combinar de antemano juntos y de esta manera se empacan en un recipiente único tal como un frasco, botella, lata, saco, bolsa o recipiente. En otras modalidades, dos o más componentes de un kit se pueden empacar por separado, es decir, no

preformulados. De esta manera, los kits pueden incluir uno o más recipientes separados tales como frascos, latas, botellas, sacos, bolsas o recipientes, cada recipiente contiene un componente separado para una composición agroquímica. En ambas formas, un componente del kit se pueden aplicar por separado de o junto con los componentes adicionales o como un componente de una composición de combinación de acuerdo con la invención para preparar la composición de acuerdo con la invención.

El usuario aplica la composición de acuerdo con la invención habitualmente a partir de un dispositivo de predosificación, un aspersor de knapsack, un tanque de aspersión o un plano de aspersión. Aquí, la composición agroquímica está constituida con agua y/o amortiguador hasta la concentración de aplicación deseada, es posible, si es apropiado, para agregar auxiliares adicionales y el licor de aspersión listo para utilizarse o la composición agroquímica de acuerdo con la invención de esta manera se obtiene. En algunas modalidades, 50 a 500 litros de licor de aspersión listo para utilizarse se aplican por hectárea de área útil agrícola. En algunas modalidades, se aplican por hectárea 100 a 400 litros de licor de aspersión listo para usarse. En algunas modalidades, la invención proporciona un kit para aplicación de invernadero de una composición de la invención lista para usarse.

De acuerdo con una modalidad, los componentes individuales de la composición de acuerdo con la invención tales como partes de un kit o partes de una mezcla binaria o ternaria se pueden mezclar por el usuario mismo en un tanque de aspersión y se pueden agregar a auxiliares adicionales, si es apropiado (mezcla de tanque). En una modalidad adicional, ya sea los componentes individuales de la composición de acuerdo con la invención o componentes premezclados parcialmente, por ejemplo, componentes que comprenden compuestos de fórmula I y/o sustancias activas de los grupos A) a I), se pueden mezclar por el usuario en un tanque de aspersión y se pueden agregar auxiliares y aditivos adicionales, si es apropiado (mezcla de tanque).

En una modalidad adicional, ya sea componentes individuales de la composición de acuerdo con la invención o componentes premezclados parcialmente, por ejemplo, componentes que comprenden compuestos de fórmula I y/o sustancias activas de los grupos A) a I) se pueden aplicar de manera conjunta (por ejemplo, después del mezclado en tanque) o de modo consecutivo.

En algunas modalidades, la invención proporciona una mezcla que comprende un compuesto de fórmula I (componente 1) y por lo menos una sustancia activa que se selecciona del grupo de estrobilurinas del grupo A) (componente 2) y que se seleccionan particularmente de azoxistrobina, dimoxistrobina,

fluoxastrobina, cresoxim-metilo, orisastrobina, picoxistrobina, piraclostrobina y trifloxistrobina.

En algunas modalidades, la invención proporciona una mezcla que comprende un compuesto de fórmula I (componente I) y por lo menos una sustancia activa que se elecciona de carboxamidas del grupo B) (componente 2). En algunas modalidades, la carboxamida se selecciona del grupo que consiste de bixafeno, boscalida, sedexano, fenhexamida, metalaxilo, isopirazam, mefenoxam, ofurace, dimetomorf, flumorf, fluopicolida (picobenzamida), zoxamida, carpropamida, mandipropamida y N-(3',4',5'-trifluorobifenil-2-il)-3-difluorometil-1-metil-1H-pirazol-4-carboxamida.

En algunas modalidades, la invención proporciona una mezcla que comprende un compuesto de fórmula I (componente 1) y por lo menos una sustancia activa que se selecciona de los azoles del grupo C) (componente 2). En algunas modalidades, el azol se selecciona del grupo que consiste de ciproconazol, difenoconazol, epoxiconazol, fluquinconazol, flusilazol, flutriafol, metconazol, miclobutanilo, penconazol, propiconazol, protioconazol, triadimefon, triadimenol, tebuconazol, tetraconazol, triticonazol, procloraz, ciazofamida, benomilo, carbendazim y etaboxam.

En algunas modalidades, la invención proporciona una mezcla que comprende un compuesto de fórmula I (componente 1) y por lo menos una sustancia activa que se selecciona de

compuestos heterocíclicos del grupo D) (componente 2). En algunas modalidades, los compuestos heterocíclicos del grupo D) se seleccionan del grupo que consiste de fluazinam, ciprodinilo, fenarimol, mepanipirim, pirimetanil, triforina, fludioxonilo, dodemorf, fenpropimorf, tridemorf, fenpropidina, iprodiona, vinclozolina, famoxadona, fenamidona, probenazol, proquinazid, acibenzolar-S-metilo, captafol, folpet, fenoxanilo, quinoxifeno y 5-etil-6-octil-[1,2,4]triazolo[1,5-a]pirimidin-7-il-amina.

En algunas modalidades, la invención proporciona una mezcla que comprende un compuesto de fórmula I (componente 1) y por lo menos una sustancia activa que se selecciona de los carbamatos del grupo E) (componente 2). En algunas modalidades, los carbamatos se seleccionan del grupo que consiste de mancozeb, metiram, propineb, tiram, iprovalicarb, bentiavilacarb y propamocarb.

En algunas modalidades, la invención proporciona una mezcla que comprende un compuesto de fórmula I (componente 1) y por lo menos una sustancia activa que se selecciona de los fungicidas indicados en el grupo F) (componente 2). En algunas modalidades, los fungicidas del grupo F) se seleccionan del grupo que consiste de ditianon, sales de fentina, tales como acetato de fentina, fosetil, fosetil aluminio, H3PO3 y sales de los mismos, clortalonilo, diclofluanida, tiofanat-metilo, acetato de cobre, hidróxido de cobre, oxicloruro de cobre,

sulfato de cobre, azufre, cimoxanilo, metrafenona y espiroxamina.

Las sustancias activas a las que se hace referencia como el componente 2, su preparación y su actividad contra hongos dañinos es conocida en el ámbito. En algunas modalidades, estas sustancias están disponibles comercialmente. Los compuestos descritos por la nomenclatura de IUPAC, su preparación y su actividad fungicida también se conoce en el ámbito (véase Can. J. Plant Sci. 48(6), 587-94, 1968; EP-A 141 317; EP-A 152 031; EP-A 226 917; EP-A 243 970; EP-A 256 503; EP-A 428 941; EP-A 532 022; EP-A 1 028 125; EP-A 1 035 122; EP-A 1 201 648; EP-A 1 122 244, JP 2002316902; DE 19650197; DE 10021412; DE 102005009458; US 3,296,272; US 3,325,503; WO 98/46608; WO 99/14187; WO 99/24413; WO 99/27783; WO 00/29404; WO 00/46148; WO 00/65913; WO 01/54501; WO 01/56358; WO 02/22583; WO 02/40431; WO 03/10149; WO 03/1 1853; WO 03/14103; WO 03/16286; WO 03/53145; WO 03/61388; WO 03/66609; WO 03/74491; WO 04/49804; WO 04/83193; WO 05/120234; WO 05/123689; WO 05/123690; WO 05/63721; WO 05/87772; WO 05/87773; WO 06/15866; WO 06/87325; WO 06/87343; WO 07/82098; WO 07/90624).

Las mezclas de sustancias activas se pueden preparar como composiciones que comprenden además de los ingredientes activos, por lo menos un ingrediente inerte por medios habituales, por ejemplo, por los medios indicados para las

composiciones de los compuestos de fórmula I.

Respecto a los ingredientes habituales de estas composiciones se puede hacer referencia a las explicaciones indicadas para las composiciones que contienen compuestos de fórmula I.

Las mezclas de las sustancias activas de acuerdo con la presente invención son adecuadas como fungicidas dado que son compuestos de fórmula I. En algunas modalidades, las mezclas y composiciones de la presente invención son útiles para la protección de plantas contra un espectro amplio de hongos fitopatogénicos. En algunas modalidades, los hongos fitopatogénicos son de las clases de Ascomycetes, Basidiomycetes, Deuteromycetes y Peronosporomycetes (sinónimo, Oomycetes).

Los compuestos de fórmula I y sales farmacéuticamente aceptables de los mismos también son adecuados para tratar enfermedades en el hombre y en animales, especialmente como antimicóticos, para tratar cáncer y para tratar infecciones por virus. El término "antimicótico", como se distingue el término "fungicida" se refiere a un medicamento para combatir hongos zoopatogénicos o humanopatogénicos, es decir, para combatir hongos en animales, especialmente en mamíferos (que incluyen humanos) y aves.

En algunas modalidades, la presente invención proporciona un medicamento que comprende por lo menos un

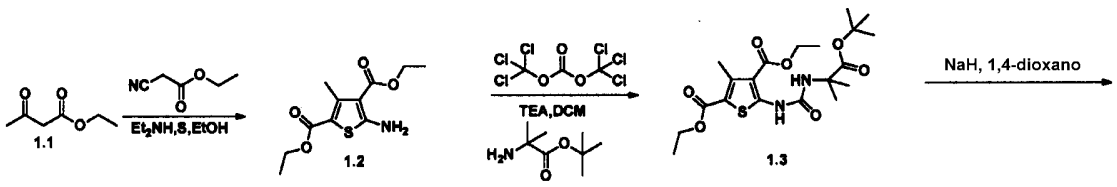
compuesto de fórmula I o una sal farmacéuticamente aceptable del mismo y un portador farmacéuticamente aceptable.

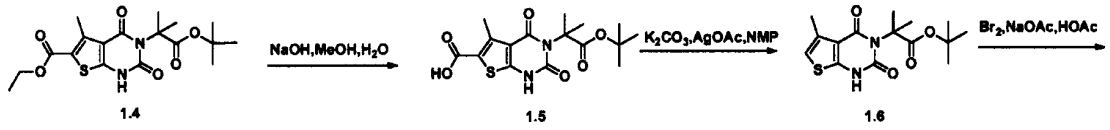
En algunas modalidades, la invención se relaciona con el uso de un compuesto de fórmula I o una sal farmacéuticamente aceptable del mismo para preparar un medicamento antimicótico; es decir, para preparar un medicamento para el tratamiento y/o profilaxis de infección con hongos patogénicos para los humanos y/o patogénicos para los animales.

EJEMPLIFICACION

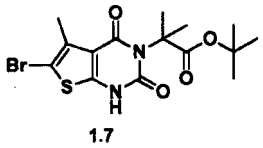
Como se muestra en los ejemplos siguientes, en algunas modalidades ejemplares, los compuestos se preparan de acuerdo con los siguientes procedimientos generales. Se apreciará que aunque los métodos generales muestran la síntesis de ciertos compuestos de la presente invención, los siguientes métodos generales y otros métodos conocidos por una persona habitualmente experta en el ámbito se pueden aplicar a todos los compuestos y subclases y especies de cada uno de estos compuestos, como se describe en la presente.

Ejemplo 1: intermediario 1.7.





1.4 1.5 1.6



1.7

Síntesis del compuesto 1.2. En un matraz de fondo redondo de 2000 ml se coloca una solución de 3-oxobutanoato de etilo (320 g, 2.46 moles, 1.00 equivalente), azufre (80 g, 1.00 equivalente) y 2-cianoacetato de etilo (280 g, 2.48 moles, 1.00 equivalente) en 600 ml de etanol. Esto es seguido por la adición de morfolina a gotas (235 g, 1.00 equivalentes) con agitación a 45°C durante 30 min. La solución resultante se agita durante 5 h a 60°C. Los sólidos se separan por filtración. La solución se diluye con 3000 ml de H_2O. Los sólidos se recolectan por filtración y la torta de filtro se lava con 1 l de EtOH 30%. La purificación proporciona 380 g (60%) de 5-amino-3-metiltiofen-2,4-dicarboxilato de 2,4-dietilo como un sólido amarillo.

Síntesis del compuesto 1.3. En un matraz de fondo redondo de 3 cuellos de 2000 ml purgado y mantenido bajo una atmósfera inerte de nitrógeno se coloca 5-amino-3-metiltiofen-2,4-dicarboxilato de 2,4-dietilo (200 g, 777.28 mmol, 1.00 equivalentes) y 1000 ml de diclorometano. Esto es seguido por

la adición de carbonato de ditriclorometilo (76.9 g, 259.14 mmol, 0.33 equivalentes) a 0°C. Esto es seguido por la adición de TEA (314 g, 3.10 moles, 3.99 equivalentes) a gotas con agitación, a 0°C durante 2 h. La solución resultante se agita durante 3 h a 0°C. A esto se agrega 2-amino-2-metilpropanoato de terbutilo (152 g, 776.70 mmol, 1.00 equivalentes) a 0°C. La solución resultante se agita durante la noche a temperatura ambiente. La reacción después se suspende por la adición de 1 l de agua. La mezcla resultante se concentra bajo vacío. El producto crudo se recristaliza a partir de EA/PE en la relación de 1:10 para proporcionar 105 g (31%) de 1.3 como un sólido amarillo.

Síntesis del compuesto 1.4. En un matraz de fondo redondo de 3 cuellos de 1 l, purgado y mantenido con una atmósfera inerte de nitrógeno se coloca 1.3 (42 g, 94.91 mmol, 1.00 equivalentes) en 400 ml de 1,4-dioxano. Esto es seguido por la adición de hidruro de sodio (5.7 g, 142.50 mmol, 1.50 equivalentes) a 10°C. La solución resultante se agita durante 2 h a 110°C. La reacción después se suspende por la adición de 500 ml de NH_4Cl acuoso saturado. La solución resultante se extrae con 3 x 200 ml de acetato de etilo y las capas orgánicas se combinan y concentran bajo vacío. El producto crudo se recristaliza a partir de EA/PE en la relación de 1:10. La purificación proporciona 24.4 g (65%) de 1.4 como un sólido blanco.

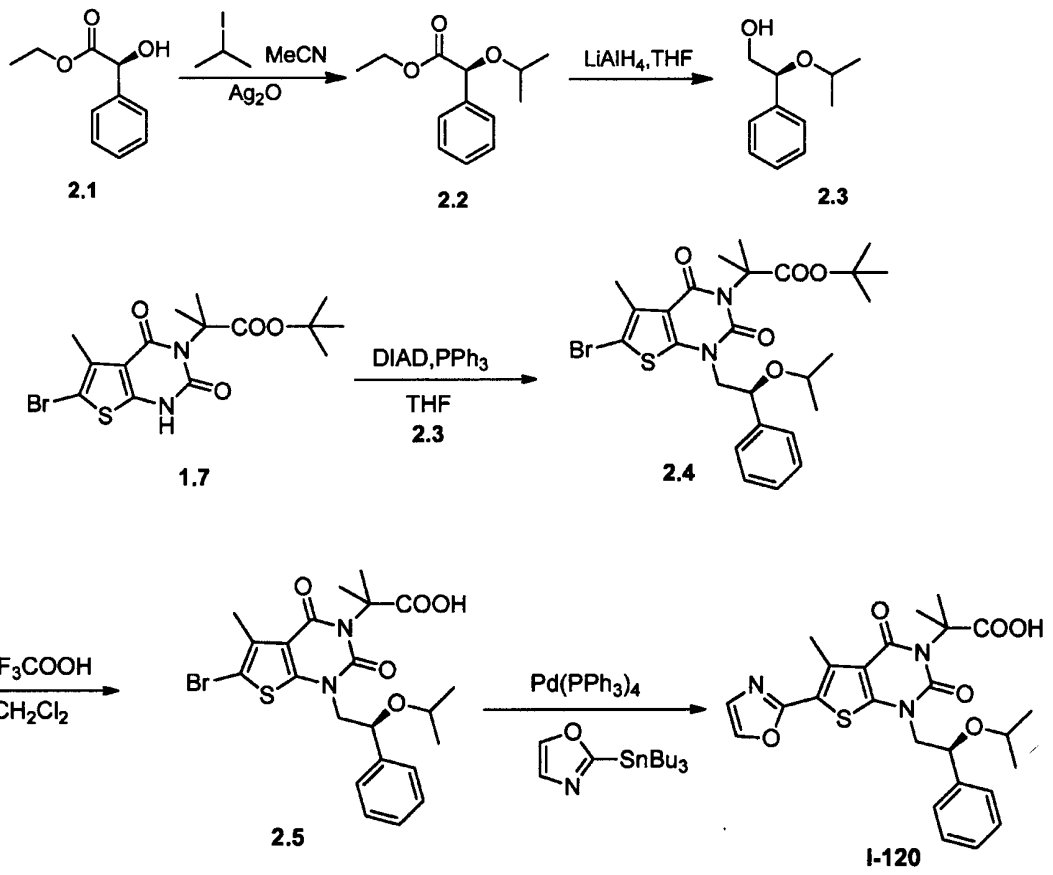
Síntesis del compuesto 1.5. En un matraz de fondo redondo de 3 cuellos de 500 ml se coloca 1.5 (24.4 g, 61.54 mmol, 1.00 equivalentes), hidróxido de sodio (12.2 g, 305.00 mmol, 4.96 equivalentes), 20 ml de agua y 250 ml de metanol. La solución resultante se agita durante 4 h a 50°C. La mezcla resultante se concentra bajo vacío. Se ajusta el valor de pH de la solución a 2 con cloruro de hidrógeno 10%. La solución resultante se extrae con 3 x 300 ml de acetato de etilo y las capas orgánicas se combinan, se secan sobre sulfato de sodio anhidro y se concentran bajo vacío para proporcionar 19.4 g (86%) de 1.5 como un sólido blanco.

Síntesis del compuesto 1.6. Un matraz de fondo redondo de 3 cuellos y 1 l se carga con 1.5 (19.4 g, 52.66 mmol, 1.00 equivalentes), carbonato de potasio (8.7 g, 62.95 mmol, 1.20 equivalentes), 10.5 de CH_3COOAg y 400 ml de NMP. La solución resultante se agita durante 2 h a 110°C. La reacción después se suspende por la adición de 1 l de agua. La solución resultante se extrae con 5 x 200 ml de acetato de etilo y las capas orgánicas se combinan y concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:20). La purificación proporciona 15.3 g (90%) de 1.6 como un sólido blanco.

Síntesis del compuesto 1.7. En un matraz de fondo redondo de 3 cuellos de 1000 ml se coloca 1.6 (15.3 g, 47.16 mmol, 1.00 equivalentes), CH_3COONa 8.5 g, 103.66 mmol,

2.20 equivalentes) y 300 ml de ácido acético. Esto es seguido por la adición de Br_2 (8.3 g, 51.94 mmol, 1.10 equivalentes) a gotas, con agitación. La solución resultante se agita durante 1 h a temperatura ambiente, se concentra bajo vacío y se lava con 500 ml de H_2O para proporcionar 17 g (89%) de 1.7 como un sólido blanco.

Ejemplo 2: Síntesis de ácido 2-metil-2-[5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1-[(2S)-2-fenil-2-(propan-2-iloxi)etil]-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-120)



Síntesis del compuesto 2.2. Un matraz de fondo redondo de 500 ml se carga con 2.1 (15 g, 83.24 mmol, 1.00 equivalentes), 200 ml de prop-1-ino, Ag_2O (52 g, 225.11 mmol, 2.70 equivalentes) y 2-yodopropano (60 g, 352.96 mmol, 4.24 equivalentes). La solución resultante se agita durante la noche a 40°C en un baño de aceite. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con EA/PE (1:50). La purificación proporciona 3.2 g (crudo) de 2.2 como un aceite amarillo.

Síntesis del compuesto 2.3. Un matraz de fondo redondo de 3 cuellos de 100 ml se carga con 10 ml de tetrahidrofurano y 2.2 (300 mg, 1.35 mmol, 1.00 equivalentes). Esto es seguido por la adición de $LiAlH_4$ (51 mg, 1.34 mmol, 1.00 equivalentes) en porciones, a 0°C. La solución resultante se agita durante 1 h a temperatura ambiente. La reacción después se suspende por la adición de 20 ml de NH_4Cl acuoso. La solución resultante se extrae con 3 x 50 ml de acetato de etilo y las capas orgánicas se combinan, se secan sobre sulfato de magnesio anhidro y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:10). La purificación proporciona 210 mg (86%) de 2.3 como un aceite amarillo.

Síntesis del compuesto 2.4. Un matraz de fondo redondo de 3 cuellos de 100 ml se carga con 10 ml de tetrahidrofurano, 2.3 (500 mg, 1.24 mmol, 1.00 equivalentes),

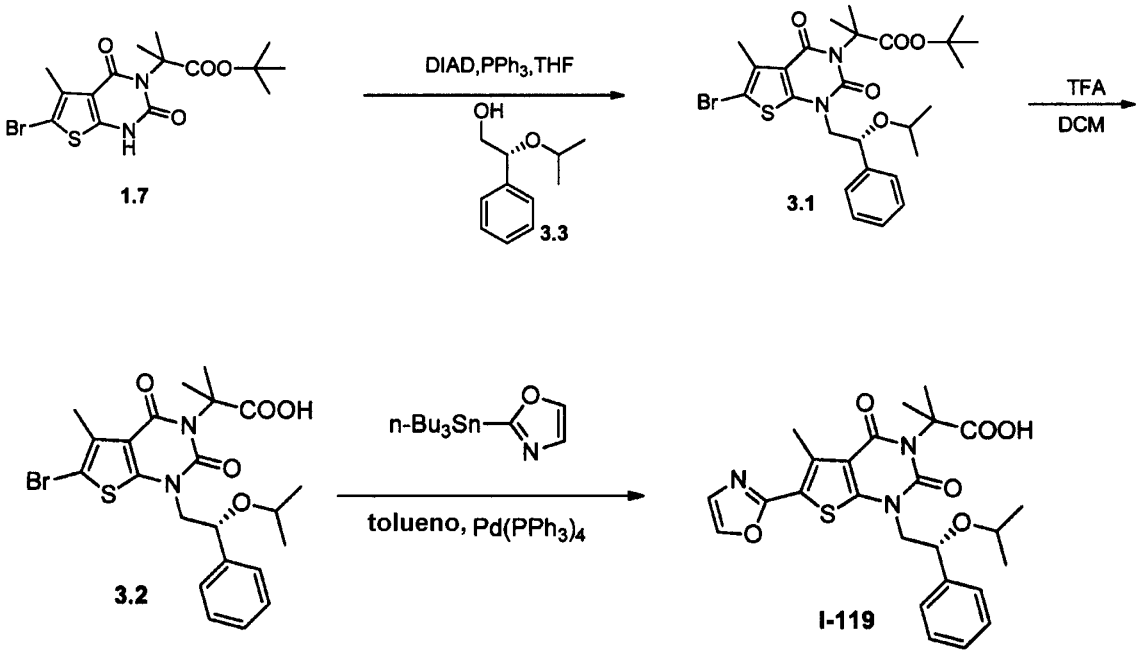
PPh_3 (650 mg, 2.48 mmol, 2.00 equivalentes), DIAD (362 mg, 1.79 mmol, 1.44 equivalentes) y 2.3 (268 mg, 1.49 mmol, 1.20 equivalentes) bajo una atmósfera de nitrógeno. La solución resultante se agita durante la noche a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:15). La purificación proporciona 0.430 g (61%) de 2.4 como un aceite incoloro.

Síntesis del compuesto 2.5. Un matraz de fondo redondo de 25 ml se carga con 5 ml de diclorometano, 2.4 (428 mg, 0.76 mmol, 1.00 equivalentes) y 2 ml de CF_3COOH. La solución resultante se agita durante la noche a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:5). La purificación proporciona 0.282 g (73%) de 2.4 como un aceite incoloro.

Síntesis del compuesto I-120. Un matraz de fondo redondo de 3 cuellos de 100 ml de carga con 10 ml de tolueno, 2.5 (282 mg, 0.55 mmol, 1.00 equivalentes), $Pd(PPh_3)_4$ (200 mg, 0.17 mmol, 0.31 equivalentes) y 2-(tripropilestanil)-1,3-oxazol (238 mg, 0.75 mmol, 1.36 equivalentes) bajo una atmósfera de nitrógeno. La solución resultante se calienta a reflujo durante la noche en un baño de aceite. La mezcla resultante se concentra bajo vacío. Se purifican 300 mg del producto crudo por *HPLC* preparativa bajo las siguientes

condiciones (SHIMADZU): columna: Sunfire Prep C18, 19*150 mm 5 μm; fase móvil: agua con NH_4HCO_3 0.05% y CH_3CN (CH_3CN 7.0% hasta 46.0% en 10 min); detector: UV 254/220 nm, 0.193 g (70%)del compuesto I-120 se obtiene como un sólido blanco. EM (ES): m/z 498 $(M+H)^+$. RMN ^1H (CD_3OD, 300 MHz): δ 0.97 (m, 6H), 1.77 (d, J = 6.0 Hz, 6H), 3.04 (s, 3H), 3.46 (m, 1H), 3.82 (m, 1H), 4.13 (m, 1H), 4.88 (m, 1H), 7.24-7.44 (m, 6H), 7.94 (d, J = 0.9 Hz, 1H).

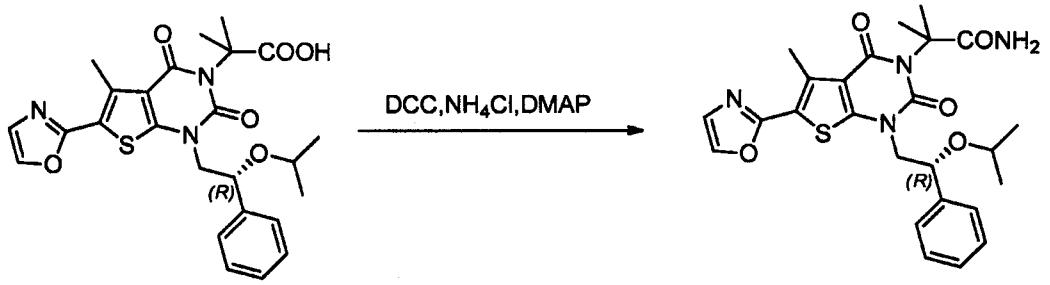
Ejemplo 3: Síntesis del ácido 2-metil-2-[5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1-[(2R)-2-fenil-2-(propan-2-iloxi)etil]-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-119)



Se sintetiza el compuesto I-119 de una manera

análoga al ejemplo 2 excepto que se utiliza (2R)-2-fenil-2-(propan-2-iloxi)etan-1-ol en vez de (2S)-2-fenil-2-(propan-2-iloxi)etan-1-ol. Se obtiene el compuesto I-119 con rendimiento general de 11% como un sólido amarillo. EM (ES): m/z 498 $(M+H)^+$. RMN ^1H (CD_3OD, 300 MHz): δ 0.97 (d, J = 6.3 Hz, 3H), 0.99 (d, J = 6.3 Hz, 3H), 1.77 (d, J = 6.3 Hz, 6H), 2.77 (s, 3H), 3.50 (m, 1H), 3.81 (m, 1H), 4.13 (m, 1H), 4.89 (m, 1H), 7.24-7.45 (m, 6H), 7.94 (d, J = 0.9 Hz, 1H).

Ejemplo 4: Síntesis de 2-metil-2-[5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1-[(2R)-2-fenil-2-(propan-2-iloxi)etil]-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanamida (I-121).

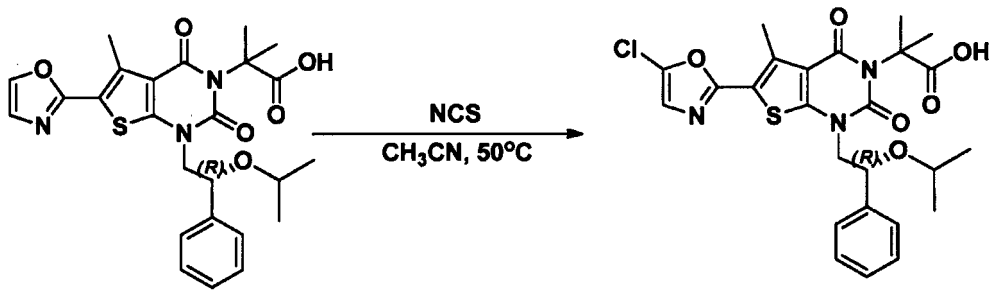


I-119 I-121

Un matraz de fondo redondo de 25 ml se carga con 10 ml de diclorometano, compuesto I-119 (70 mg, 0.14 mmol, 1.00 equivalentes), DCC (39 mg, 0.19 mmol, 1.34 equivalentes), 4-dimetilaminopiridina (19 mg, 0.16 mmol, 1.11 equivalentes) y NH_4Cl (20 mg, 0.37 mmol, 2.66 equivalentes). La solución resultante se agita durante la noche a 40°C en un baño de

aceite. La reacción después se suspende por la adición de 10 ml de agua. La solución resultante se extrae con 5 x 20 ml de acetato de etilo y las capas orgánicas se combinan y concentran bajo vacío. El residuo se purifica por CCD preparativa (DCM: MeOH = 15:1). El producto obtenido de esta manera (50 mg) se vuelve a purificar por *HPLC* preparativa bajo las siguientes condiciones (SHIMADZU): columna: SunFirePrep C18, 19*150 mm 5 μm; fase móvil: agua con NH_4HCO_3 0.05% y CH_3CN (CH_3CN 6.0% hasta 48.0% en 13 min); detector: UV254/220 nm. Se obtienen 0.030 g (43%) del compuesto I-121 como un sólido blanco. EM (ES): m/z 497 $(M+H)^+$. RMN ^1H (CD_3OD, 300 MHz): δ 0.90 (m, 6H), 1.79 (d, J = 5.1 Hz, 6H), 2.77 (s, 3H), 3.54 (m, 1H), 3.81 (m, 1H), 4.11 (m, 1H), 4.90 (m, 1H), 7.24-7.44 (m, 6H), 7.94 (d, J = 0.9 Hz, 1H).

Ejemplo 5: Síntesis de ácido 2-[6-(5-cloro-1,3-oxazol-2-il)-5-metil-2,4-dioxo-1-[(2R)-2-fenil-2-(propan-2-iloxi)etil]-1H,2H,3H,4H-tieno[2.3-d]pirimidin-3-il]-2-metilpropanoico (I-156)

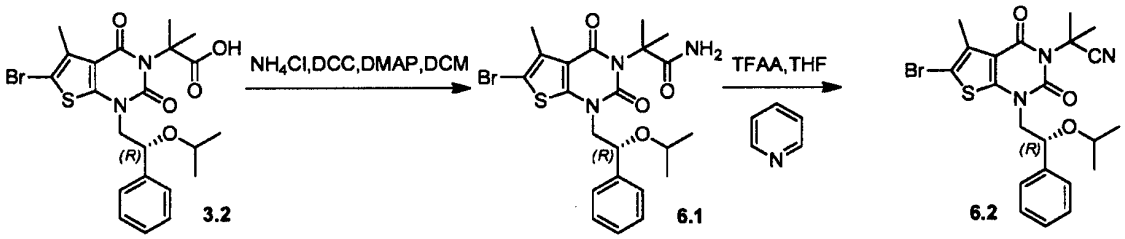


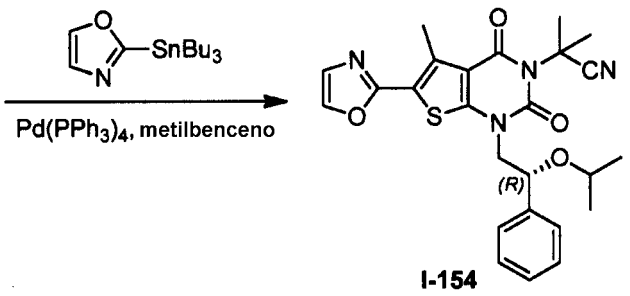
I-119 I-156

En un matraz de fondo redondo de 50 ml protegido por

nitrógeno se colocan 10 ml de CH_3CN, compuesto I-119 (60 mg, 0.12 mmol, 1.00 equivalente) y NCS (32 mg, 0.24 mmol, 1.99 equivalentes). La solución resultante se agita durante 3 días a 50°C en un baño de aceite y se monitorea por CLEM. La mezcla resultante se concentra bajo vacío. El producto crudo (60 mg) se purifica por *HPLC* preparativa bajo las siguientes condiciones (Waters): columna: Xbridge Prep C18, 5 μm, 19*50 mm; fase móvil: agua en NH_4HCO_3 50 mmol y CH_3CN (CH_3CN 10% hasta 35% en 10 min, hasta 95% en 1.5 min, reducción a 10% en 1.5 min); detector: UV 254/220 nm. Se obtienen 0.010 g (16%) de I-156 como un sólido blanco. RMN ^1H (CD_3OD, 400 MHz): δ 1.00 (dd, 6H), 1.82 (d, J = 8.0 Hz, 6H), 2.79 (s, 3H), 3.54 (m, 1H), 3.85 (dd, J = 1H), 4.18 (dd, 1H), 4.93 (dd, 1H), 7.16 (s, 1H), 7.34 (t, J = 7.2 Hz, 1H), 7.41 (t, J = 7.6 Hz, 2H), 7.47 (d, J = 7.2 Hz).

Ejemplo 6: Síntesis de 2-metil-2-[5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1-[(2R)-2-fenil-2-(propan-2-iloxi)etil]-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanitrilo (I-154).





I-154

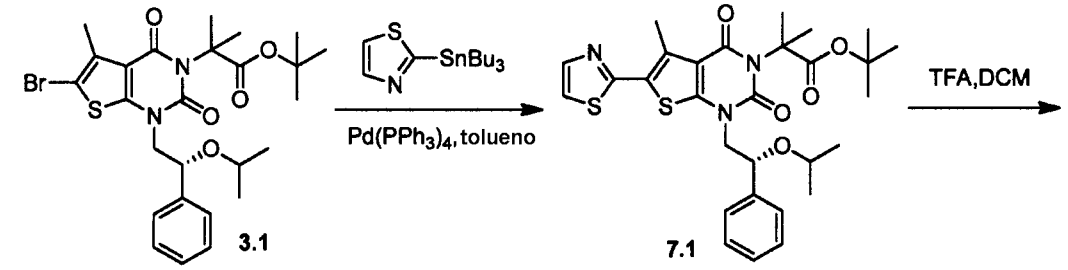
Síntesis del compuesto 6.1. Se prepara el compuesto 6.1 de una manera análoga al compuesto I-121 (ejemplo 4). Se aíslan 100 mg (42%) de 6.1 como un sólido blanco.

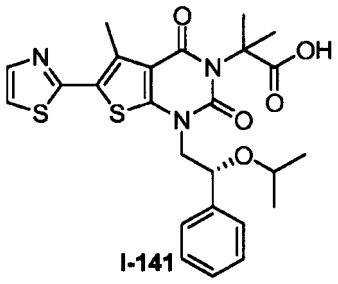
Síntesis del compuesto 6.2. Un matraz de fondo redondo de 25 ml se carga con 6.1 (100 mg, 0.20 mmol, 1.00 equivalentes), 5 ml de tetrahidrofurano y piridina (78 mg, 0.99 mmol, 5.01 equivalentes). Este es seguido por la adición de TFAA (103 mg, 0.49 mmol, 2.49 equivalentes) a gotas con agitación a 0°C. La solución resultante se agita durante 3 h a temperatura ambiente y después se concentra bajo vacío. El residuo se purifica por CCD preparativa con acetato de etilo/éter de petróleo (1:3). La purificación proporciona 90 mg (93%) de 6.2 como un sólido blanco.

Síntesis del compuesto I-154. En un matraz de fondo redondo de 25 ml se coloca 6.2 (100 mg, 0.20 mmol, 1.00 equivalentes), $Pd(PPH_3)_4$ (60 mg, 0.05 mmol, 0.26 equivalentes), 2-(tributilestanil)-1,3-oxazol (153 mg, 0.43 mmol, 2.17 equivalentes) y 5 ml de metilbenceno. La solución resultante se agita durante la noche a 110°C y después se concentra bajo vacío. El residuo se purifica por

CCD preparativa con acetato de etilo/éter de petróleo (1:2). La purificación proporciona 5.2 mg (6%) del compuesto I-154. RMN ^{1}H (300 MHz, CD_3OD): δ 1.00-1.06 (m, 6H), 2.09-2.10 (d, 6H), 2.84-2.89 (s, 3H), 3.49-3.57 (m, 1H), 3.89-3.96 (m, 1H), 4.18-4.25 (m, 1H), 4.94-4.98 (m, 1H), 7.30-7.32 (s, 1H), 7.34-7.49 (m, 5H), 8.01 (s 1H). EM (ES): m/z 479 $(M+H)^+$.

Ejemplo 7: Síntesis de ácido 2-metil-2-[5-metil-2,4-dioxo-1-[(2R)-2-fenil-2-(propan-2-iloxi)etil]-6-(1,3-tiazol-2-il)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-141).





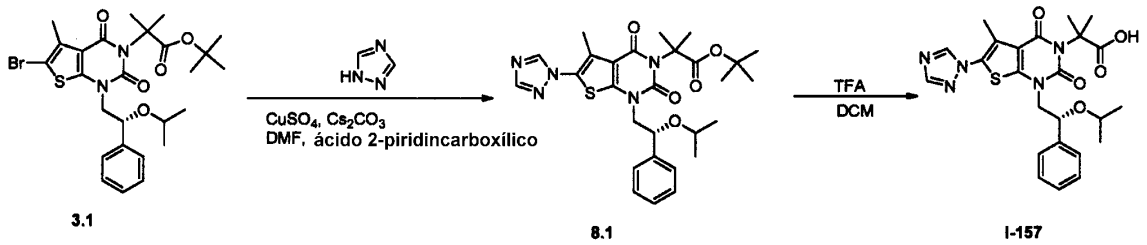
Síntesis del compuesto 7.1. A un matraz de fondo redondo de 25 ml, purgado y mantenido con una atmósfera inerte de nitrógeno, se agregan 3.1 (210 mg, 0.37 mmol, 1.00 equivalentes) 2-(tributilestanil)-1,3-tiazol (208 mg, 0.56

mmol, 1.50 equivalentes), 5 ml de metilbenceno y $Pd(PPh_3)_4$ (200 mg, 0.17 mmol, 0.47 equivalentes). La solución resultante se agita durante la noche a 110°C. La mezcla de reacción se enfría a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:20). La purificación proporciona 137 mg (65%) de 7.1 como un sólido blanco.

Síntesis del compuesto I-141. Un matraz de fondo redondo de 10 ml se carga con el compuesto 7.1 (137 mg, 0.24 mmol, 1.00 equivalentes), 2 ml de ácido trifluoroacético y 3 ml de diclorometano. La solución resultante se agita durante la noche a temperatura ambiente y después se concentra bajo vacío. Se purifican 130 mg del producto crudo por *HPLC* preparativa bajo las siguientes condiciones (SHIMADZU): columna: Xbridge Prep Phenyl 5 μm, 19*150 mm; fase móvil: agua (NH_4HCO_3 0.05%) y CH_3CN (CH_3CN 6.0% hasta 50.0% en 11.5 min); detector: UV 220/254 nm. Se obtienen 43.9 mg (36%) del compuesto I-141 como un sólido blanco. EM (ES): m/z 514 $(M+H)^+$. RMN ^1H (CD_3OD, 400 MHz): δ 0.99-1.05 (m, 6H), 1.82-1.84 (d, 6H), 2.76 (s, 3H), 3.49-3.55 (m, 1H), 3.85-3.89 (m, 1H), 4.14-4.19 (m, 1H), 4.92-4.95 (m, 1H), 7.31-7.35 (t, 1H), 7.39-7.43 (t, 2H), 7.47-7.49 (d, 2H), 7.66-7.66 (d, 1H), 7.83-7.84 (d, 1H).

Ejemplo 8: Síntesis de ácido 2-metil-2-[5-metil-2,4-

dioxo-1-[(2R)-2-fenil-2-(propan-2-iloxi)etil]-6-(1H-1,2,4-triazol-1-il)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-157)

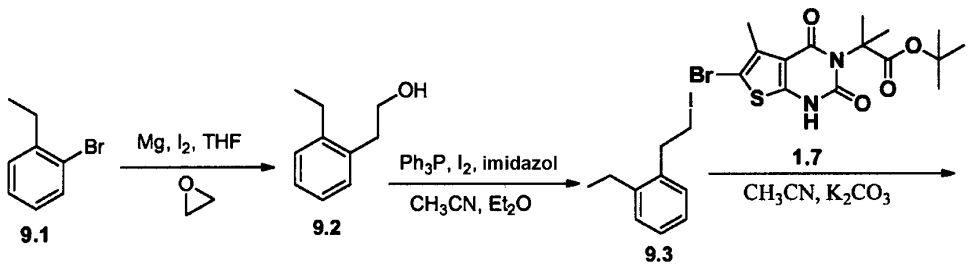


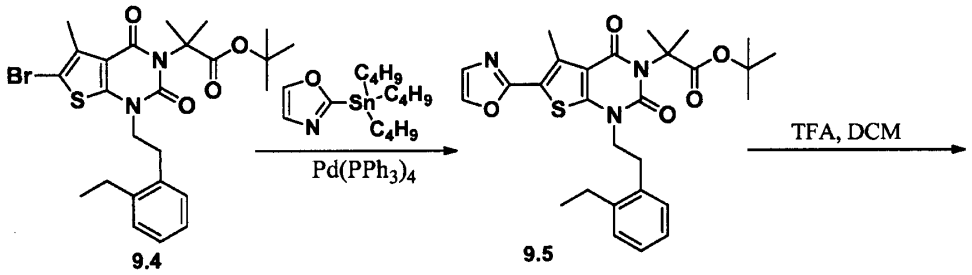
Síntesis del compuesto 8.1. Un tubo sellado de 8 ml se carga con 1H-1,2,4-triazol (100 mg, 1.45 mmol, 8.19 equivalentes), 3.1 (100 mg, 0.18 mmol, 1.00 equivalentes), ácido piridin-2-carboxílico (70 mg, 0.57 mmol, 3.22 equivalentes), 5 ml de $CuSO_4$, N,N-dimetilformamida (100 mg, 1.37 mmol, 7.74 equivalentes) y Cs_2CO_3 (70 mg, 3.22 equivalentes). La mezcla de reacción se irradia con radiación de microondas durante 30 min a 170°C. La reacción después se suspende por la adición de 20 ml de NH_4Cl saturado. La solución resultante se extrae con 2 x 20 ml de acetato de etilo y las capas orgánicas se combinan y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:10). La purificación proporciona 30 mg (31%) de 8.1 como un sólido blanco.

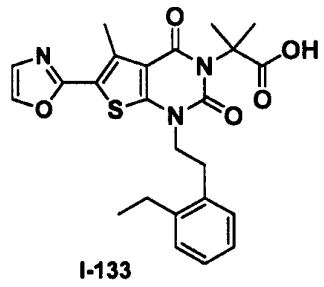
Síntesis del compuesto I-157. Un matraz de fondo redondo de 50 ml se carga con 8.1 (57 mg, 0.10 mmol, 1.00 equivalentes), 10 ml de diclorometano y 2 ml

de ácido trifluoroacético. La solución resultante se agita durante la noche a 30°C. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con diclorometano/metanol (50:1). Se purifican 60 mg del producto crudo por *HPLC* preparativa bajo las siguientes condiciones (Waters): columna: SunFire Prep C18, 19*150 mm 5 µm; fase móvil: agua (NH_4HCO_3 50 mM) y CH_3CN (CH_3CN 5.0% hasta 50.0% en 10 min, hasta 95.0% en 2 min, disminuye a 5.0% en 2 min); detector: UV 254/220 nm. La purificación proporciona 9.9 mg (19%) del compuesto I-157 como un sólido blanco. RMN ^1H (CD_3OD, 400 MHz): 1.06 (m, 6H), 1.82 (d, 6H), 2.35 (s, 3H), 3.51 (m, 1H), 3.78 (m, 1H), 4.17 (m, 1H), 4.91 (m, 1H), 7.42 (m, 5H), 8.25 (s, 1H), 8.86 (s, 1H). EM (ES): 498 *m/z* $(M+H)^+$.

Ejemplo 9: Síntesis del ácido 2-[1-[2-(2-etilfenil)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-133).







Síntesis del compuesto 9.2. En un matraz de fondo redondo de 250 ml protegido por N_2 se colocan 100 ml de tetrahidrofurano, Mg (1.0 g, 41.67 mmol, 2.14 equivalentes) y 0.010 g de I_2. Después se agrega a gotas una solución de 1-bromo-2-etilbenceno (3.6 g, 19.45 mmol, 1.00 equivalentes) en 15 ml de THF. La mezcla resultante se calienta a reflujo durante 1 h. Después se enfría a 0°C y se agregan 50 ml de oxirano. La solución resultante se agita a temperatura ambiente durante la noche. La reacción después se suspende por la adición de 20 ml de NH_4Cl acuoso. La solución resultante se extrae con 3 x 50 ml de acetato de etilo y las capas orgánicas se combinan y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:5). La purificación proporciona 1.83 g (63%) de 2-(2-etilfenil)etan-1-ol como un aceite incoloro.

Síntesis del compuesto 9.3. En un matraz de fondo redondo de 50 ml se colocan 10 ml de éter, 5 ml de CH_3CN y 2-(2-etilfenil)etan-1-ol (900 mg, 5.99 mmol, 1.00 equivalentes). Después se agregan a 0°C imidazol (570 mg, 8.38 mmol, 1.40 equivalentes), PPh_3 (2.20 g, 8.39 mmol, 1.40 equivalentes) e I_2 (1.98 g, 7.80 mmol, 1.30 equivalentes). La solución resultante se agita durante 6 h a temperatura ambiente. La reacción después se suspende por la adición de 10 ml de una solución saturada de Na_2SO_3. La solución resultante se extrae con 3 x 50 ml de acetato de etilo y las capas orgánicas se combinan, se secan sobre Na_2SO_4 y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:20). La purificación proporciona 1.16 g (74%) de 1-etil-2-(2-yodoetil)benceno como un aceite incoloro.

Síntesis del compuesto 9.4. Un matraz de fondo redondo de 50 ml se carga con 9.3 (200 mg, 0.50 mmol, 1.00 equivalentes), carbonato de potasio (205 mg, 1.48 mmol, 2.99 equivalentes), 20 ml de acetonitrilo y 1-etil-2-(2-yodoetil)benceno (258 mg, 0.99 mmol, 2.00 equivalentes). La solución resultante se calienta a reflujo durante la noche en un baño de aceite. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:50). La purificación proporciona 220 mg (83%) del compuesto 9.4 como un sólido

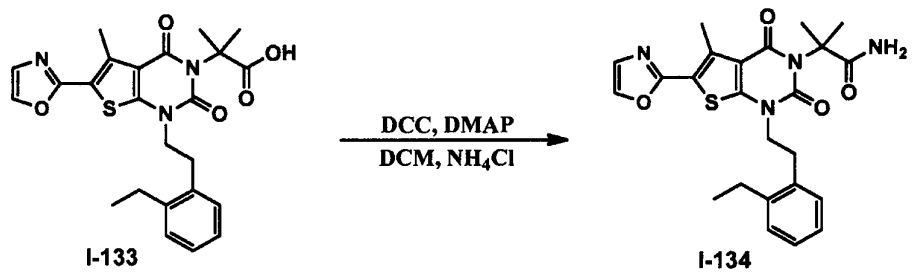
blanco.

Síntesis del compuesto 9.5. Un matraz de fondo redondo de 50 ml, purgado y mantenido con una atmósfera inerte de nitrógeno se carga con 9.4 (220 mg, 0.41 mmol, 1.00 equivalentes), 20 ml de tolueno, 2-(tributilestanil)-1,3-oxazol (280 mg, 0.78 mmol, 1.90 equivalentes) y tetrakis(trifenilfosfano) paladio (67 mg, 0.06 mmol, 0.14 equivalentes). La solución resultante se agita durante la noche a 110°C en un baño de aceite. La mezcla resultante se concentra bajo vacío. El residuos se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:25). La purificación proporciona 180 mg (84%) de 9.5 como un sólido blanco.

Síntesis del compuesto I-133. En un matraz de fondo redondo de 50 ml se coloca el compuesto 9.5 (180 mg, 0.34 mmol, 1.00 equivalentes), 10 ml de diclorometano y 3 ml de ácido trifluoroacético. La solución resultante se agita durante 3 h a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:2). La purificación proporciona 130 mg (81%) del compuesto I-133 como un sólido blanco. RMN ^{1}H (300 MHz, DMSO-d_6): δ 1.19 (t, *J* =7.5, 3H), 1.68 (s, 6H), 2.50 (c, *J* = 1.8, 2H), 2.74 (s, 3H), 3.03 (t, *J* = 7.8, 2H), 4.04 (t, *J* = 7.8, 2H), 7.10-7.21 (m, 4H), 7.38 (s, 1H), 8.23 (s, 1H). EM (ES): *m/z* 468 $(M+H)^{+}$, 509

$(M+CH_3CN)^+$.

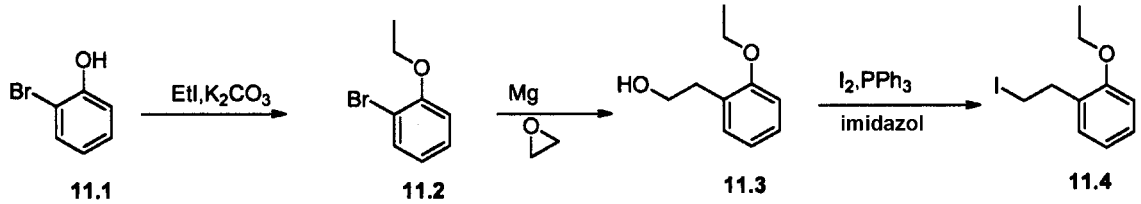
Ejemplo 10: Síntesis de 2-[1-[2-(2-etilfenil)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanamida (I-134).



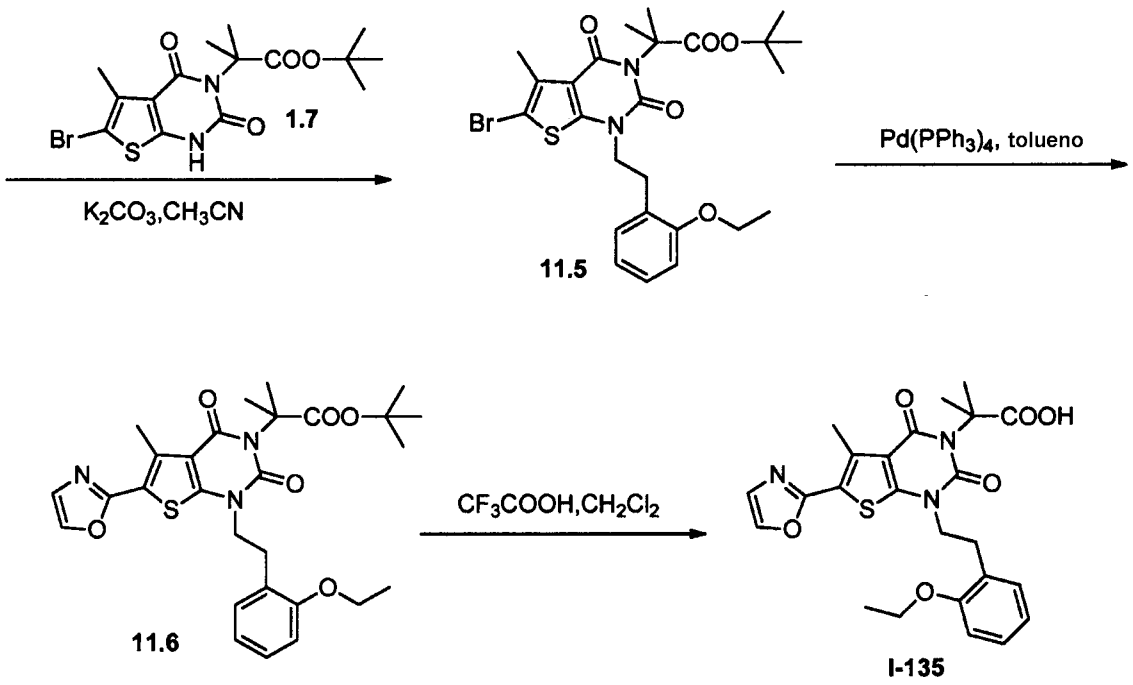
I-133 I-134

Se prepara el compuesto I-134 a partir de I-133 de una manera análoga del compuesto I-121 (ejemplo 4). Se aíslan 37.4 mg (42%) del compuesto I-134 como un sólido blanco. EM (ES): *m/z* 467 $(M+H)^+$. RMN ^1H (DMSO-d_6, 300 MHz): δ 1.20 (t, *J* = 7.8 Hz ,3H), 1.66 (s, 6H), 2.67-2.74 (m, 5H), 3.01 (t, *J* = 7.2 Hz, 2H), 4.00 (t, *J* = 7.2 Hz, 2H), 7.14-7.20 (m, 4H), 7.38 (s,1H), 8.22 (s, 1H).

Ejemplo 11: Síntesis de ácido 2-[1-[2-(2-etoxifenil)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-135).



11.1 11.2 11.3 11.4



Síntesis del compuesto 11.2. En un matraz de fondo redondo de 500 ml se colocan 200 ml de CH_3COCH_3, 2-bromofenol (10.38 g, 60.00 mmol, 1.00 equivalentes), yodoetano (28.08 g, 180.04 mmol, 3.00 equivalentes) y carbonato de potasio (33.12 g, 239.64 mmol, 3.99 equivalentes). La solución resultante se calienta a reflujo durante la noche en un baño de aceite. Los sólidos se separan por filtración. El filtrado se concentra bajo vacío. El residuo se aplica sobre una columna de gel se sílice con acetato de etilo/éter de petróleo (1:100). La purificación proporciona 11.48 g (95%) de 1-bromo-2-etoxibenceno como un aceite incoloro.

Síntesis del compuesto 11.3. En un matraz de fondo redondo de 3 cuellos de 250 ml mantenido con una atmósfera inerte de nitrógeno se coloca Mg (1.0 g, 41.67 mmol,

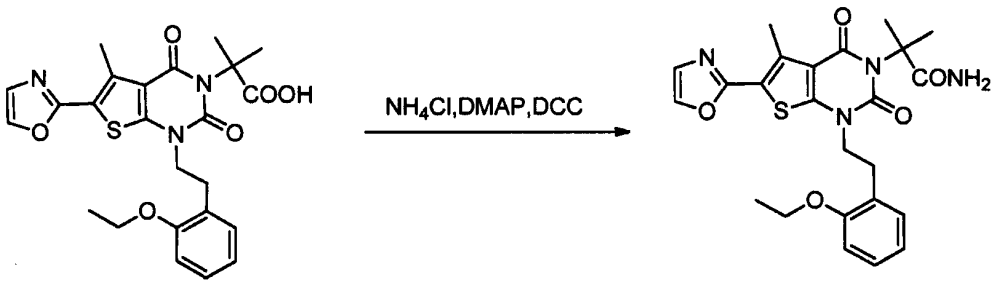
2.09 equivalentes) y 10 mg de I_2. Después se agrega a gotas una solución de 1-bromo-2-etoxibenceno (4.0 g, 19.89 mmol, 1.00 equivalentes) en 25 ml de THF y la mezcla resultante se calienta a reflujo durante 0.5 h. Después de que se ha completado la reacción, la mezcla resultante se enfría a 0°C y después se agregan 50 ml de oxidano en una porción. La mezcla de reacción se agita durante la noche a temperatura ambiente. La reacción después se suspende por la adición de 50 ml de NH_4Cl acuoso y se extrae con 3 x 50 ml de acetato de etilo. Las capas orgánicas se combinan, se secan sobre sulfato de sodio anhidro y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:10). La purificación proporciona 2.14 g (65%) de 2-(2-etoxifenil)etan-1-ol como un aceite amarillo.

Síntesis del compuesto 11.4. En un matraz de fondo redondo de 50 ml se colocan 20 ml de diclorometano y 2-(2-etoxifenil)etan-1-ol (1.33 g, 8.00 mmol, 1.00 equivalentes). La solución se enfría a 0°C en un baño de agua/hielo. Después se agregan PPh_3 (2.72 g, 10.37 mmol, 1.30 equivalentes), imidazol (707 mg, 10.40 mmol, 1.30 equivalentes) e I_2 (2.44 g, 9.61 mmol, 1.20 equivalentes). La solución resultante se agita a temperatura ambiente durante la noche. La reacción después se suspende por la adición de 50 ml de $NaHSO_3$ acuoso. La capa orgánica se separa y se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de

etilo/éter de petróleo (0:100). La purificación proporciona 1.34 g (61%) de 1-etoxi-2-(2-yodoetil)benceno como un aceite incoloro.

Síntesis del compuesto I-135. El compuesto I-135 se prepara a partir de 11.4 y 1.7 de una manera análoga al ejemplo 9. Se aísla un sólido blanco con un rendimiento general de 50% para las dos etapas. EM (ES): *m/z* 484 $(M+H)^+$. RMN ^{1}H (DMSO-d_6, 300 MHz): δ 1.37 (t, *J* = 7.2 Hz, 3H), 1.64 (s, 6H), 2.73 (s, 3H), 3.00 (t, *J* = 7.2 Hz, 2H), 4.05 (m, 4H), 6.84 (m, 1H), 6.92 (m, 1H) , 7.16 (m, 2H), 7.38 (d, *J* = 0.6 Hz, 1H), 8.22 (d, *J* = 0.6 Hz, 1H).

Ejemplo 12: Síntesis de 2-[1-[2-(2-etoxifenil)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanamida (I-139).

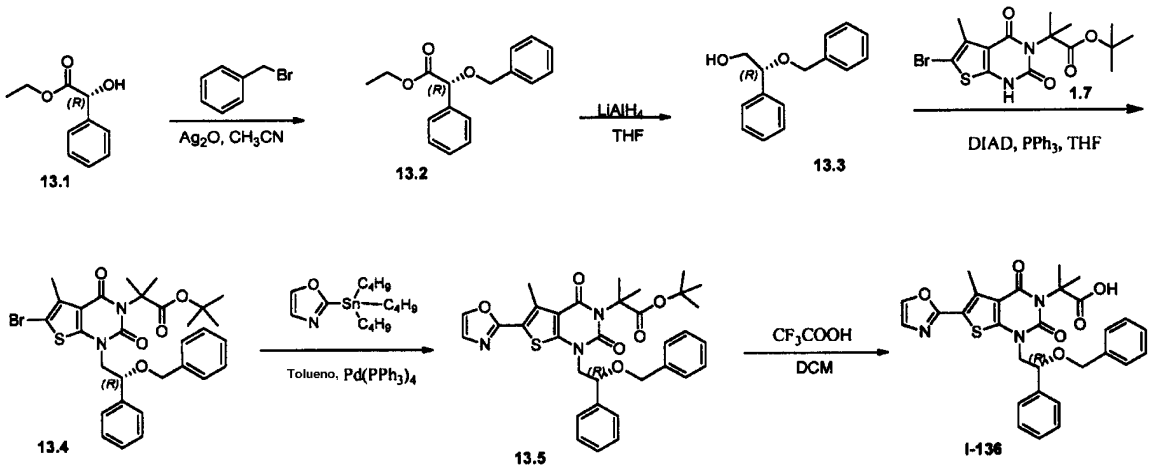


I-135 I-139

Se prepara el compuesto I-139 a partir del compuesto I-135 de una manera análoga al ejemplo 10. Se aísla un sólido blanco con un rendimiento de 67%. EM (ES): *m/z* 505 $(M+Na)^+$. RMN ^{1}H (DMSO-d_6, 300 MHz): δ 1.41 (t, *J* = 7.2 Hz, 3H), 1.64 (s, 6H), 2.74 (s, 3H), 2.98 (t, *J* = 7.2 Hz, 2H), 4.05 (m, 4H), 6.65 (s, 1H), 6.86 (t, *J* = 7.2 Hz, 1H), 6.95 (d, *J* = 7.8 Hz,

1H), 7.11 (m, 2H), 7.38 (s, 1H), 8.22 (s, 1H).

Ejemplo 13: Síntesis de ácido 2-[1-[(2R)-2-(benciloxi)-2-feniletil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-136).



Síntesis del compuesto 13.2. En un matraz de fondo redondo de 500 ml se coloca una solución de 13.1 (5.2 g, 28.86 mmol, 1.00 equivalentes) en 250 ml de CH_3CN, (bromometil)benceno (14.7 g, 85.95 mmol, 2.98 equivalentes), Ag_2O (10 g, 43.29 mmol, 1.50 equivalentes). La solución resultante se agita durante la noche a 40°C en un baño de aceite. Los sólidos se separan por filtración. El filtrado se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:10). Purificación, 6.38 g (crudo) de 13.2 como un aceite amarillo.

Síntesis del compuesto 13.3. En un matraz de fondo redondo de 500 ml se colocan 200 ml de tetrahidrofurano y 13.2

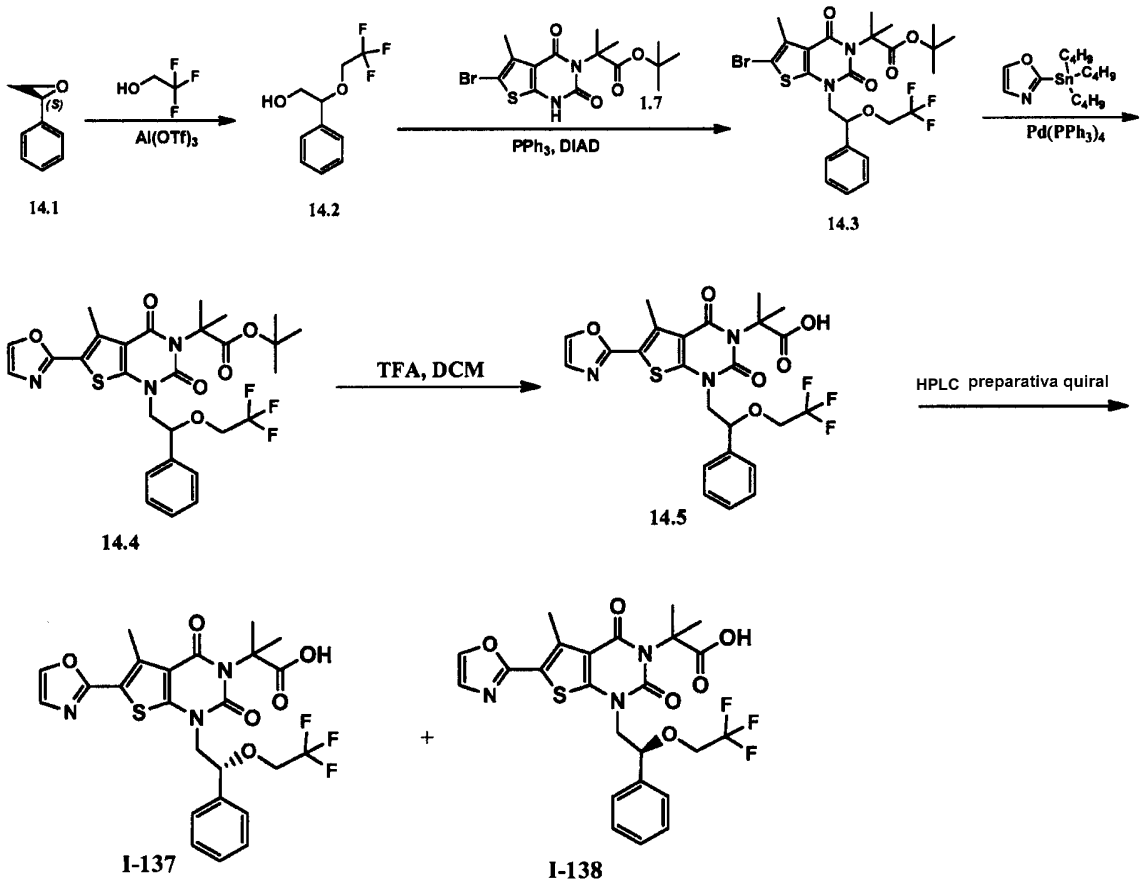
(6.38 g, 23.60 mmol, 1.00 equivalentes). Después se agrega LiAlH (898 mg, 23.66 mmol, 1.00 equivalentes) a 0°C, lentamente. La solución resultante se agita durante 2 h a 0°C en un baño de hielo/sal. La reacción después se suspende por la adición de 2 ml de NH_4Cl acuoso. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:5). La purificación proporciona 1.80 g (33%) de 13.3 como un aceite amarillo.

Síntesis del compuesto 13.4. En un matraz de fondo redondo de 3 cuellos de 100 ml que se mantiene con una atmósfera inerte de nitrógeno se colocan 10 ml de tetrahidrofurano, el intermediario 1.7 (175 mg, 0.43 mmol, 1.00 equivalentes), DIAD (133 mg, 0.66 mmol, 1.52 equivalentes), PPh_3 (173 mg, 0.66 mmol, 1.52 equivalentes) y 13.3 (150 mg, 0.66 mmol, 1.51 equivalentes). La solución se agita durante la noche a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:10). La purificación proporciona 0.422 g (crudo) del compuesto 13.4 como un aceite amarillo.

Síntesis del compuesto I-136. Se prepara el compuesto I-136 a partir de 13.4 y 2-(tributilestanil)-1,3-oxazol de una manera análoga del ejemplo 9. Se aísla un sólido blanco con un rendimiento de 24% para las dos etapas. RMN ^1H

(DMSO-d_6, 300 MHz): δ 1.64 (s, 6H), 2.76 (s, 3H), 4.10 (m, 2H), 4.18 (d, J = 12.9 Hz, 1H), 4.46 (d, J = 12.9 Hz, 1H), 4.80 (t, J = 6.0 Hz, 1H), 7.08 (d, J = 2.1 Hz, 2H), 7.18 (t, J = 3.0 Hz, 3H), 7.42 (m, 6H), 8.24 (d, J = 0.6 Hz, 1H).

Ejemplo 14: Síntesis de ácido 2-metil-2-[5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1-[2-fenil-2-(2,2,2-trifluoroetoxi)etil]-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-137) y ejemplo 15: ácido (S)-2-metil-2-(5-metil-6-(oxazol-2-il)-2,4-dioxo-1-(2-fenil-2-(2,2,2-trifluoroetoxi)etil)-1,2-dihidrotieno[2,3-d]pirimidin-3(4H)-il)propanoico (I-138).



Síntesis del compuesto 14.2. En un matraz de fondo redondo de 25 ml se colocan (2S)-2-feniloxirano (1 g, 8.32 mmol, 1.00 equivalentes), 5 ml de 2,2,2-trifluoroetan-1-ol y trifluorometansulfonato de bis[(trifluorometan)sulfoniloxi]alumanilo (197 mg, 0.42 mmol, 0.05 equivalentes). La solución resultante se agita durante 2 h a temperatura ambiente. La mezcla se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:20). La purificación proporciona 410 mg (22%) de 2-fenil-2-(2,2,2-trifluoroetoxi)etan-1-ol como un aceite incoloro.

Síntesis del compuesto 14.3. En un matraz de fondo redondo de 25 ml, purgado y mantenido con una atmósfera inerte de nitrógeno, se coloca una solución de 1.7 (300 mg, 0.74 mmol, 1.00 equivalentes), PPh_3 (390 mg, 1.49 mmol, 2.00 equivalentes), 2-fenil-2-(2,2,2-trifluoroetoxi)etan-1-ol (310 mg, 1.41 mmol, 1.89 equivalentes), DIAD (300 mg, 1.48 mmol, 1.99 equivalentes) en 10 ml de tetrahidrofurano. La solución se agita durante la noche a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:10). La purificación proporciona 260 mg (58%) de 14.3 como un sólido blanco.

Síntesis del compuesto 14.4. En un matraz de fondo redondo de 50 ml, purgado y mantenido con una atmósfera inerte

de nitrógeno, se coloca una solución de 14.3 (260 mg, 0.43 mmol, 1.00 equivalentes), $Pd(PPPh_3)_4$ (74 mg, 0.06 mmol, 0.14 equivalentes) y 2-(tributilestanil)-1,3-oxazol (231 mg, 0.65 mmol, 1.43 equivalentes) en 10 ml de tolueno. La solución se agita durante la noche a 110°C en un baño de aceite. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:10). La purificación proporciona 150 mg (59%) de 14.4 como un sólido blanco.

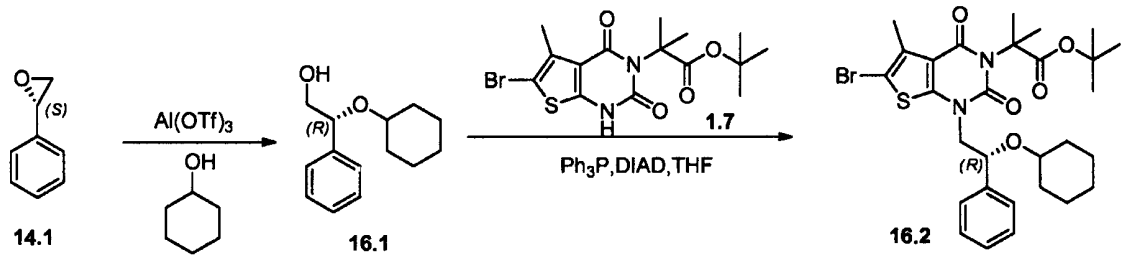
Síntesis del compuesto 14.5. En un matraz de fondo redondo de 50 ml se coloca 14.4 (150 mg, 0.25 mmol, 1.00 equivalentes), 10 ml de diclorometano y 2 ml de ácido trifluoroacético. La solución resultante se agita durante 4 h a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:1). La purificación proporciona 70 mg (52%) de 14.5 como un sólido blanco.

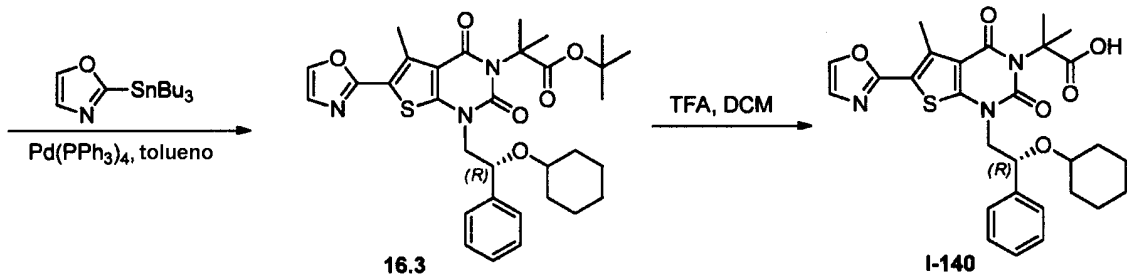
Síntesis de los compuestos I-137 y I-138. Los enantiómeros del producto de la etapa previa (64 mg) se purifican por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): columna: Chiralpak IC, 2*25 cm, 5 µm; fase móvil: hexanos y etanol (que se mantiene en etanol 15.0% en 25 min); detector: UV 220/254 nm. Se obtienen 6.8 mg (sólido blancuzco) del compuesto I-137 **y** 20 mg (sólido blancuzco) del compuesto I-138.

Datos analíticos para el compuesto I-137: EM (ES): *m/z* 538 $(M+H)^+$, 579 $(M+ CH_3CN)^+$. RMN ^1H (400 MHz, CD_3OD): δ 1.82 (s, 6H), 2.82 (s, 3H), 3.84 (m, 2H), 4.09 (dd, *J* = 10.8, 6.9, 1H), 4.23 (dd, *J* = 11.1, 2.7, 1H) , 5.05 (m,1H), 7.29 (s, 1H), 7.38-7.50 (m, 5H), 7.99 (s, 1H).

Datos analíticos I-138: EM (ES): *m/z* 538 $(M+H)^+$, 560 $(M+ Na)^+$. RMN ^1H (400 MHz, CD_3OD): δ 1.82 (s, 6H), 2.82 (s, 3H), 3.84 (m, 2H), 4.09 (dd, *J* = 10.8, 6.9, 1H), 4.23 (dd, *J* = 11.1, 2.7, 1H) , 5.05 (m, 1H), 7.29 (s, 1H), 7.38-7.50 (m, 5H), 7.99 (s, 1H).

Ejemplo 16: Síntesis de ácido 2-[1-[(2R)-2-(ciclohexiloxi)-2-feniletil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-140).





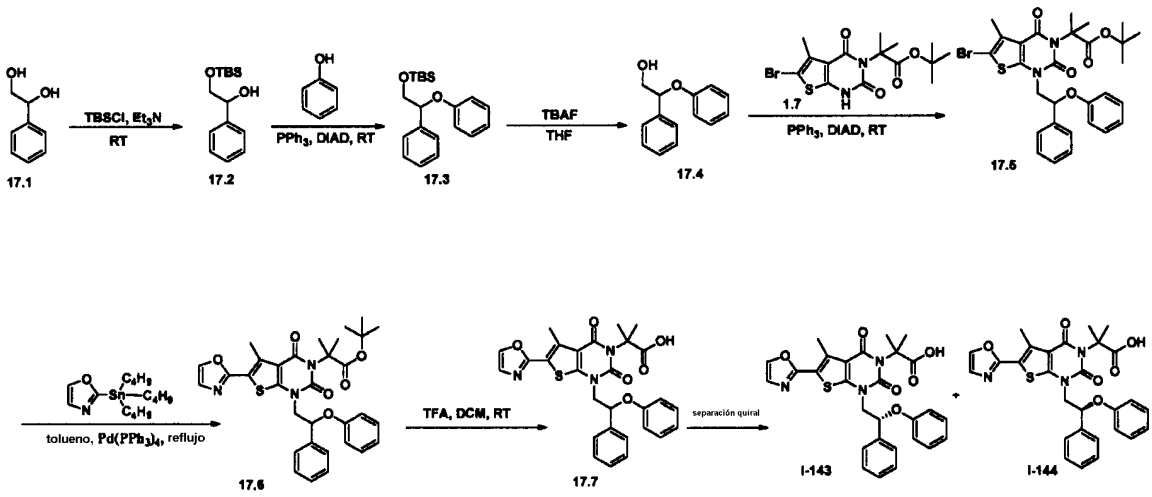
Síntesis del compuesto 16.1. En un matraz de fondo

redondo de 50 ml se coloca $Al(OTf)_3$ (237 mg, 0.50 mmol, 0.05 equivalentes), 7 ml de ciclohexanol. Esto es seguido por la adición de (2S)-2-feniloxirano (1.2 g, 9.99 mmol, 1.00 equivalentes) a gotas, con agitación. La solución resultante se agita durante 3 h a temperatura ambiente. La reacción después se suspende por la adición de 20 ml de agua. La solución resultante se extrae con 3 x 50 ml de acetato de etilo y las capas orgánicas se combinan. La mezcla resultante se lava con agua. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:50). Esto resulta en 1 g (45%) de (2R)-2-(ciclohexiloxi)-2-feniletan-1-ol como un sólido amarillo.

Síntesis del compuesto I-140. El compuesto I-140 se prepara de una manera análoga a 14.5 a partir de 16.1 y 1.7. Se aísla un semi-sólido blanco con un rendimiento de 16% a partir de 1.7. EM: (ES): *m/z* 538 $(M+H)^+$, 579 $(M+CH_3CN)^+$. MRN ^1H (400 MHz, CD_3OD): δ 1.17-1.61 (m, 10H), 1.84 (d, *J* = 6.8, 6H), 2.86 (s, 3H), 3.21-3.29 (m, 1H), 3.80-3.88 (m, 1H), 4.22-4.27 (m, 1H), 4.97-5.00 (m, 1H), 7.30 (s, 1H), 7.33-7.50 (m, 5H), 8.00 (s, 1H).

Ejemplo 17: Síntesis de ácido 2-metil-2-[5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1-[(2S)-2-fenoxi-2-feniletil]-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-143) y ejemplo 18: Síntesis de ácido 2-metil-2-[5-metil-6-(1,3-

oxazol-2-il)-2,4-dioxo-1-[(2S)-2-fenoxi-2-feniletil]-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-144).



Síntesis del compuesto 17.2. En un matraz de fondo redondo de 3 cuellos de 250 ml se coloca una solución de 1-feniletan-1,2-diol (10 g, 72.38 mmol, 1.00 equivalentes), TBSCl (22 g, 145.97 mmol, 2.00 equivalentes) y trietilamina (14.7 g, 145.27 mmol, 2.00 equivalentes) en 100 ml de tetrahidrofurano. La solución se agita durante la noche a temperatura ambiente. Al siguiente día se diluye con 150 ml de H_2O y la mezcla se extrae con 3 x 80 ml de acetato de etilo. Las capas orgánicas se combinan, se secan sobre sulfato de sodio anhidro y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1/10). La purificación proporciona 17 g (93%) de 2-[(terbutildimetilsilil)oxi]-1-feniletan-1-ol como un sólido blanco.

Síntesis del compuesto 17.3. En un matraz de fondo redondo de 100 ml, purgado y mantenido con una atmósfera inerte de nitrógeno, se coloca 17.2 (20 mg, 0.08 mmol, 1.00 equivalentes), fenol (15 mg, 0.16 mmol, 2.00 equivalentes), 3 ml de tetrahidrofurano, DIAD (32 mg, 0.16 mmol, 2.00 equivalentes) y PPh_3 (41 mg, 0.16 mmol, 2.00 equivalentes). La solución resultante se agita durante 2 h a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:10). Esto resulta en 15 mg (58%) de terbutildimetil(2-fenoxi-2-feniletoxi)silano como un sólido blanco.

Síntesis del compuesto 17.4. En un matraz de fondo redondo de 50 ml se coloca una solución de 17.3 (1.16 g, 3.53 mmol, 1.00 equivalentes) en 10 ml de tetrahidrofurano. Después se agregan a 0°C TBAF (1.8 g, 6.88 mmol, 2.00 equivalentes). La solución resultante se agita durante la noche a temperatura ambiente. La reacción después se suspende por la adición de 30 ml de agua. La solución resultante se extrae con 3 x 20 ml de acetato de etilo y las capas orgánicas se combinan, se secan y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con PE/EA (10/1). La purificación proporciona 480 mg (63%) de 17.4 como un sólido blanco.

Síntesis del compuesto 17.7. El compuesto 17.7 se

prepara de una manera análoga con 14.5 a partir de 17.4 y 1.7. Se aísla el producto crudo con un rendimiento de 32% para las tres etapas.

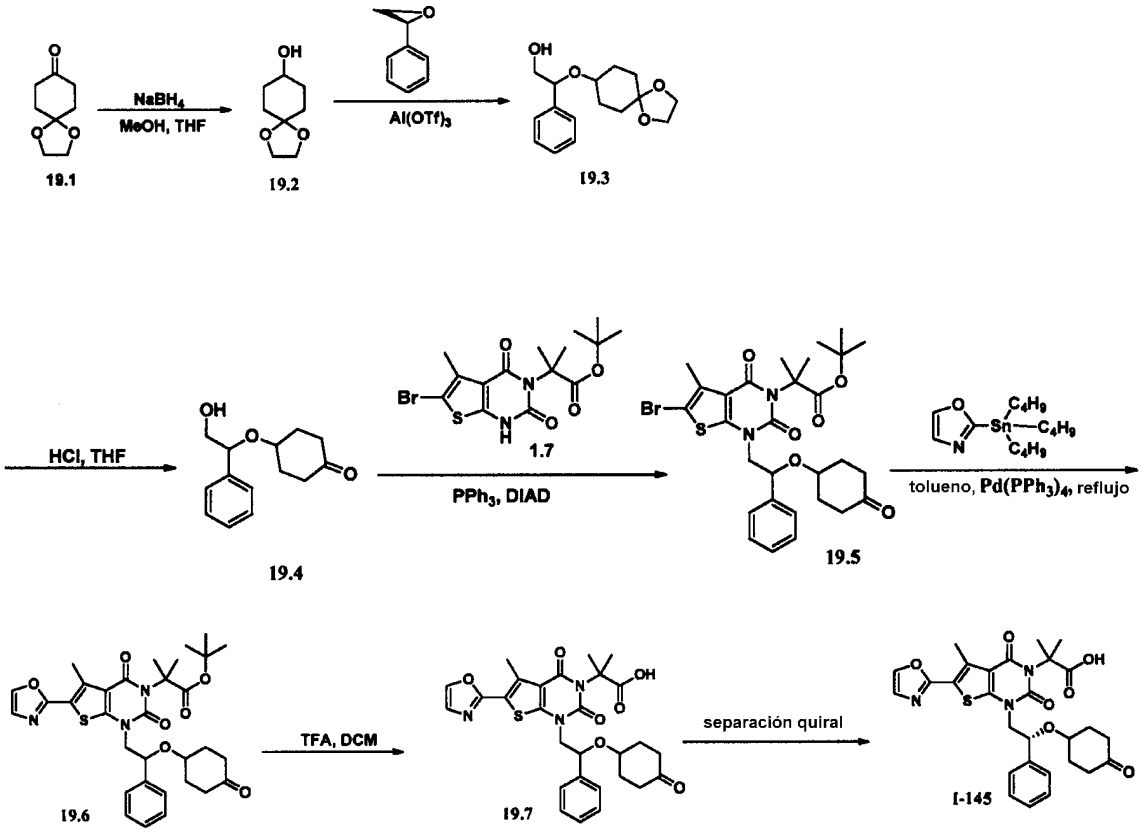
Síntesis de los compuestos I-143 y I-144. Se purifican 110 mg del producto crudo por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): columna: Chiralpak IC, 2*25 cm, 5 µm; fase móvil: hexanos (TFA 0.1%) y etanol (que se mantiene en etanol 15.0% durante 5 min); detector: UV 220/254 nm. Esta purificación proporciona 6.6 mg (9%) del compuesto I-143 como un sólido blanco y 15.9 mg (21%) del compuesto I-144 como un sólido blanco.

Datos analíticos para el compuesto I-143: EM (ES): *m/z* 532 $(M+H)^+$. RMN ^1H (CD_3OD, 400 MHz): 1.79 (s, 6H), 2.71 (s, 3H), 4.22 (m, 1H), 4.39 (d, 2H), 5.71 (m, 1H), 6.83 (m, 3H), 7.12 (t, 2H), 7.31 (m, 2H), 7.38 (t, 2H), 7.51 (d, 2H), 8.01 (s, 1H).

Datos analíticos para el compuesto I-144: EM (ES): *m/z* 532 $(M+H)^+$. RMN ^1H (CD_3OD, 400 MHz): 1.79 (s, 6H), 2.71 (s, 3H), 4.22 (m, 1H), 4.39 (d, 1H), 5.71 (m, 1H), 6.83 (m, 3H), 7.12 (t, 2H), 7.31 (m, 2H), 7.38 (t, 2H), 7.51 (d, 2H), 8.01 (s, 1H).

Ejemplo 19: Síntesis del ácido (R)-2-metil-2-(5-metil-6-(oxazol-2-il)-2,4-dioxo-1-(2-((4-oxociclohexil)oxi)-2-feniletil)-1,2-dihidrotieno[2,3-d]pirimidin-3(4H)-

il)propanoico (I-145).



Síntesis del compuesto 19.2. En un matraz de fondo redondo de 3 cuellos de 500 ml se coloca 1,4-dioxaspiro[4.5]decan-8-ona (20 g, 128.06 mmol, 1.00 equivalentes), 250 ml de metanol y $NaBH_4$ (7.3 g, 98.23 mmol, 1.55 equivalentes). La solución resultante se agita durante 2 h a temperatura ambiente. La reacción después se suspende por la adición de 150 ml de NH_4Cl acuoso saturado. La solución resultante se extrae con 2 x 300 ml de acetato de etilo y las capas orgánicas se combinan y se secan sobre sulfato de sodio anhidro y se concentran bajo vacío. El

residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:10). La purificación proporciona 19.6 g (97%) de 1,4-dioxaspiro[4.5]decan-8-ol como un aceite incoloro.

Síntesis del compuesto 19.3. En un matraz de fondo redondo de 50 ml se coloca 1,4-dioxaspiro[4.5]decan-8-ol (10 g, 63.21 mmol, 3.80 equivalentes), (2S)-2-feniloxirano (2 g, 16.65 mmol, 1.00 equivalentes) y $Al(OTf)_3$ (197 mg, 0.42 mmol, 0.02 equivalentes). La solución resultante se agita durante 2 h a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:10). La purificación proporciona 2.7 g (crudo) de 19.3 como un aceite incoloro.

Síntesis del compuesto 19.4. En un matraz de fondo redondo de 50 ml se coloca 19.3 (2.7 g, 9.70 mmol, 1.00 equivalentes), 15 ml de tetrahidrofurano y 15 ml de cloruro de hidrógeno (18%). La solución resultante se agita durante la noche a 70°C. La reacción después se suspende por la adición de 30 ml de carbonato de sodio acuoso. La solución resultante se extrae con 2 x 50 ml de acetato de etilo y las capas orgánicas se combinan y se secan sobre sulfato de sodio anhidro y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:5). La purificación proporciona 1.6 g (70%) de

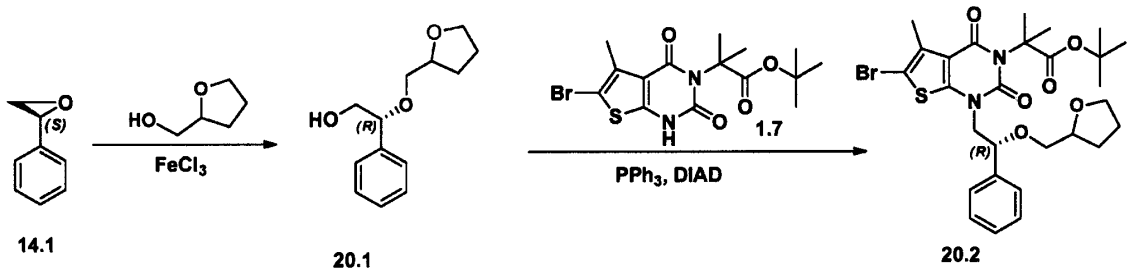
19.4 como un aceite incoloro.

Síntesis del compuesto 19.7. El compuesto 19.7 se prepara de una manera análoga a 14.5, a partir de 19.4 y 1.7. Se aísla un sólido amarillo claro con un rendimiento de 21% para las tres etapas.

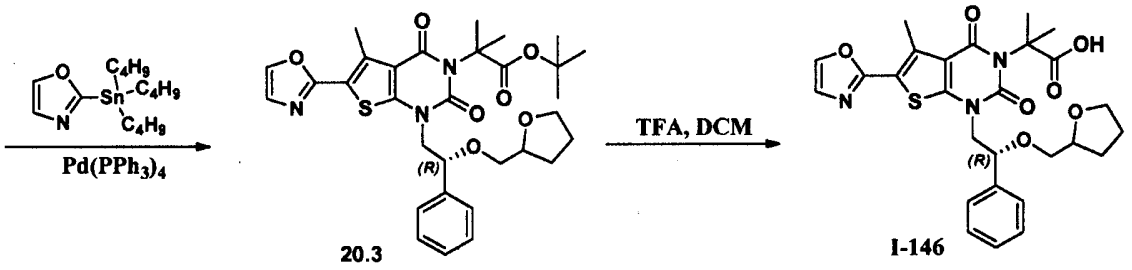
Síntesis del compuesto I-145. Se purifican 58 mg del producto crudo por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): columna: Chiralpak IC, 2*25 cm, 5 µm; fase móvil: hexanos y etanol (que se mantiene a 25.0% de etanol por 25 min); detector: UV 220/254 nm. Se obtienen 20.1 mg de un producto sólido blanco. EM (ES): *m/z* 552 $(M+H)^+$.

RMN ^1H (300 MHz, CD_3OD): δ 1.25 (m, 1H), 1.55 (m, 7H), 1.82 (s, 3H), 1.85 (s, 3H), 2.83 (s, 3H), 3.33 (m, 1H), 3.78 (m, 1H), 4.29 (m, 1H), 4.92 (m,1H), 7.29 (s, 1H), 7.33-7.51 (m, 5H), 7.99 (s, 1H).

Ejemplo 20: Síntesis del ácido 2-metil-2-[5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1-[(2R)-2-(oxolan-2-ilmetoxi)-2-feniletil]-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-146).



14.1 20.1 20.2

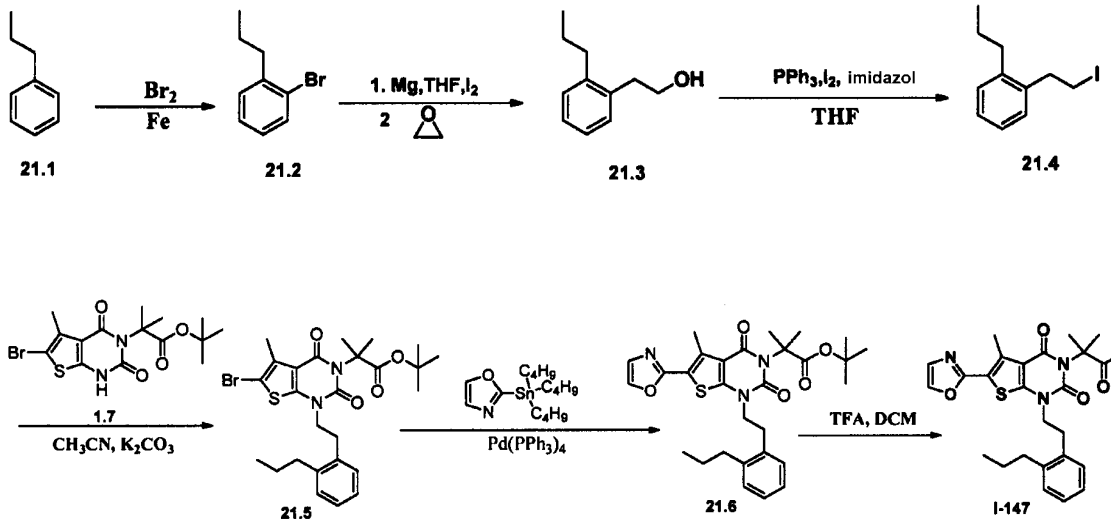


Síntesis del compuesto 20.1. En un matraz de fondo redondo de 50 ml, purgado y mantenido con una atmósfera inerte de nitrógeno se coloca (2R)-2-feniloxirano (1 g, 8.32 mmol, 1.00 equivalentes), 5 ml de oxolan-2-ilmetanol y $FeCl_3$ (68 mg, 0.42 mmol, 0.05 equivalentes). La solución resultante se agita durante la noche a temperatura ambiente. La reacción después se suspende por adición de 20 ml de agua. La solución resultante se extrae con 3 x 10 ml de acetato de etilo y las capas orgánicas se combinan y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1/10). La purificación proporciona 360 mg (19%) de 20.1 como un aceite blanco.

Síntesis del compuesto I-146. Se prepara el compuesto I-146 de una manera análoga a 14.5 a partir de 20.1 y 1.7. EM (ES): *m/z* 562 $(M+Na)^+$. RMN ^1H (CD_3OD, 300 MHz): δ 7.99 (s, 1H), 7.48-7.29 (m, 6H), 4.93-4.92 (m, 1H), 4.25-4.19 (m, 1H), 3.99-3.85 (m, 2H), 3.70-3.61 (m, 2H), 3.59-3.41 (m, 1H), 3.32-3.13 (m, 1H), 2.81 (s, 3H), 1.85 (s, 6H), 1.82-1.70 (m, 3H), 1.68-1.47 (m, 1H).

Ejemplo 21: Síntesis del ácido 2-metil-2-[5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1-[2-(2-propilfenil)etil]-

1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-147).



Síntesis del compuesto 21.2. En un matraz de fondo redondo de 250 ml se coloca propilbenceno (20 g, 166.40 mmol, 1.00 equivalentes) y Fe (10 g, 178.57 mmol, 1.07 equivalentes). Esto es seguido por la adición de Br_2 (26.6 g, 166.45 mmol, 1.00 equivalentes) a gotas con agitación. La solución resultante se agita durante la noche a temperatura ambiente. La reacción después se suspende por la adición de 100 ml de $NaHSO_3$ acuoso. La mezcla se extrae con 3 x 100 ml de acetato de etilo y las capas orgánicas se combinan y se secan sobre sulfato de sodio anhidro y se concentran bajo vacío. La purificación proporciona 29.4 g (crudo) de 1-bromo-2-propilbenceno como un aceite amarillo.

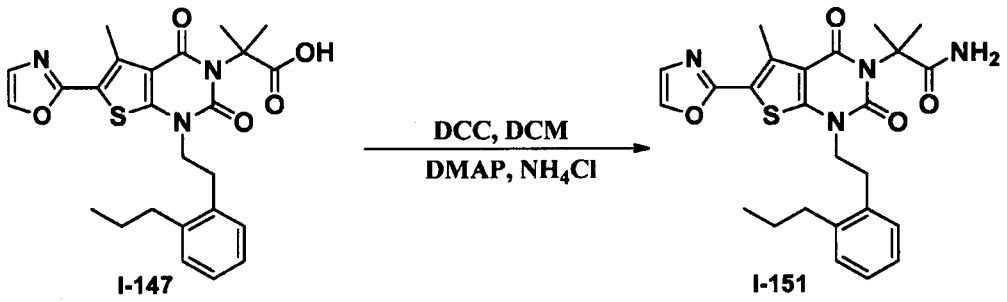
Síntesis del compuesto 21.3. En un matraz de fondo redondo de 3 cuellos de 250 ml, que se mantiene con una atmósfera de nitrógeno se coloca I_2 (10 mg, 0.04 mmol) y Mg

(500 mg, 20.83 mmol, 2.07 equivalentes). Después se agrega a gotas 1-bromo-2-propilbenceno (2.0 g, 10.05 mmol, 1.00 equivalentes) disuelto en 50 ml tetrahidrofurano dentro del matraz y la mezcla se calienta a reflujo. Después de que se completa la reacción, la mezcla resultante se enfría a 0°C y después se agregan, en una porción, 50 ml de oxirano la solución resultante se agita durante la noche a temperatura ambiente. La reacción después se suspende por la adición de 5 ml de NH_4Cl acuoso. Los sólidos se separan por filtración. El filtrado se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:5). La purificación proporciona 0.24 g (15%) de 2-(2-propilfenil)etan-1-ol como un aceite incoloro.

Síntesis del compuesto 21.4. En un matraz de fondo redondo de 50 ml se coloca 2-(2-propilfenil)etan-1-ol (240 mg, 1.46 mmol, 1.00 equivalentes), PPh_3 (498 mg, 1.90 mmol, 1.30 equivalentes), 446 mg de I_2, 129 ml de imidazol y 20 ml de diclorometano. La solución resultante se agita durante 16 h a 30°C. La reacción después se suspende por la adición de 100 ml de $NaHSO_3$ acuoso. La solución resultante se extrae con 2 x 50 ml de diclorometano y las capas orgánicas se combinan y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:100). La purificación proporciona 200 mg (50%) de 1-(2-yodoetil)-2-propilbenceno como un aceite incoloro.

Síntesis del compuesto I-147. Se prepara el compuesto I-147 a partir de 21.4 y 1.7 de una manera análoga al ejemplo 9. Se aísla un sólido blanco con un rendimiento de 45% para las tres etapas. EM (ES): *m/z* 538 $(M+H)^+$. RMN ^1H (CD_3OD, 300 MHz): 1.30 (t, 3H), 1.70-1.80 (m, 2H), 1.95 (s, 6H), 2.74 (t, 2H), 2.8 (s, 3H), 3.13 (t, 2H), 4.13 (t, 2H), 7.10-7.15 (m, 4H), 7.28 (s, 1H), 7.97 (s, 1H).

Ejemplo 22. Síntesis de 2-metil-2-[5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1-[2-(2-propilfenil)etil]-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanamida (I-151).

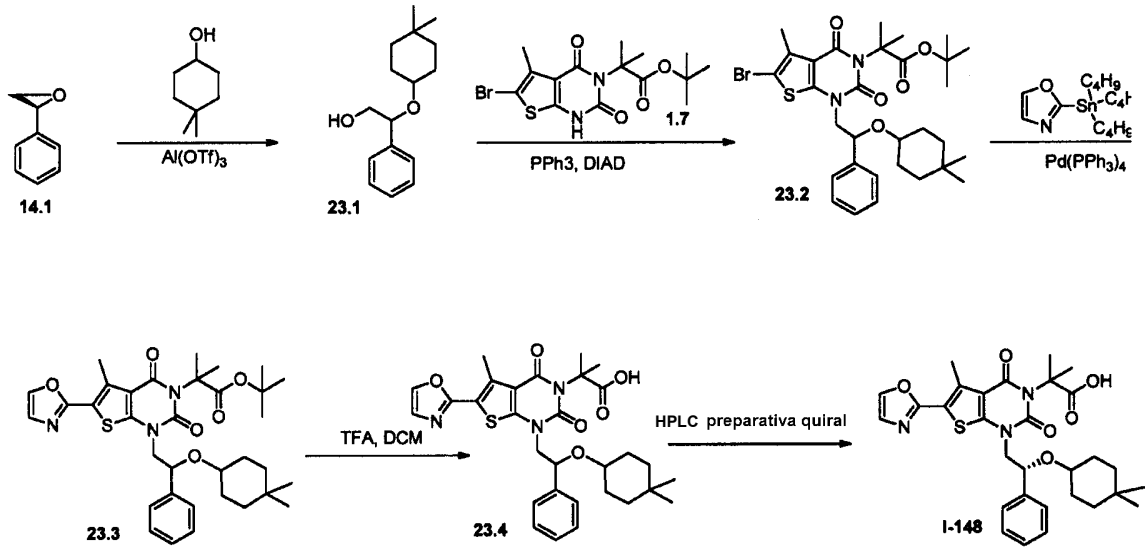


I-147 I-151

Se prepara el compuesto I-151 de una manera análoga al compuesto I-121 (ejemplo 4). Se aísla un sólido blanco con un rendimiento de 11%. EM (ES): *m/z* 464 $(M-NH_2)^+$. ^1H (CD_3OD, 400 MHz): 1.05 (t, 3H), 1.65 (m, 2H), 1.83 (s, 6H), 2.74 (t, 2H), 2.81 (s, 3H), 3.11 (t, 3H), 4.11 (t, 2H), 7.19 (ArH, 4H), 7.28 (s, 1H), 7.98 (s, 1H).

Ejemplo 23. Síntesis del ácido 2-[1-[(2R)-2-[(4,4-dimetilciclohexil)oxi]-2-feniletil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-

metilpropanoico (I-148).

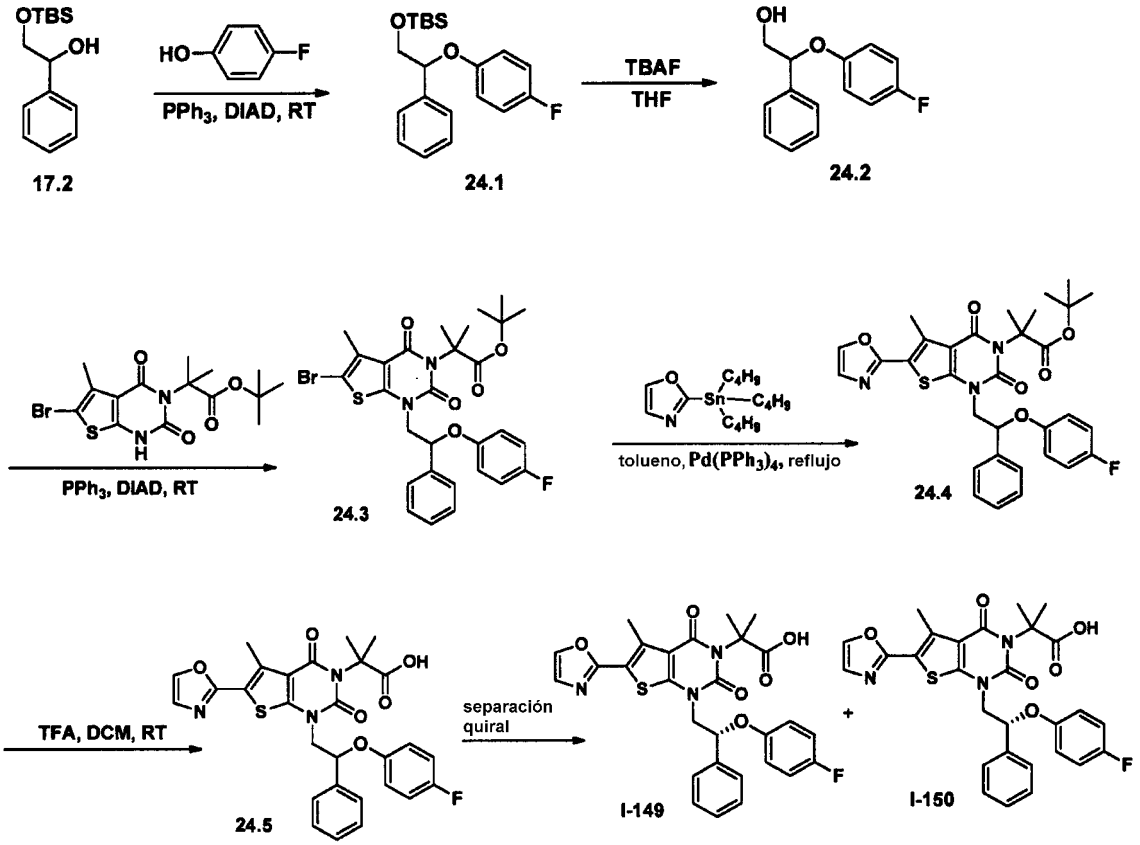


Síntesis del compuesto 23.4. El compuesto 23.4 se prepara de una manera análoga al compuesto 14.5 sustituyendo 4,4-dimetilciclohexanol por 2,2,2-trifluoroetan-1-ol. Se aísla un sólido blanco con un rendimiento de d 34% a partir de 1.7.

Purificación del compuesto I-148. Se purifica 23.4 crudo por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): columna: Chiralpak IC, 2*25 cm, 5 µm; fase móvil: hexanos (TFA 0.1%) y etanol (TFA 0.1%) (se mantiene en etanol 5.0% (TFA 0.1%) durante 8 min); detector: UV 220/254 nm. La purificación proporciona 73 mg (36.5%) del compuesto I-148 como un sólido blanco. EM (ES): *m/z* 566 $(M+H)^+$. RMN ^1H (CD_3OD, 400 MHz): 0.62 (s, 3H), 0.83 (s, 3H), 1.02 (m, 3H), 1.24 (m, 1H), 1.51 (m, 4H), 1.81 (d, 6H), 2.82 (s, 3H), 3.31 (s, 1H), 3.75 (m, 1H), 4.31 (d, 1H), 4.96 (d,

1H), 7.31 (s, 1H), 7.41 (m, 3H), 7.55 (d, 2H), 8.01 (s, 1H).

Ejemplo 24: Síntesis del ácido (R)-2-(1-(2-(4-fluorofenoxi)-2-feniletil)-5-metil-6-(oxazol-2-il)-2,4-dioxo-1,2-dihidrotieno[2,3-d]pirimidin-3(4H)-il)-2-metilpropanoico (I-149) y Ejemplo 25: Síntesis del ácido (S)-2-(1-(2-(4-fluorofenoxi)-2-feniletil)-5-metil-6-(oxazol-2-il)-2,4-dioxo-1,2-dihidrotieno[2,3-d]pirimidin-3(4H)-il)-2-metilpropanoico (I-150).



Síntesis del compuesto 24.2. Se prepara 2-(4-fluorofenoxi)-2-feniletan-1-ol (24.2) de una manera análoga al

compuesto 17.4, sustituyendo 4-fluorofenol por fenol. Se aísla a un aceite incolora con un rendimiento aproximadamente de 31% (crudo).

Síntesis del compuesto 24.5. Se prepara 24.5 de una manera análoga al compuesto 14.5. Se aísla un sólido blanco con un rendimiento de 28% a partir de 1.7.

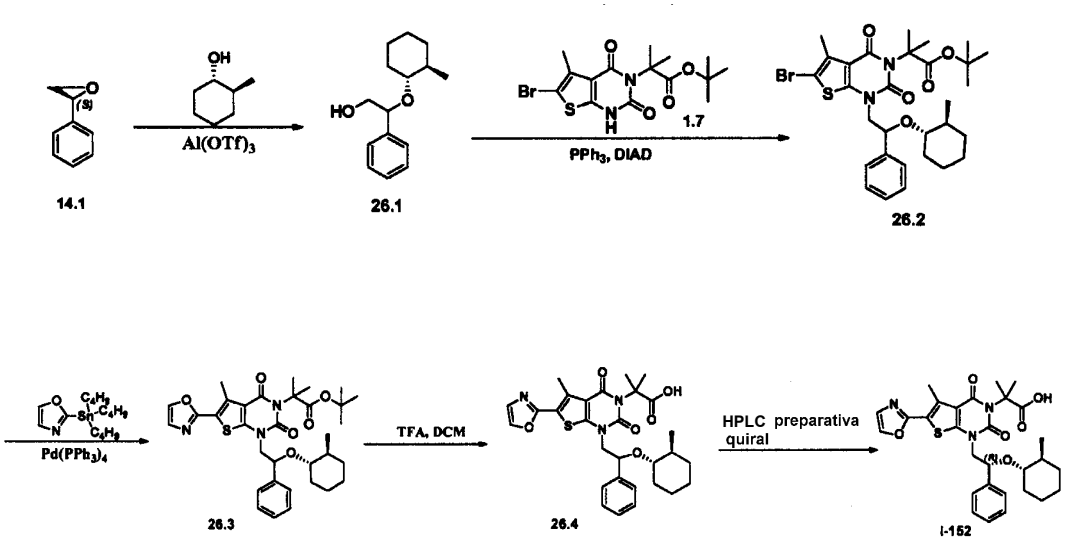
Purificación del compuesto I-149 y el compuesto I-150. Los enantiómeros de 24.5 (140 mg) se separan por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): columna: Chiralpak IC, 2*25 cm, 5 µm; fase móvil: hexanos (TFA 0.1%) y etanol (que se mantiene en etanol 15.0% durante 30 min; detector: UV 220/254 nm. Se obtienen 48.1 mg de un producto sólido blanco.

Datos analíticos para el compuesto I-149: EM (ES): *m/z* 550 $(M+H)^+$, 591 $(M+CH_3CN)^+$. RMN ^1H (300 MHz, CD_3OD): 1.79 (s, 6H), 278 (s, 3H), 4.20 (dd, *J* = 14.7, 8.7, 1H), 4.36 (dd, *J* = 14.7, 3.9, 1H), 5.65 (m, 1H) , 6.77-6.89 (m, 4H), 7.29-7.53 (m, 6H) , 7.99 (s, 1H).

Datos analíticos para el compuesto I-150: EM (ES): *m/z* 550 $(M+H)^+$, 591 $(M+ CH_3CN)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.79 (s, 6H), 28 (s, 3H), 4.20 (dd, *J* = 14.7,8.7, 1H), 4.36 (dd, *J* = 14.7, 3.9, 1H), 5.65 (m, 1H) , 6.77-6.89 (m, 4H), 7.29-7.53 (m, 6H) , 7.99 (s, 1H).

Ejemplo 26: Síntesis del ácido 2-metil-2-[5-metil-1-[(2R)-2-[[(1S,2S)-2-metilciclohexil]oxi]-2-feniletil]-6-(1,3-

oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-152).



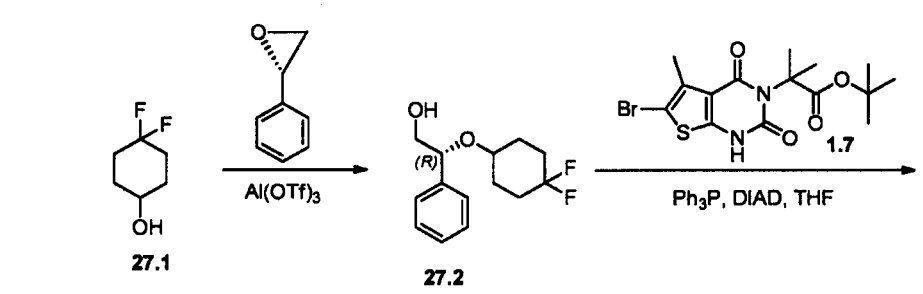
Síntesis del compuesto 26.1. Se prepara 26.1 de una manera análoga a 14.2, sustituyendo metilciclohexan-1-ol por 2,2,2-trifluoroetan-1-ol. Se aísla un aceite incoloro con un rendimiento de 18%.

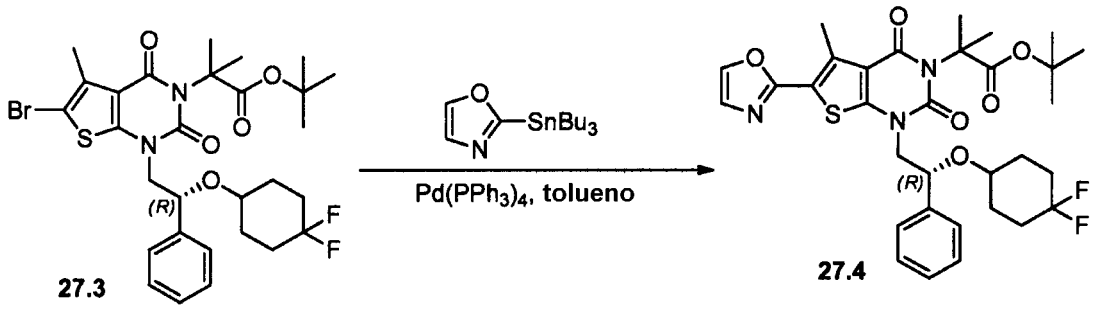
Síntesis del compuesto 26.4. Se prepara 26.4 de una manera análoga a 14.5. Se aísla un sólido blanco en aproximadamente 34% de rendimiento a partir de 1.7.

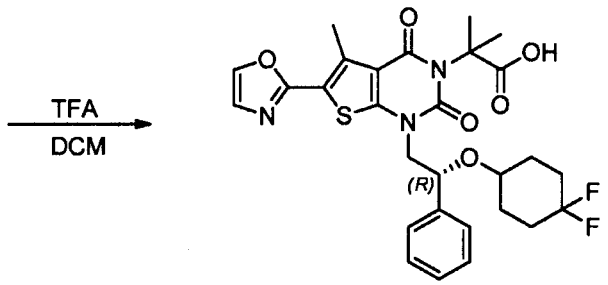
Purificación del compuesto I-152. Los enantiómeros de 26.4 (110 mg) se separan por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): columna: Chiralpak IC, 2*25 cm, 5 µm; fase móvil: hexanos (TEA 0.2%) y etanol (TEA 0.2%) (que se mantiene en etanol 2.0% (TEA 0.2%) durante 20 min);

detector: UV 220/254 nm. La purificación proporciona 58.7 mg (53%) del compuesto I-152 como un sólido blanco. EM (ES): *m/z* 552 $(M+H)^+$, 615 $(M+Na+CH_3CN)^+$. RMN ^1H (300 MHz, CD_3OD): δ 0.76 (d, *J* = 6.3, 2H), 0.86 (d, *J* = 6.6 2H), 1.07 (m, 2H), 1.50 (m, 5H), 1.81 (s, 6H), 2.00 (d, *J* = 14.1, 1H), 2.80 (m, 4H), 3.91 (m, 1H), 4.17 (m, 1H) , 5.09 (m, 1H), 7.29-7.49 (m, 6H), 8.00 (s, 1H).

Ejemplo 27: Síntesis del ácido 2-[1-[(2R)-2-[(4,4-difluorociclohexil)oxi]-2-feniletil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-155).







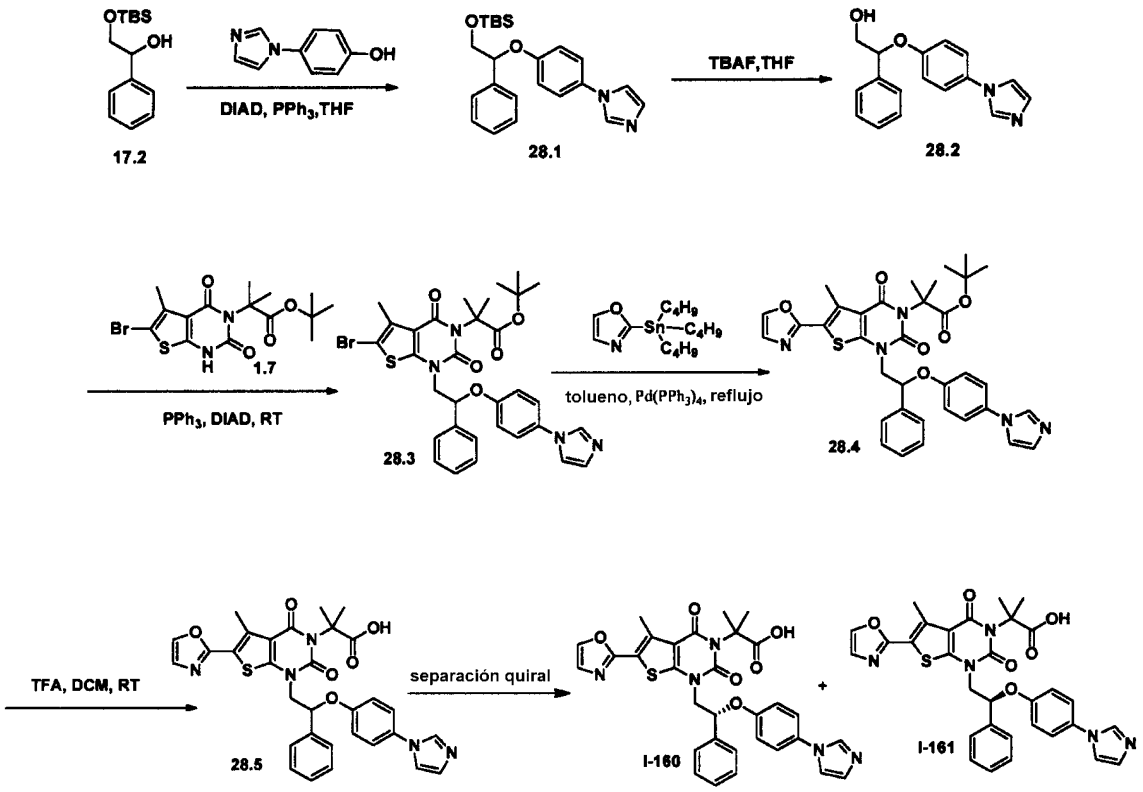
I-155

Síntesis del compuesto 27.2. Se prepara el compuesto 27.2 de una manera análoga a 14.2, sustituyendo 4,4-difluorociclohexan-1-ol por 2,2,2-trifluoroetan-1-ol. Se aísla un aceite amarillo con un rendimiento de 18%.

Síntesis del compuesto I-155. El compuesto I-155 se prepara de una manera análoga al compuesto 14.5. Se aísla un aceite incoloro con un rendimiento total de 2% a partir de 1.7. EM (ES): *m/z* 574 $(M+H)^+$, 596 $(M+Na)^+$, 637 $(M+Na+CH_3CN)^+$. RMN ^1H (400 MHz, CD_3CN): δ 1.54-1.74 (m, 8H), 1.77 (d, 6H), 2.78 (s, 3H), 3.43 (s, 1H), 3.78-3.84 (m, 1H), 4.21-4.25 (m, 1H), 4.91-4.95 (m, 1H), 7.27 (s, 1H), 7.37-7.52 (m, 5H), 7.90 (s, 1H).

Ejemplo 28: Síntesis del ácido 2-[1-[(2R)-2-[4-(1H-imidazol-1-il)fenoxi]-2-feniletil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-160) y Ejemplo 29: Síntesis del ácido 2-[1-[(2S)-2-[4-(1H-imidazol-1-il)fenoxi]-2-feniletil]-5-metil-6-

(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-161).



Síntesis del compuesto 28.2. Se prepara 2-[4-(1H-imidazol-1-il)fenoxi]-2-feniletan-1-ol (28.2) de una manera análoga a 17.4, al sustituir 4-(1H-imidazol-1-il)fenol por fenol. Se aísla un sólido blanco con un rendimiento de 25% a partir de 17.2.

Síntesis del compuesto 28.5. Se prepara el compuesto 28.5 de una manera análoga a 14.5, al sustituir 28.2 por 14.2. Se aísla un sólido blanco con un rendimiento aproximadamente de 32% de partir de 1.7.

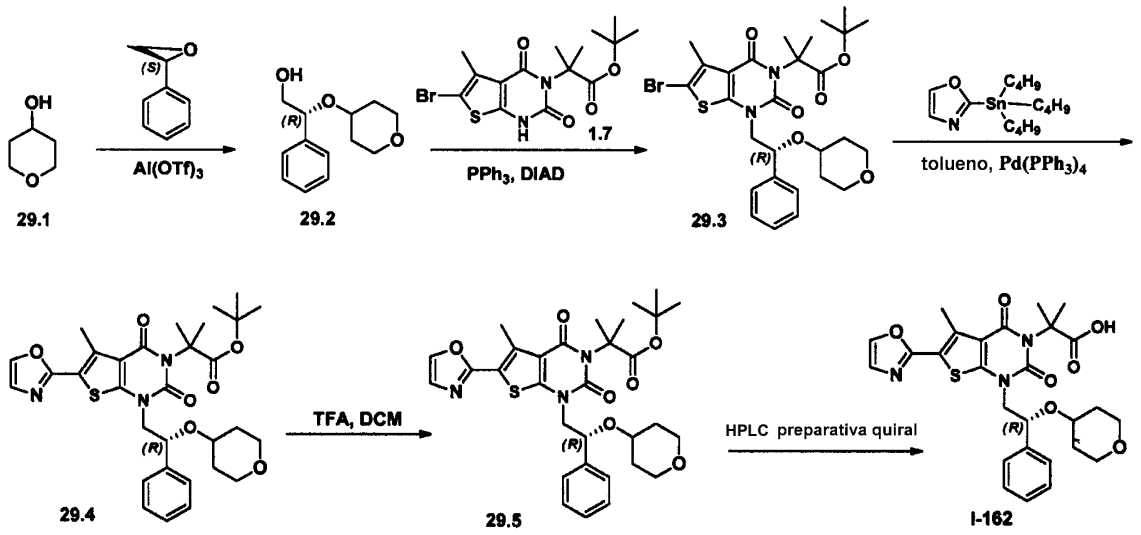
Purificación de los compuestos I-160 y I-161. Los enantiómeros de 28.5 (148 mg, 0.25 mmol) se separan por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): columna: Chiralpak IC, 2*25 cm, 5 µm; fase móvil: hexanos (TFA 0.1%) y etanol (TFA 0.1%) (que se mantiene en etanol 30% durante 70 min); detector: UV 220/254 nm. La fracción con un tiempo de reacción de 49.5 min se recolecta y concentra al vacío para proporciona 0.019 g (26%) de I-160 como un sólido blanco. La fracción con un tiempo de retención de 42.0 min se recolecta y se concentra al vacío para proporcionar 0.023 g de I-161 como un sólido blanco.

Datos analíticos para el compuesto I-160: EM (ES): *m/z* 598 $(M+H)^+$. RMN ^1H (CD_3OD, 300 MHz): δ 1.76 (s, 6H), 2.75 (s, 3H), 4.22 (m, 1H), 4.45 (m, 1H), 5.80 (d, *J* = 11.1 Hz, 1H), 7.05 (d, *J* = 8.7 Hz, 2H), 7.44 (m, 8H), 7.64 (s, 1H), 7.84 (s, 1H), 7.98 (s, 1H), 9.17 (s, 1H).

Datos analíticos para el compuesto I-161: EM (ES): *m/z* 598 $(M+H)^+$. RMN ^1H (CD_3OD, 300 MHz): δ 1.76 (d, *J* = 1.8 Hz, 6H), 2.74 (s, 3H), 4.26 (dd, *J* = 9.0 Hz, 15.0 Hz, 1H), 4.44 (dd, *J* = 3.9 Hz, 14.7 Hz, 1H), 5.81 (dd, *J* = 3.6 Hz, 8.4 Hz, 1H), 7.06 (m, 2H), 7.27-7.52 (m, 8H), 7.68 (s, 1H), 7.80 (s, 1H), 7.97 (d, *J* = 0.6 Hz, 1H), 9.18 (s, 1H).

Ejemplo 29: Síntesis del ácido 2-metil-2-[5-metil-1-[(2R)-2-(oxan-4-iloxi)-2-feniletil]-6-(1,3-oxazol-2-il)-2,4-

dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-162).



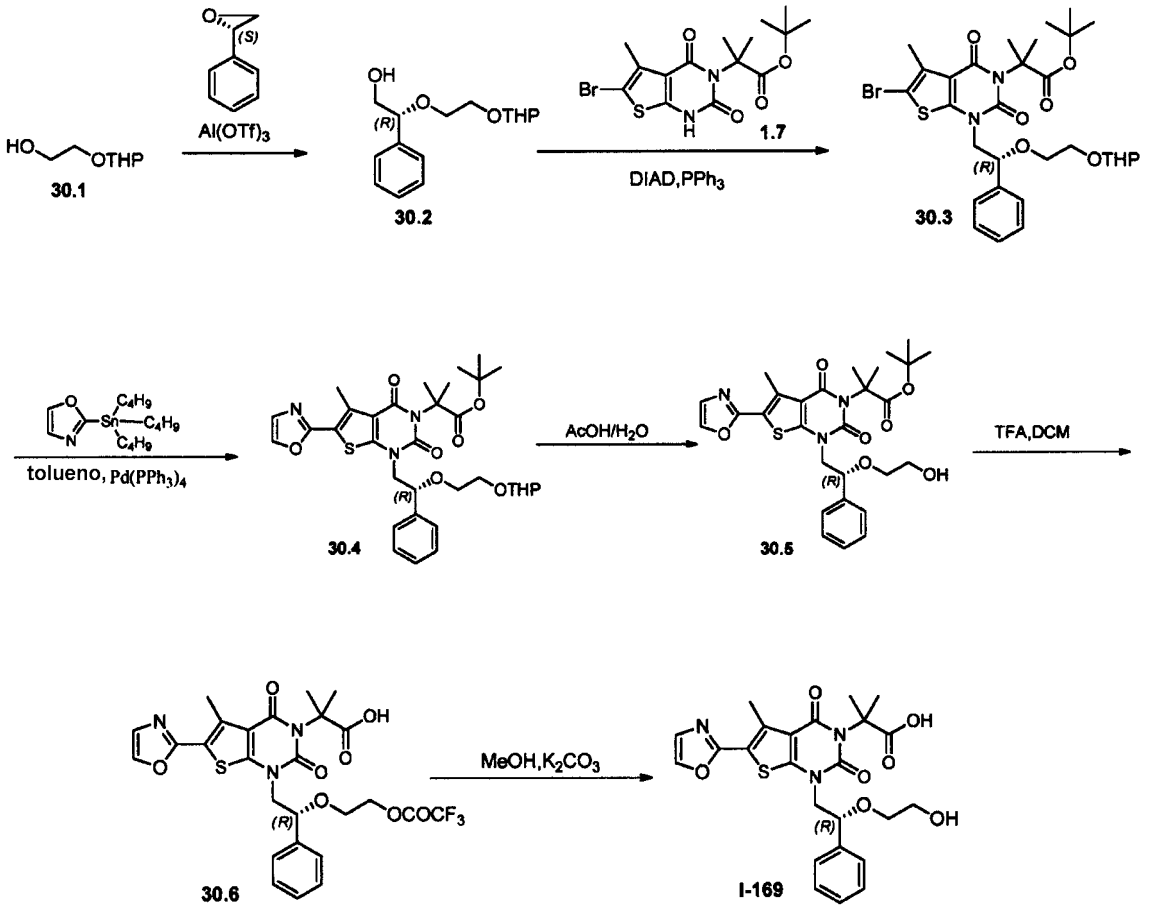
Síntesis del compuesto 29.2. Se prepara (2R)-2-(oxan-4-iloxi)-2-feniletan-1-ol (29.2) de una manera análoga a 14.2 al sustituir oxan-4-ol por 2,2,2-trifluoroetan-1-ol. Se aísla un aceite incoloro con un rendimiento de 21%.

Síntesis del compuesto 29.5. Se prepara 29.5 de una manera análoga a 14.5, al sustituir 29.2 por 14.2. Se aísla un sólido blanco con un rendimiento de 80% a partir de 1.7.

Purificación del compuesto I-162. Se repurifican 29.5 (150 mg, 0.28 mmol, 1.00 equivalentes) por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): columna: Chiralpak IC, 2*25 cm, 5 µm; fase móvil: hexanos (TFA 0.1%) y etanol (con TFA 0.1%; que se mantiene en etanol 30% etanol en 13 min); detector: UV 220/254 nm. La fracción por un tiempo de retención de 8.5 min se recolecta.

esta fracción proporciona 0.050 g de I-162 como un sólido blanco. EM (ES): *m/z* 540 $(M+H)^+$. RMN ^1H (DMSO-d_6, 400 MHz): δ 1.20 (m, 2H), 1.70 (m, 8H), 2.80 (s, 3H), 3.21-3.50 (m, 5H), 3.82 (s, 1H), 4.17 (d, *J* = 13.6 Hz, 1H), 4.91 (d, *J* = 6.8 Hz, 1H), 7.40 (m, 6H), 8.24 (s, 1H), 12.44 (s, 1H).

Ejemplo 30: ácido 2-[1-[(2R)-2-(2-hidroxietoxi)-2-feniletil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-169).



Síntesis del compuesto 30.2. Se prepara el compuesto

30.2 a partir de 2-((tetrahidro-2H-piran-2-il)oxi)etanol de una manera análoga a la síntesis del compuesto 14.2. Se aísla un aceite incoloro con un rendimiento de 5%.

Síntesis del compuesto 30.4. Se prepara el compuesto 30.4 de una manera análoga al compuesto 14.4. Se aísla un sólido amarillo en 40% de rendimiento total a partir de los compuestos 30.2 y 1.7.

Síntesis del compuesto 30.5. En un matraz de fondo redondo de 25 ml se coloca 30.4 (150 mg, 0.27 mmol, 1.00 equivalentes), 4 ml de AcOH y 1 ml de agua. La solución resultante se agita durante la noche a 35°C en un baño de aceite. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con PE/EA (2:1). Se purifican 100 mg del producto crudo por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): columna: CHIRALPAK AD-H SFC, 5*25cm, 5 µm; fase móvil: hexanos (TEA 0.2% y etanol (TEA 0.2%) (que se mantiene en etanol 10% (TEA 0.2%) durante 17 min); detector: UV 220/254 nm. La fracción con un tiempo de retención de 12.9 min es la que se recolecta. La concentración proporciona 25 mg (17%) de 30.5 como un sólido blanco.

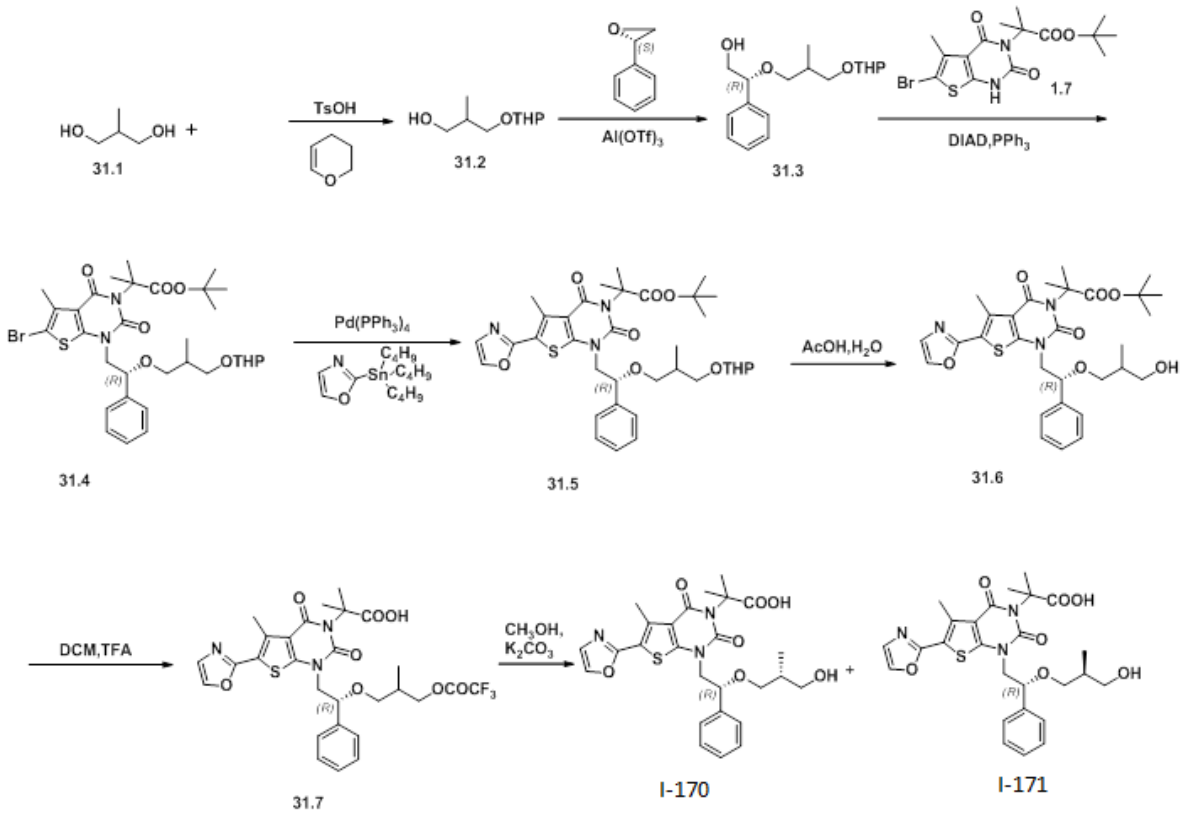
Síntesis del compuesto 30.6. En un matraz de fondo redondo de 25 ml se colocan 5 ml de diclorometano, 30.5 (20 mg, 0.04 mmol, 1.00 equivalentes) y 1.5 ml de CF_3COOH. La

mezcla resultante se concentra bajo vacío. La purificación proporciona 0.020 g (crudo) de 30.6 como un aceite incoloro.

Síntesis del compuesto I-169. En un matraz de fondo redondo de 25 ml se colocan 5 ml de metanol, 30.6 (20 mg, 0.03 mmol, 1.00 equivalentes) y carbonato de potasio (30 mg, 0.22 mmol, 6.46 equivalentes). La solución se agita durante la noche a temperatura ambiente. La mezcla resultante se concentra bajo vacío. Se purifican 30 mg del producto crudo por *HPLC* preparativa bajo las siguientes condiciones (Waters): columna: SunFire Prep C18, 19*150 mm 5 µm; fase móvil: agua ($NH_4CO_3$50 mM) y CH_3CN (CH_3CN 5.0% hasta 45.0% en 10 min, hasta 95.0% en 2 min, disminución a 5.0% en 2 min); detector: UV 254/220 nm. Este procedimiento proporciona 0.013 g (77%) del compuesto I-169 como un sólido blanco. EM (ES): *m/z* 500 $(M+H)^+$. RMN ^1H (CD_3OD, 400 MHz): δ 1.80 (s, 6H), 2.80 (s, 3H), 3.39-3.49 (m, 3H), 3.59 (c, *J* = 6.0 Hz, 2H), 4.03 (t, *J* = 8.8 Hz, 1H), 4.15 (m, 1H), 7.27 (s, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 6.8 Hz, 2H), 7.48 (d, *J* = 7.2 Hz, 2H), 7.97 (s, 1H).

Ejemplo 31: Síntesis del ácido 2-(1-((R)-2-((R)-3-hidroxi-2-metilpropoxi)-2-feniletil)-5-metil-6-(oxazol-2-il)-2,4-dioxo-1,2-dihidrotieno[2,3-d]pirimidin-3(4H)-il)-2-metilpropanoico (I-170) y Ejemplo 32: Síntesis del ácido 2-(1-((R)-2-((S)-3-hidroxi-2-metilpropoxi)-2-feniletil)-5-metil-6-(oxazol-2-il)-2,4-dioxo-1,2-dihidrotieno[2,3-d]pirimidin-

3(4H)-il)-2-metilpropanoico (I-171).



Síntesis del compuesto 31.2. En un matraz de fondo redondo de 3 cuellos de 50 ml se coloca 2-metilpropan-1,3-diol (20 g, 221.92 mmol, 1.00 equivalentes) y ácido 4-metilbenceno-1-sulfónico (11 mg, 0.06 mmol). Después se agrega a 0°C 3,4-dihidro-2H-pirano (5 g, 59.44 mmol, 0.27 equivalentes). La solución resultante se agita durante 3 h a temperatura ambiente. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:20). La purificación proporciona 6.9 g (18%) de 2-metil-3-(oxan-2-iloxi)propan-1-ol como un líquido amarillo claro.

Síntesis del compuesto 31.3. Se prepara el compuesto 31.3 a partir de 31.2 de una manera análoga a la síntesis del compuesto 14.2. Se aísla un aceite incoloro con un rendimiento de 5%.

Síntesis del compuesto 31.7. Se prepara el compuesto 31.7 de una manera análoga al compuesto 30.6. Se aísla un aceite incoloro con un rendimiento general de 30% de a partir de 31.3 y 1.7.

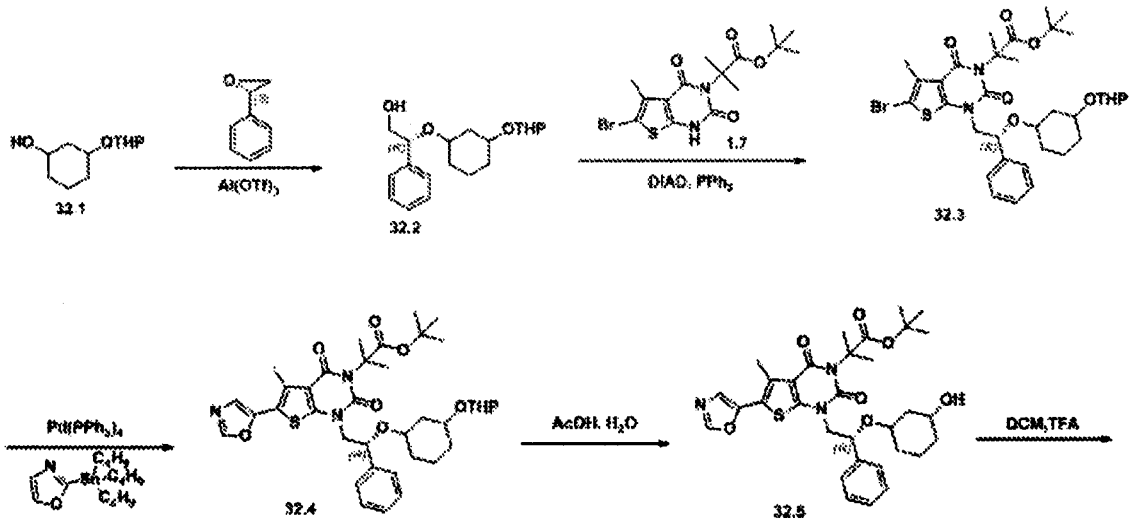
Síntesis de los compuestos I-170 y I-171. En un matraz de fondo redondo de 50 ml se colocan 5 ml de metanol, compuesto 31.7 (100 mg, 0.16 mmol, 1.00 equivalentes) y metanperoxoato de potasio y potasio (50 mg, 0.36 mmol, 2.24 equivalentes). La solución resultante se agita durante la noche a temperatura ambiente. La mezcla resultante se concentra bajo vacío. Se purifican 100 mg del producto crudo por *HPLC* preparativa bajo las siguientes condiciones (Waters): columna: XBridge Prep C18 OBD columna, 5 µm, 19*150 mm; fase móvil: agua ($NH_4HCO_3$50 mM) y CH_3CN (CH_3CN 10% hasta 27% en 2 min, se mantiene en 27% en 15 min, asciende a 95% en 2 min, disminuye a 10% en 2 min); detector: UV 254/220 nm. La purificación proporciona 0.024 g (57%) del compuesto I-170 como un sólido blanco (tR = 10.28 min) y 0.023 g (57%) del compuesto I-171 también como un sólido blanco (tR = 11.62 min).

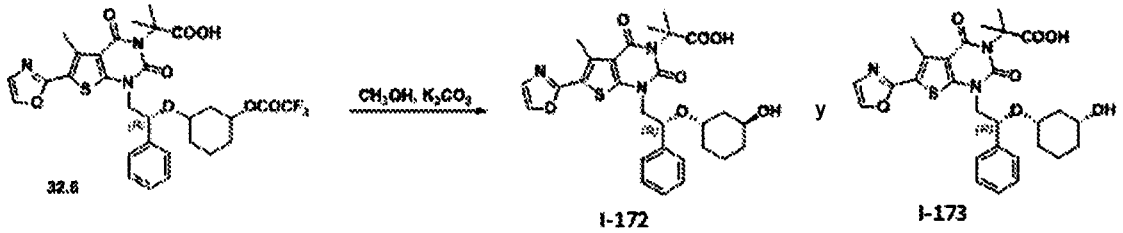
Datos analíticos para el compuesto I-170: EM (ES):

m/z 528 $(M+H)^+$. RMN ^1H (CD_3OD, 400 MHz): δ 0.74-0.81 (m, 3H), 1.81 (m, 7H), 2.83 (s, 3H), 3.24 (m, 4H), 3.88 (m, 1H), 4.20 (m, 1H), 7.28 (s, 1H), 7.35 (m, 1H), 7.44 (m, 4H), 7.98 (s, 1H).

Datos analíticos para el compuesto I-171: EM (ES): *m/z* 528 $(M+H)^+$. RMN ^1H (CD_3OD, 400 MHz): δ 0.74-0.81 (m, 3H), 1.81 (m, 7H), 2.83 (s, 3H), 3.24 (m, 4H), 3.88 (m, 1H), 4.20 (m, 1H), 7.28 (s, 1H), 7.35 (m, 1H), 7.44 (m, 4H), 7.98 (s, 1H).

Ejemplo 32: Síntesis del ácido 2-(1-((R)-2-(((1S,3S)-3-hidroxiciclohexil)oxi)-2-feniletil)-5-metil-6-(oxazol-2-il)-2,4-dioxo-1,2-dihidrotieno[2,3-d]pirimidin-3(4H)-il)-2-metilpropanoico (I-172) y Ejemplo 33: ácido 2-(1-((R)-2-(((1S,3R)-3-hidroxiciclohexil)oxi)-2-feniletil)-5-metil-6-(oxazol-2-il)-2,4-dioxo-1,2-dihidrotieno[2,3-d]pirimidin-3(4H)-il)-2-metilpropanoico (I-173).





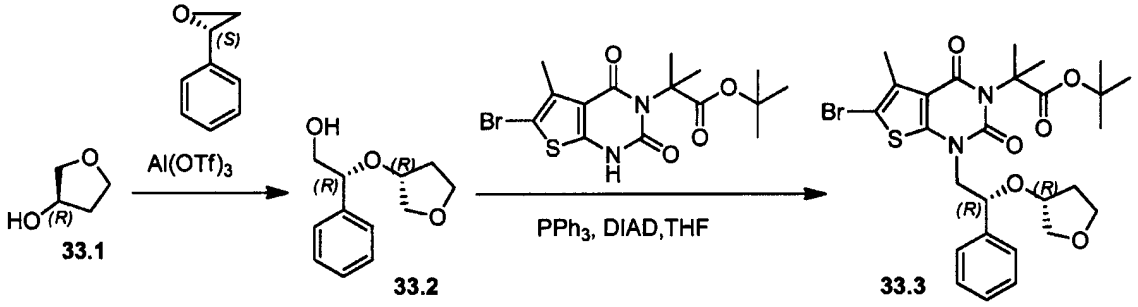
Síntesis del compuesto 32.6. Se prepara el compuesto 32.6 a partir de 32.1 y 1.7 de una manera análoga a la síntesis del compuesto 30.6. Se aísla un aceite incoloro con un rendimiento general de 14% a partir de 1.7 (1% a partir de 32.1).

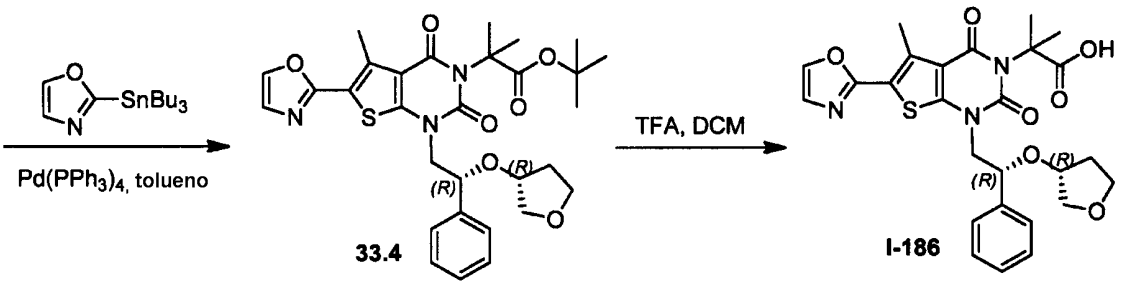
Síntesis de los compuestos I-172 y I-173. En un matraz de fondo redondo de 50 ml se colocan 5 ml de metanol, compuesto 32.6 (100 mg, 0.15 mmol, 1.00 equivalentes) y carbonato de potasio (80 mg, 0.58 mmol, 3.76 equivalentes). La solución se agita durante la noche a temperatura ambiente. La mezcla resultante se concentra bajo vacío. Se purifican 100 mg del producto crudo por *HPLC* preparativa bajo las siguientes condiciones (Waters): columna: XBridge Prep C18 OBD, 5 µm, 19*150 mm; fase móvil: agua ($NH_4HCO_3$50 mM) y CH_3CN (CH_3CN 17.0% hasta 40.0% en 10 min, hasta 95.0% en 2 min, disminución a 17.0% en 2 min); detector: UV 254/220 nm. La purificación proporciona 17.2 mg (42%) del compuesto I-172 como un sólido blanco y 16.1 mg (40%) del compuesto I-173, también como un sólido blanco.

Datos analíticos para el compuesto I-172: EM (ES): *m/z* 554 $(M+H)^+$. RMN ^1H (CD_3OD, 400 MHz): δ 0.88 (m, 1H), 1.20 (m, 3H), 1.35 (m, 1H), 1.60 (m, 2H), 1.80 (m, 6H), 2.10 (m, 1H), 2.83 (s, 3H), 3.20 (m, 1H), 3.60 (m, 1H), 3.80 (m, 1H), 4.20 (m, 1H), 5.00 (m, 1H), 7.29 (d, *J* = 2.4 Hz, 1H), 7.35 (dd, *J* = 6.8, 14.4 Hz, 1H), 7.43 (dd, *J* = 7.6, 15.2 Hz, 2H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.99 (d, *J* = 2.0 Hz, 1H).

Datos analíticos para el compuesto I-173: EM (ES): *m/z* 554 $(M+H)^+$. RMN ^1H (CD_3OD, 400 MHz): δ 1.20 (m, 3H), 1.35 (m, 2H), 1.55 (m, 2H), 1.82 (m, 6H), 2.04 (m, 1H), 2.84 (s, 3H), 3.47 (d, *J* = 12.0 Hz, 1H), 3.61 (s, 1H), 3.70 (m, 1H), 4.33 (d, *J* = 12.8 Hz, 1H), 5.05 (m, 1H), 7.28 (s, 1H), 7.35 (t, *J* = 6.8 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.50 (d, *J* = 7.2 Hz, 2H), 7.99 (s, 1H).

Ejemplo 33: Síntesis del ácido 2-metil-2-[5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1-[(2R)-2-[(3R)-oxolan-3-iloxi]-2-feniletil]-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-186).



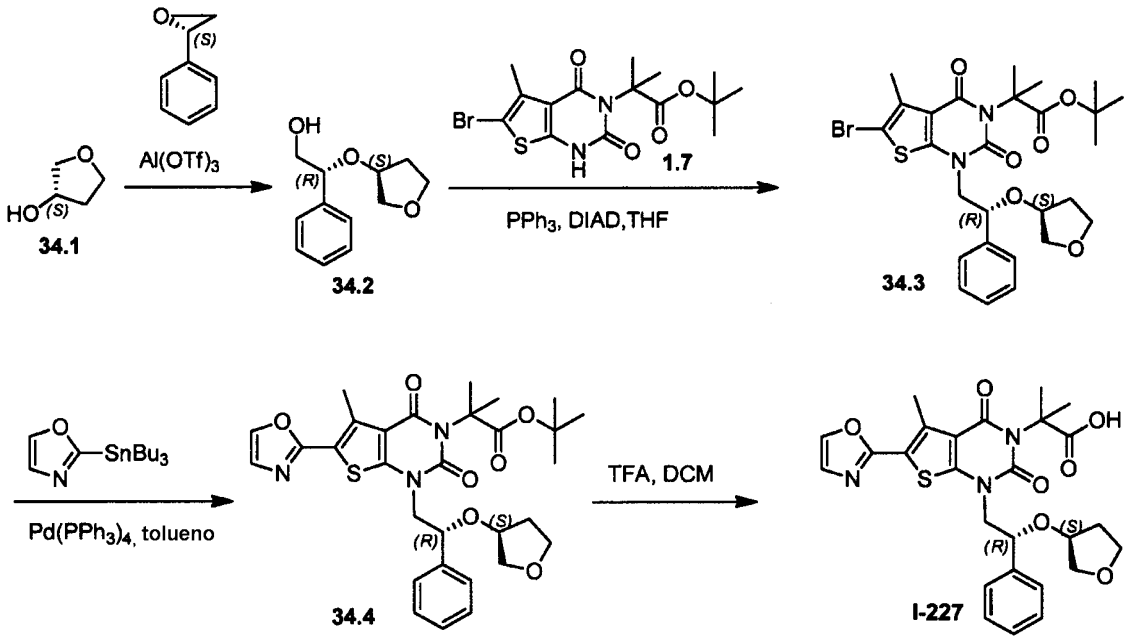


Síntesis del compuesto 33.4. Se prepara el compuesto 33.4 a partir de 33.1 de una manera análoga a la síntesis del compuesto 14.4. Se aísla un sólido blanco con un rendimiento general de 6% a partir de 33.1.

Síntesis del compuesto I-186. En un matraz de fondo redondo de 50 ml se colocan 5 ml de diclorometano, compuesto 33.4 (120 mg, 0.21 mmol, 1.00 equivalentes) y 1 ml de ácido trifluoroacético. La solución se agita durante 2 h a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con diclorometano/metanol (100:1). El producto (100 mg) obtenido de esta manera se repurifica por *HPLC* preparativa instantánea bajo las siguientes condiciones (IntelFlash-1): columna: gel de sílice C18; fase móvil: acetonitrilo: agua = 0:100 que aumenta a acetonitrilo: agua = 100:0 en los siguientes 25 min; detector: UV 254 nm. La purificación proporciona 72.7 mg (67%) del compuesto I-186 como un sólido blanco. EM (ES): *m/z* 526 $(M+H)^+$, 548 $(M+Na)^+$. RMN ^1H (300 MHz, DEMO-d_6): δ 1.59-1.60 (m, 6H), δ 1.64-1.67 (m, 2H), 2.70 (s, 3H), 3.27-3.32 (m, 1H), 3.40-3.43 (m, 1H), 3.49-3.55 (m, 2H),

3.70-3.78 (m, 1H), 3.92 (s, 1H), 4.05-4.11 (m, 1H), 4.77-4.80 (m, 1H), 7.28-7.39 (m, 6H), 8.19 (s, 1H).

Ejemplo 34: Síntesis del ácido 2-metil-2-[5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1-[(2R)-2-[(3S)-oxolan-3-iloxi]-2-feniletil]-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-227).

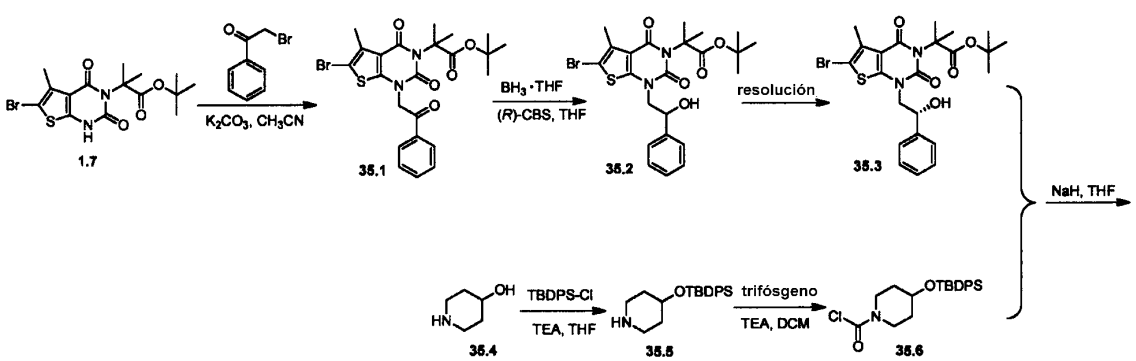


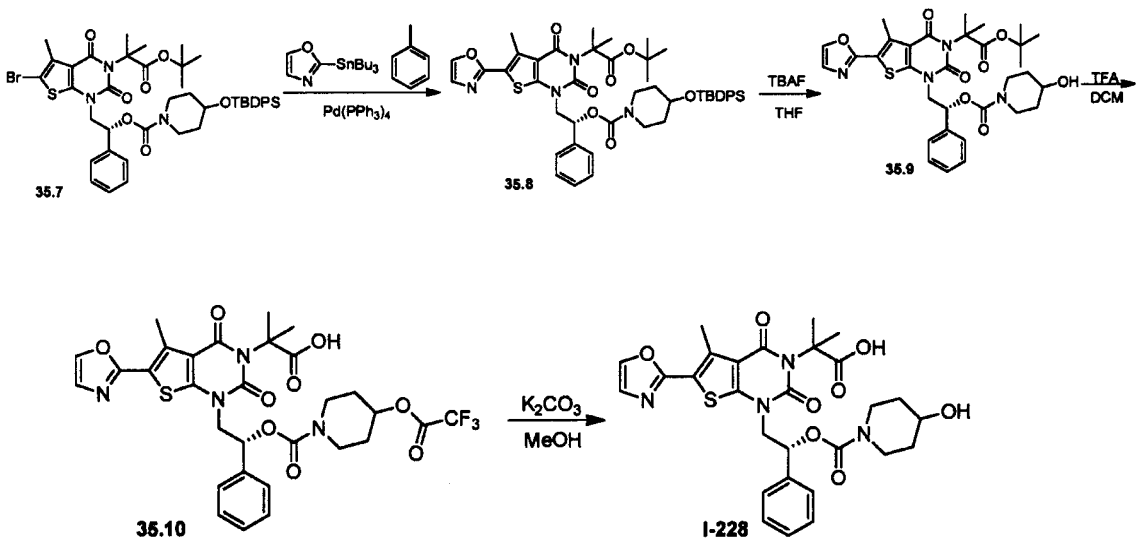
Síntesis del compuesto 34.4. El compuesto 34.4 se sintetiza de una manera análoga a la síntesis del compuesto 33.4. Se aísla un sólido blanco con un rendimiento general de 12% a partir de 34.1.

Síntesis del compuesto I-227. En un matraz de fondo redondo de 50 ml se colocan 5 ml de diclorometano, 34.4 (170 mg, 0.29 mmol, 1.00 equivalentes) y 1 ml de ácido trifluoroacético. La solución se agita durante 2 h a

temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con diclorometano/metanol (100:1). El producto (120 mg) obtenido de esta manera se repurifica por *HPLC* preparativa instantánea bajo las siguientes condiciones (IntelFlash-1): columna: gel de sílice C1; fase móvil: acetonitrilo: agua = 0:100 aumentando a acetonitrilo: agua = 100:0 en los siguientes 29 min; detector, UV 254 nm. La purificación proporciona 53.3 mg (35%) del compuesto I-227 como un sólido blanco. EM (ES): *m/z* 526 $(M+H)^+$, 548 $(M+Na)^+$. RMN ^1H (400 MHz, CD_3OD): δ 1.59-1.60 (m, 6H), 1.64-1.67 (m, 2H), 2.83 (s, 3H), 3.60-3.72 (m, 4H), 3.81-3.88 (m, 1H), 4.11-4.25 (m, 2H), 4.89-4.95 (m, 1H), 7.28 (s, 1H), 7.33-7.37 (m, 1H), 7.4 3 (t, *J* =7.6, 2H), 7.51 (d, *J* = 7.2, 2H), 7.98 (s, 1H).

Ejemplo 35: Síntesis del ácido 2-[1-[(2R)-2-[(4-hidroxipiperidin-1-il)carboniloxi]-2-feniletil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-228).





Síntesis del compuesto 35.5. En un matraz de fondo redondo de 250 ml se coloca una solución de piperidin-4-ol (4 g, 39.55 mmol, 1.00 equivalentes) en 100 ml de tetrahidrofurano, TEA (12 g, 118.59 mmol, 3.00 equivalentes) y terbutil(cloro)difenilsilano (16 g, 58.21 mmol, 1.47 equivalentes). La solución resultante se agita durante 16 h a temperatura ambiente. Los sólidos se separan por filtración. El filtrado se seca sobre sulfato de sodio anhidro y se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:2). La purificación proporciona 1.1 g (8%) de 4-[(terbutildifenilsilil)oxi]piperidina como un aceite incoloro.

Síntesis del compuesto 35.6. En un matraz de fondo redondo de 50 ml se coloca una solución de 4-[(terbutildifenilsilil)oxi]piperidina (1.00 g, 2.95 mmol, 1.00 equivalentes) en 20 ml de diclorometano, trietilamina (780 mg,

7.71 mmol, 2.62 equivalentes), carbonato de ditriclorometilo (2.07 g, 6.98 mmol, 2.37 equivalentes). La solución resultante se agita durante la noche a temperatura ambiente, después de lo cual se diluye con 40 ml de DCM y se lava con 3 x 15 ml de agua y 2 x 20 ml de cloruro de sodio saturado. Las soluciones orgánicas combinadas se secan sobre sulfato de sodio anhidro y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:4). La purificación proporciona 1.15 g (97%) del 35.6 como un aceite amarillo claro.

Síntesis del compuesto 35.1. A una solución del intermediario 1.7 (1.5 g, 3.72 mmol, 1.00 equivalentes) en 20 ml de CH_3CN se agrega carbonato de potasio (1.54 g, 11.14 mmol, 3.00 equivalentes) y 2-bromo-1-feniletan-1-ona (770 mg, 3.87 mmol, 1.05 equivalentes). La solución resultante se agita durante 3 h a temperatura ambiente. La reacción después se suspende por la adición de 20 ml de agua. La solución resultante se extrae con 3 x 30 ml de acetato de etilo y las capas orgánicas se combinan. La mezcla resultante se lava con 2 x 40 ml de cloruro de sodio saturado. La mezcla se seca sobre sulfato de sodio anhidro y se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:5). La purificación proporciona 1.8 g (93%) de 35.1 como un sólido blanco.

Síntesis del compuesto 35.2. En un matraz de fondo

redondo de 50 ml se coloca una solución de 35.1 (1.5 g, 2.88 mmol, 1.00 equivalentes) en 15 ml de tetrahidrofurano y (R)-CBS (239 mg, 0.86 mmol, 0.30 equivalentes). Esto es seguido por la adición de una solución de BH_3-THF (4 ml, 1.50 equivalentes) en 5 ml de tetrahidrofurano, a gotas, con agitación durante 8 h. La solución resultante se agita durante la noche a temperatura ambiente. La reacción después se suspende por la adición de 15 ml de NH_4Cl (saturado). La solución resultante se extrae con 3 x 20 ml de acetato de etilo y las capas orgánicas se combinan. La mezcla resultante se lava con 2 x 30 ml de cloruro de sodio saturado. La mezcla se seca y se concentra. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:15). La purificación proporciona 1.4 g (93%) de 35.2 como un sólido blanco.

Síntesis del compuesto 35.3. Los enantiómeros del compuesto 35.2 (1.4 g, 2.67 mmol, 1.00 equivalentes) se separan por SFC preparativa bajo las siguientes condiciones: columna: Fenomenex Lux 5u Cellulose-3, 5*25 cm,5 µm; fase móvil: CO_2 (80%), metanol (20%); detector: UV 254 nm. La purificación proporciona 0.98 g de 35.3 como un sólido blanco.

Síntesis del compuesto 35.7. A una solución de 35.3 (300 mg, 0.57 mmol, 1.00 equivalentes) en 10 ml de tetrahidrofurano se agrega hidruro de sodio (69 mg, 1.73 mmol, 3.00 equivalentes, 60%) a 0°C bajo N_2. La mezcla se agita

durante 30 min y después la solución de 35.6 (238 mg, 0.59 mmol, 1.50 equivalentes) en 3 ml de tetrahidrofurano se agrega. La solución resultante se agita durante la noche a temperatura ambiente. La reacción después se suspende por la adición de 10 ml de agua. La solución resultante se extrae con 3 x 20 ml de acetato de etilo y las capas orgánicas se combinan. La mezcla resultante se lava con 2 x 20 ml de cloruro de sodio saturado. La mezcla se seca sobre sulfato de sodio anhidro y se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:6). La purificación proporciona 360 mg (71%) de 35.7 como un sólido blanco.

Síntesis del compuesto 35.8. En un matraz de fondo redondo de 25 ml, purgado y mantenido con una atmósfera inerte de nitrógeno, se coloca 35.7 (140 mg, 0.16 mmol, 1.00 equivalentes), $Pd(PPh_3)_4$ (28 mg, 0.02 mmol, 0.15 equivalentes), 2-(tributilestanil)-1,3-oxazol (85 mg, 0.24 mmol, 1.51 equivalentes) y 5 ml de tolueno. La solución resultante se agita durante la noche a 110°C. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:40). La purificación proporciona 100 mg (72%) de 35.8 como un aceite incoloro.

Síntesis del compuesto 35.9. En un matraz de fondo redondo de 50 ml se colocan 5 ml de tetrahidrofurano y 35.8

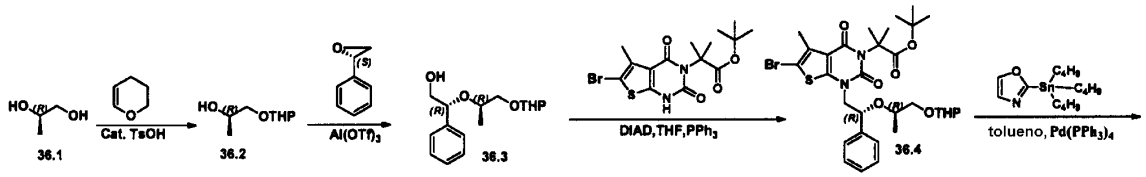
(100 mg, 0.11 mmol, 1.00 equivalentes). Esto es seguido por la adición de TBAF (33 mg, 0.13 mmol, 1.11 equivalentes) en porciones. La solución resultante se agita durante 2 h a temperatura ambiente. La reacción después se suspende por la adición de 0.5 ml de agua. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:5). La purificación proporciona 50 mg (69%) de 35.9 como un aceite amarillo.

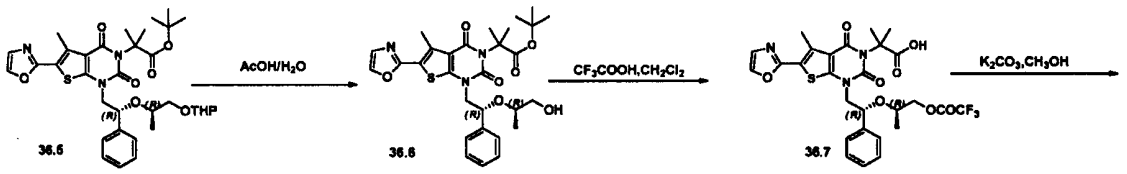
Síntesis del compuesto 35.10. En un matraz de fondo redondo de 50 ml se colocan 5 ml de diclorometano, 35.9 (50 mg, 0.08 mmol, 1.00 equivalentes) y 1 ml de ácido trifluoroacético. La solución resultante se agita durante 2 h a temperatura ambiente y después se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con diclorometano/metanol (100:1). La purificación proporciona 40 mg (crudo) de 35.10 como un aceite incoloro.

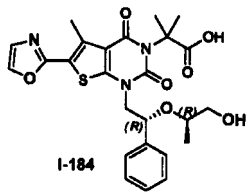
Síntesis del compuesto I-228. En un matraz de fondo redondo de 50 ml se colocan 35.10 (40 mg, 0.06 mmol, 1.00 equivalentes), carbonato de potasio (21 mg, 0.15 mmol, 2.58 equivalentes) y 5 ml de metanol. La solución resultante se agita durante 2 h a temperatura ambiente. Los sólidos se separan por filtración. El valor de pH del filtrado se ajusta a 6 con TFA. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con

diclorometano/metanol (100:1). La purificación proporciona 22.7 mg (66%) del compuesto I-228 como un sólido blanco. EM (ES): *m/z* 583 $(M+H)^+$. RMN ^1H (400 MHz, CD_3OD): δ 1.05-1.40 (m, 2H), 1.67-1.74 (m, 2H), 1.80 (s, 6H), 2.84 (s, 3H), 3.03-3.23 (m, 2H), 3.50-4.16 (m, 4H), 4.33-4.43 (m, 1H), 6.19-6.22 (m, 1H), 7.29 (s, 1H), 7.36-7.51 (m, 5H), 7.99 (s, 1H).

Ejemplo 36: Síntesis del ácido 2-[1-[(2R)-2-[[(2R)-1-hidroxipropan-2-il]oxi]-2-feniletil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-184).



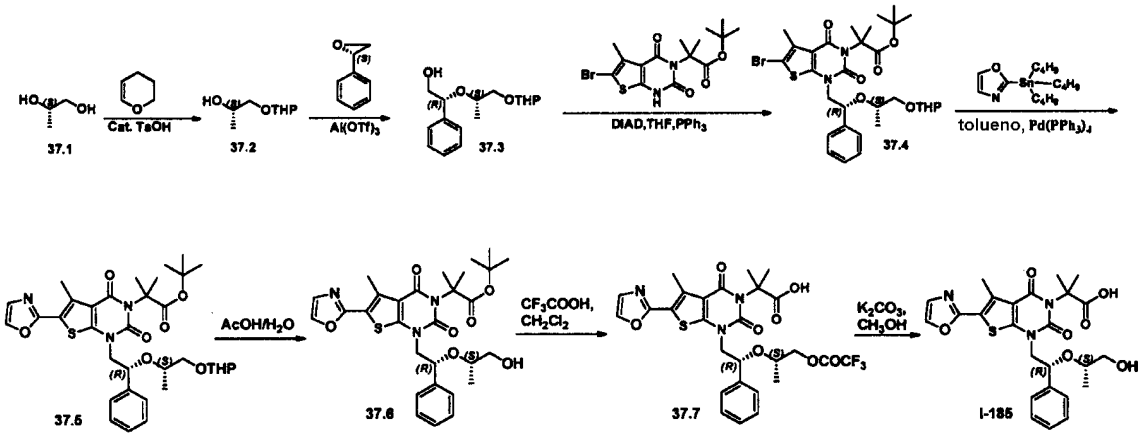




El compuesto I-184 se prepara de una manera análoga al ejemplo 31. Purificación: cromatografía en capa delgada

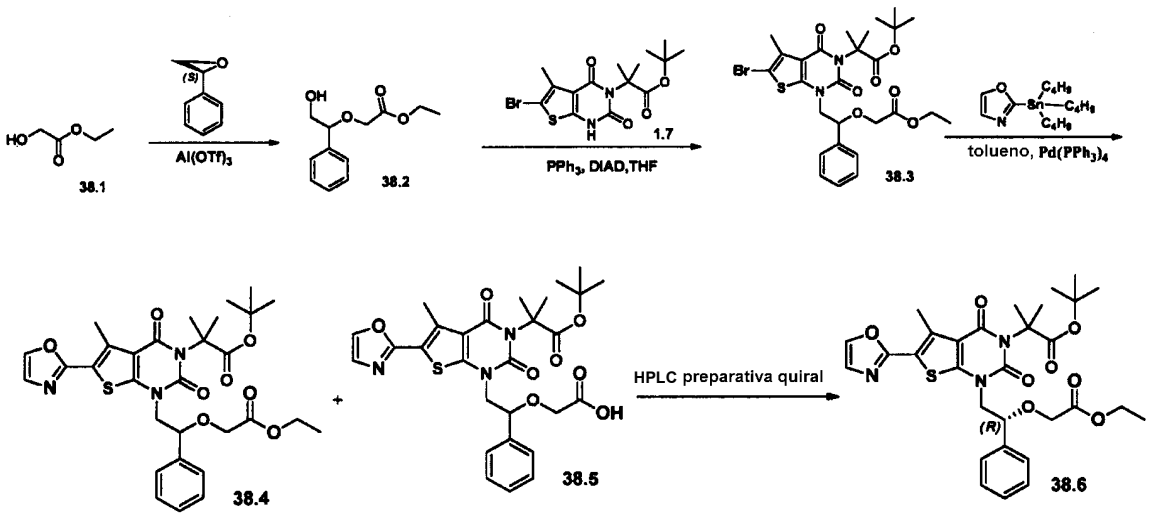
revelada con diclorometano/metanol (40:1). Se aísla un sólido blanco con un rendimiento total de 0.17% a partir de 36.1. EM (ES): *m/z* 514 $(M+H)^+$. RMN ^1H (300 MHz, CD_3OD): δ 0.94 (s, 3H), 1.75-1.78 (d, 6H), 2.77 (s, 3H), 3.42-3.47 (m, 2H), 3.87-3.95 (m, 1H), 4.11-4.17 (m, 1H), 4.94-4.98 (m, 1H), 7.24-7.50 (m, 6H), 7.94 (s, 1H).

Ejemplo 37: Síntesis del ácido 2-[1-[(2R)-2-[[(2S)-1-hidroxipropan-2-il]oxi]-2-feniletil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-185).



El compuesto I-185 se sintetiza de una manera análoga al ejemplo 31. Se aísla un sólido blanco con un rendimiento total de 0.061% a partir de 37.1. EM (ES): *m/z* 514 $(M+H)^+$.RMN ^1H (300 MHz, CD_3OD): δ 0.94 (s, 3H), 1.76 (s, 6H), 2.76 (s, 3H), 3.42-3.48 (m, 2H), 3.89-3.97 (m, 1H), 4.08-4.14 (m, 1H), 5.03-5.08 (m, 1H), 7.24-7.45 (m, 6H), 7.94 (s, 1H).

Ejemplo 38: Síntesis del intermediario 38.6.

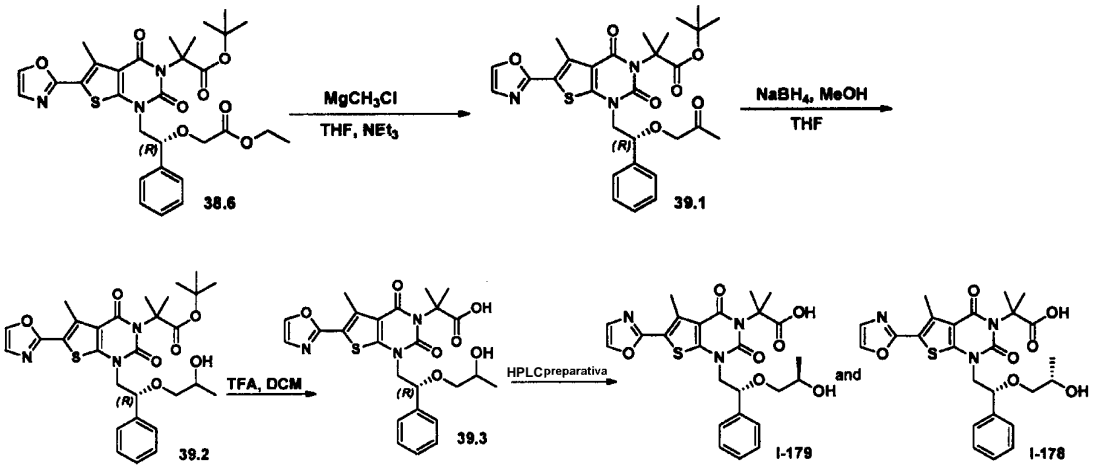


Síntesis del compuesto 38.4. El compuesto 38.4 se prepara a partir de 38.1 de una manera análoga a la síntesis del compuesto 14.4. Se aísla un sólido blanco con un rendimiento total 16% a partir de 1.7 (1.1% a partir de 38.1). El producto secundario 38.5 también se aísla.

Síntesis del compuesto 38.6. Los enantiómero de 38.4 (240 mg) se separan por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): columna: Chiralpak IC(SFC), 2*25 cm, 5 µm; fase móvil: hexanos y etanol (que se mantiene en etanol 25.0% durante 25 min); detector: UV 220/254. Se obtienen 160 mg del un producto sólido blanco.

Ejemplo 39: Síntesis del ácido 2-[1-[(2R)-2-[(2R)-2-hidroxipropoxi]-2-feniletil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-179) y Ejemplo 40: ácido 2-[1-[(2R)-2-

[(2S)-2-hidroxipropoxi]-2-feniletil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-178).



Síntesis del compuesto 39.1. En un matraz de fondo redondo de 3 cuellos de 100 ml se coloca 38.6 (160 mg, 0.27 mmol, 1.00 equivalentes), 20 ml de tetrahidrofurano y Et_3N (54.1 mg, 0.54 mmol, 2.00 equivalentes). Esto es seguido por la adición de cloro(metil)magnesio (0.26 ml, 3M) en porciones. La solución resultante se agita durante 3 h a -50°C. La reacción después se suspende por la adición de 20 ml de NH_4Cl acuoso saturado. La solución resultante se extrae con 2 x 30 ml de acetato de etilo y las capas orgánicas se combinan y se secan sobre sulfato de sodio anhidro y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:15). La purificación proporciona 40 mg (26%) de 39.1 como un sólido blanco.

Síntesis del compuesto 39.2. En un matraz de fondo redondo de 25 ml se coloca 39.1 (40 mg, 0.07 mmol, 1.00 equivalentes),10 ml de metanol y $NaBH_4$ (2.6 mg, 0.07 mmol, 0.98 equivalentes). La solución resultante se agita durante 3 h a temperatura ambiente. La reacción después se suspende por la adición de 10 ml de agua. La solución resultante se extrae con 2 x 15 ml de acetato de etilo y las capas orgánicas se combinan y se secan en un horno bajo presión reducida. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:2). La purificación proporciona 30 mg (75%) de 39.2 como un sólido blanco.

Síntesis del compuesto 39.3. En un matraz de fondo de 25 ml se coloca 39.2 (30 mg, 0.05 mmol, 1.00 equivalentes), 5 ml de diclorometano y 1 ml de ácido trifluoroacético. La solución resultante se agita durante la noche a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se purifica por cromatografía en capa delgada revelado con diclorometano/metanol (20:1) apara proporcionar 20 mg (74%) de 39.3 como un sólido blanco.

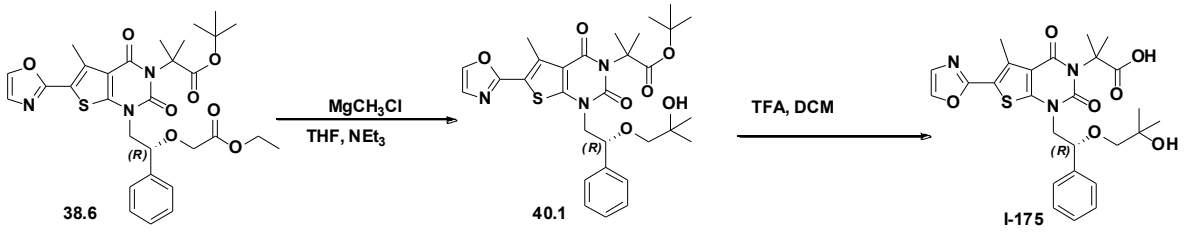
Resolución de compuestos I-179 y I-178. Los enantiómeros de 39.3 (20 mg) se purifican por *HPLC* preparativa bajo las siguientes condiciones (Waters): columna: XBridge Prep Fenil OBD 5 µm, 19*150 mm; fase móvil: agua ($NH_4HCO_3$50 mM) y CH_3CN (CH_3CN 5.0% hasta 95.0% en 10 min, se mantiene a

95.0% durante 2 min y después desciende a 5.0% en 2 min); detector: UV 254/220 nm. La purificación proporciona 6.7 mg (34%; tR = 8.55 min) del compuesto I-179 como un sólido blanco y 2.3 mg (12%, tR = 9.47 min) del compuesto I-178 como un sólido blanco.

Datos analíticos para el compuesto I-179: EM (ES): *m/z* 514 $(M+H)^+$. RMN ^1H (300 MHz, CD_3OD): δ 0.94 (d, *J* = 6.3Hz, 3H), 1.75 (s, 6H), 2.76 (s, 3H), 3.05 (m, 1H), 3.76 (m,1H), 3.92 (m, 1H), 4.16 (m, 1H), 7.22-7.46 (m, 6H), 7.92 (s, 1H).

Datos analíticos para el compuesto I-178: EM (ES): *m/z* 514 $(M+H)^+$. RMN ^1H (300 MHz, CD_3OD): δ 0.94 (d, *J* = 6.3Hz, 3H), 1.75 (s, 6H), 2.76 (s, 3H), 3.05 (m, 1H), 3.76 (m,1H), 3.94 (m, 1H), 4.16 (m, 1H), 7.22-7.48 (m, 6H), 7.93 (s, 1H).

Ejemplo 40: Síntesis del ácido 2-[1-[(2R)-2-(2-hidroxi-2-metilpropoxi)-2-feniletil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-175).



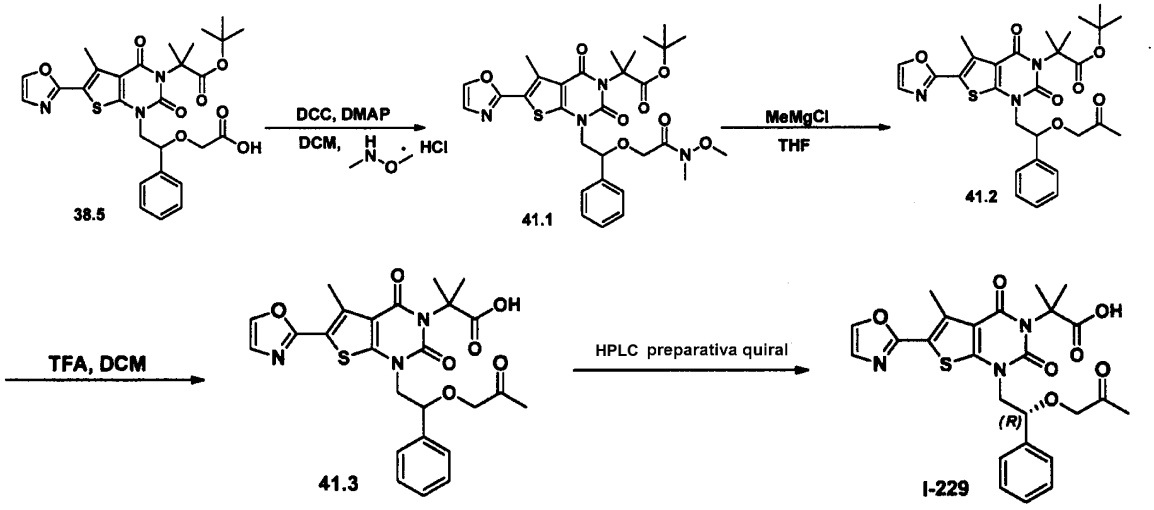
Síntesis del compuesto 40.1. En un matraz de fondo redondo de 25 ml, purgado y mantenido con una atmósfera inerte de nitrógeno se coloca el intermediario 38.6 (160 mg, 0.27 mmol, 1.00 equivalentes), 10 ml de tetrahidrofurano, Et_3N

(54.1 mg, 0.54 mmol, 2.00 equivalentes). Esto es seguido por la adición a gotas de cloro(metil)magnesio (0.26 ml, 3 M) con agitación, a -78°C. La solución resultante se agita durante 3 h a -50°C. La reacción después se suspende por la adición de 10 ml de NH_4Cl acuoso saturado. La solución resultante se extrae con 3 x 15 ml de acetato de etilo y las capas orgánicas se combinan y se secan sobre sulfato de sodio anhidro y se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:10). La purificación proporciona 40 mg (26%) de 40.1 como un sólido blanco.

Síntesis del compuesto I-175. En un matraz de fondo redondo de 25 ml se coloca el compuesto 40.1 (40 mg, 0.07 mmol, 1.00 equivalentes), 5 ml de diclorometano y 1 ml de ácido trifluoroacético. La solución resultante se agita durante 2 h a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con diclorometano/metanol (20:1). La purificación proporciona 23.4 mg (65%) del compuesto I-175 como un sólido blanco. EM (ES): *m/z* 528 $(M+H)^+$. RMN ^1H (300 MHz, CD_3OD): δ 0.97 (s, 3H), 1.03 (s, 3H), 1.77 (s, 6H), 2.76 (s, 6H), 3.00 (d, *J* = 9.0 Hz, 1H), 3.13 (d, *J* = 9.0Hz, 1H), 3.91 (dd, *J* = 14.4, 9.0 Hz, 1H), 4.19 (dd, *J* = 14.4, 3.9 Hz, 1H), 7.24-7.44 (m, 6H) , 7.92 (s, 1H).

Ejemplo 41: Síntesis del ácido 2-metil-2-[5-metil-6-

(1,3-oxazol-2-il)-2,4-dioxo-1-[(2R)-2-(2-oxopropoxi)-2-feniletil]-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-229).



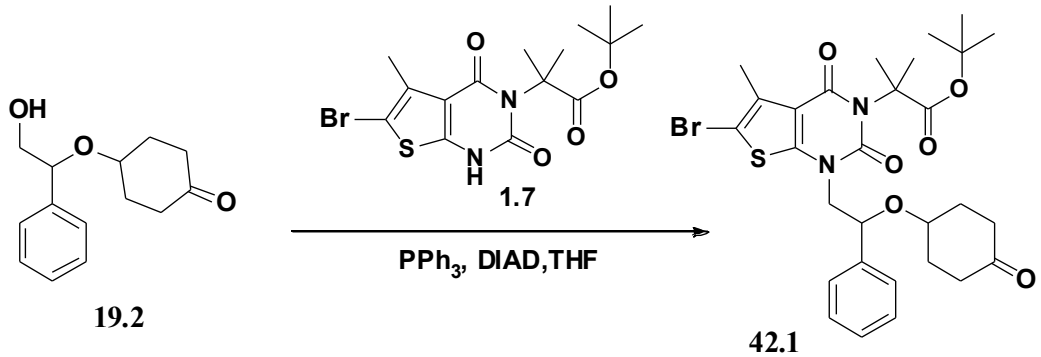
Síntesis del compuesto 41.1. El compuesto I-229 se prepara de una manera análoga al compuesto I-121 (ejemplo 4). Se aíslan 100 mg (46%) de 41.1 como un sólido blanco.

Síntesis del compuesto 41.2. En un matraz de fondo redondo de 3 cuellos de 50 ml, purgado y mantenido con una atmósfera inerte de nitrógeno se coloca 41.1 (100 mg, 0.16 mmol, 1.00 equivalentes) y 10 ml de tetrahidrofurano. Esto es seguido por la adición de cloro(metil)magnesio (3 M) (0.05 ml, 2.00 equivalentes) a gotas con agitación a 50°C. La solución resultante se agita durante 2 h a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:2). La purificación proporciona 55 mg (59%) de 41.2 como un sólido blanco.

Síntesis del compuesto 41.3. En un matraz de fondo redondo de 10 ml se coloca 1 ml de ácido trifluoroacético, 41.2 (55 mg, 0.10 mmol, 1.00 equivalentes) y 5 ml de diclorometano. La solución se agita durante la noche a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con diclorometano/metanol (40:1). La purificación proporciona 10 mg (20%) de 41.3 como un sólido blanco.

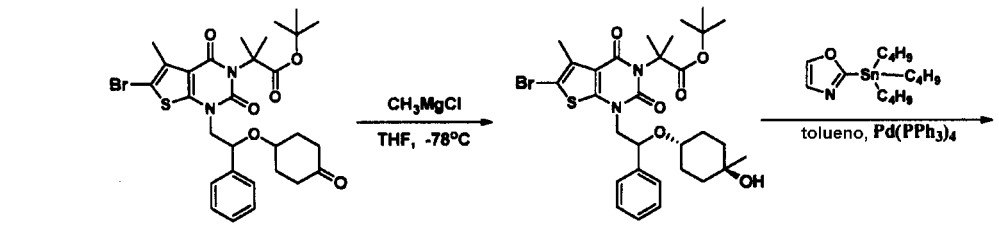
Síntesis del compuesto I-229. El producto crudo (1 g) se purifica por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): columna: Chiralpak IC, 2*25 cm, 5 µm; fase móvil: hexanos (TFA 0.1%) y etanol (TFA 0.1%) (que se mantiene en etanol 15% (TFA 0.1%) en 30 min); detector: UV 220/254 nm. La purificación proporciona 3.0 mg (30%) del compuesto I-229 como un sólido blanco. EM (ES): *m/z* 512 $(M+H)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.82 (s, 6H), 1.98 (s, 3H), 2.81 (s, 3H), 3.88-4.07 (m, 3H), 4.26 (d, 1H), 4.94 (m, 1H), 7.37 (s, 1H), 7.38-7.49 (m, 5H), 7.98 (s, 1H).

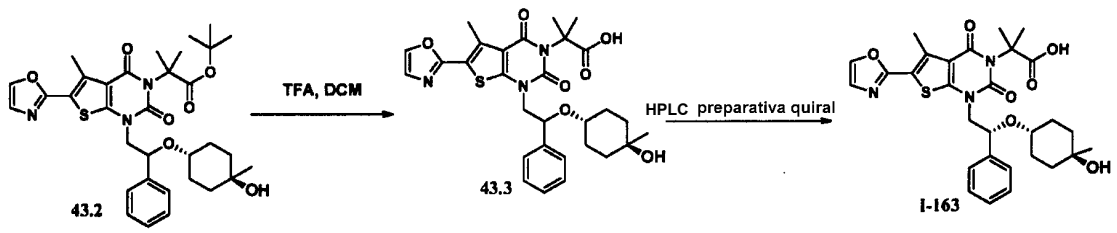
Ejemplo 42: Síntesis del intermediario 42.1.



Síntesis del intermediario 42.1. En un matraz de fondo redondo de 3 cuellos de 250 ml, purgado y mantenido con una atmósfera inerte de nitrógeno se coloca 19.2 (1.6 g, 6.83 mmol, 1.84 equivalentes), 60 ml de tetrahidrofurano, DIAD (1.5 g, 7.42 mmol, 1.99 equivalentes), PPh_3 (1.9 g, 7.24 mmol, 1.95 equivalentes) y 1.7 (1.5 g, 3.72 mmol, 1.00 equivalentes). La solución resultante se agita durante 4 h a temperatura ambiente y después se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:50). La purificación proporciona 1 g (43%) del intermediario 42.1 como un sólido blanco.

Ejemplo 43: Síntesis del ácido 2-(1-((R)-2-(((1r,4R)-4-hidroxi-4-metilciclohexil)oxi)-2-feniletil)-5-metil-6-(oxazol-2-il)-2,4-dioxo-1,2-dihidrotieno[2,3-d]pirimidin-3(4H)-il)-2-metilpropanoico (I-163).



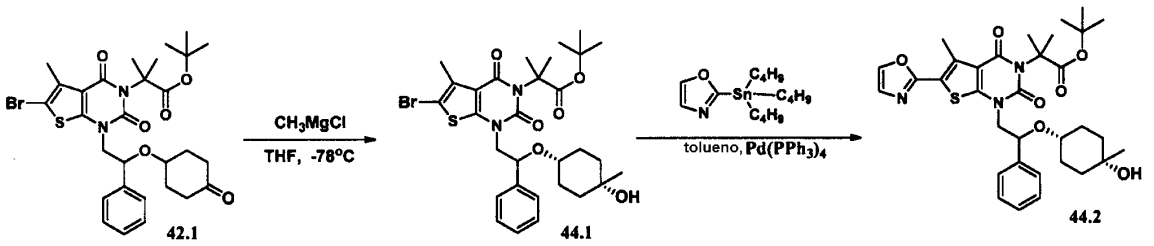


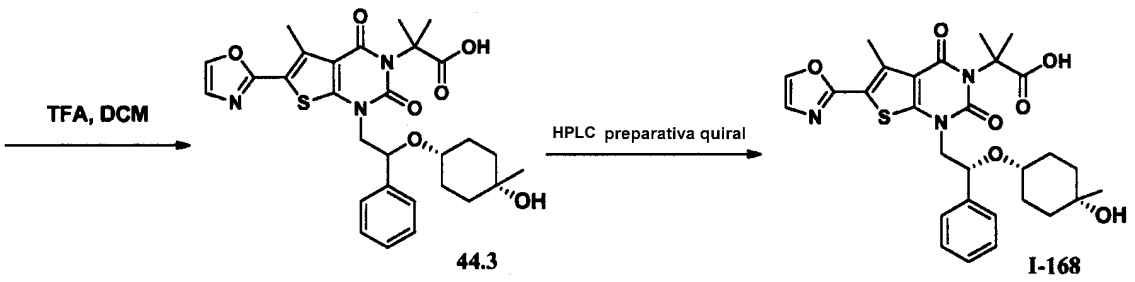
Síntesis del compuesto 43.1. En un matraz de fondo redondo de 3 cuellos de 50 ml, purgado y mantenido con una atmósfera inerte de nitrógeno se coloca el intermediario 42.1 (500 mg, 0.81 mmol, 1.00 equivalentes) y 25 ml de tetrahidrofurano. Esto es seguido por la adición de cloro(metil)magnesio (0.52 ml, 3 M) a gotas, con agitación a -78°C. La solución resultante se agita durante 4 h a -50°C en un baño de nitrógeno líquido. La reacción después se suspende por la adición de 10 ml de NH_4Cl (acuoso saturado). La solución resultante se extrae con 2 x 30 ml de acetato de etilo y las capas orgánicas se combinan, se secan sobre sulfato de sodio anhidro y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:5). La purificación proporciona 125 mg (24%) de 43.1 como un sólido blanco.

Síntesis del compuesto I-163. El compuesto I-163 se prepara a partir de 43.1 de una manera análoga al ejemplo 14. Condiciones de purificación: los enantiómeros de 43.3 (40 mg) se purifican por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): columna: Chiralpak IC, 2*25 cm, 5 µm; fase móvil: hexanos y etanol (que mantiene etanol 20.0% durante 12 min); detector: UV 220/254 nm. Se obtienen 6.8 mg (sólido blanco) de producto con un rendimiento total de 0.13% a partir de 42.1. EM (ES): *m/z* 568 $(M+H)^+$, 590 $(M+Na)^+$. RMN ^1H

(300 MHz, DMSO-d_6): δ 0.91 (s, 3H), 1.03 (m, 2H), 1.21-1.42 (m, 6H), 1.61 (s, 6H), 2.69 (s, 3H), 3.03 (m, 1H), 3.61-4.07 (m, 3H), 4.82 (m, 1H), 7.28-7.37 (m, 6H) , 8.17 (s, 1H).

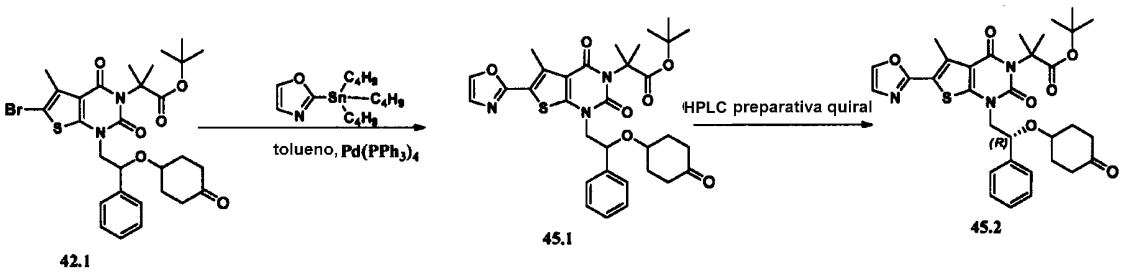
Ejemplo 44: Síntesis del ácido 2-(1-((R)-2-(((1s,4S)-4-hidroxi-4-metilciclohexil)oxi)-2-feniletil)-5-metil-6-(oxazol-2-il)-2,4-dioxo-1,2-dihidrotieno[2,3-d]pirimidin-3(4H)-il)-2-metilpropanoico (I-168).





El compuesto I-168 se prepara de una manera análoga al ejemplo 43. Se aísla un sólido blanco con un rendimiento total de 5.1% a partir de 42.1. EM (ES): *m/z* 568 $(M+H)^+$, 590 $(M+Na)^+$. RMN ^1H (300 MHz, CD_3OD): δ 0.81 (s, 3H), 0.99 (m, 1H), 1.14 (m, 2H), 1.25-1.61 (m, 5H), 1.78 (m, 6H), 2.77 (s, 3H), 3.51 (m,1H), 3.71 (m, 1H), 4.33 (m, 1H), 4.92 (m, 1H), 7.25-7.47 (m, 6H) , 7.95(s, 1H).

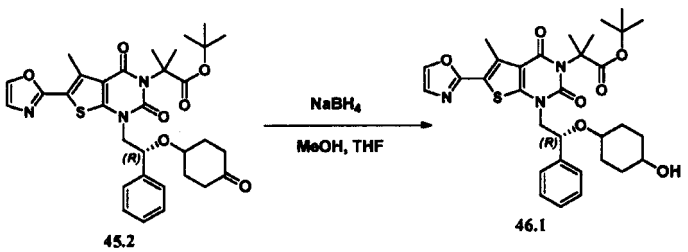
Ejemplo 45: Síntesis del intermediario 45.2.

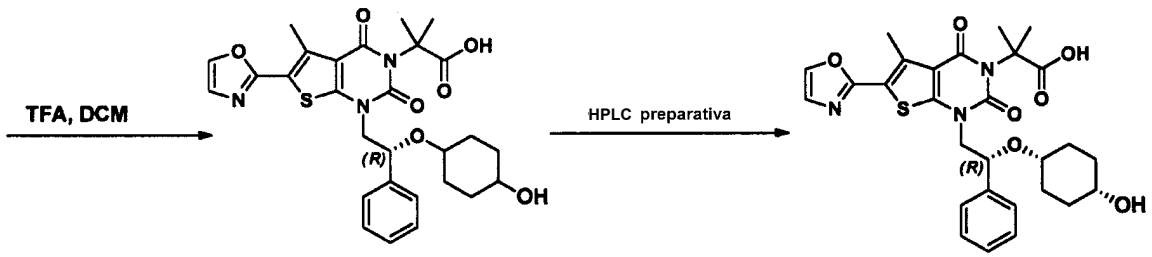


Síntesis del compuesto 45.1. El compuesto 45.1 se prepara a partir de 2-(tributilestanil)oxazol y 42.1 de una manera análoga a la síntesis de I-120 (ejemplo 2). Se aísla un sólido blanco con un rendimiento de 45%.

Síntesis del intermediario 45.2. Los enantiómeros de 45.1 racémico (220 mg) se separan por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): columna: Chiralpak IC, 2*25 cm, 5 µm; fase móvil: hexanos (TEA 0.1%) e IPA (que se mantiene en IPA 25.0% durante 40 min); detector: UV 220/254 nm. Se obtienen 80 mg (sólido blanco) del producto.

Ejemplo 46: Síntesis del ácido 2-[1-[(2R)-2-[(4-hidroxiciclohexil)oxi]-2-feniletil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-164).





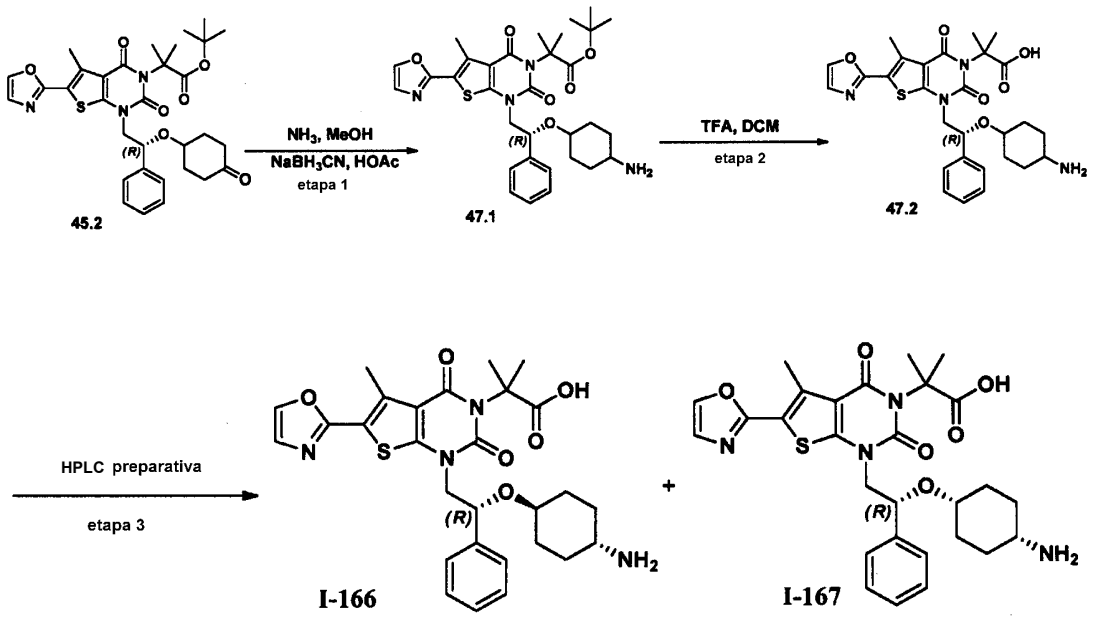
46.2 I-164

Síntesis of 46.1. En un matraz de fondo redondo de 50 ml se coloca el intermediario 45.2 (40 mg, 0.07 mmol, 1.00 equivalentes), 10 ml de metanol y $NaBH_4$ (3.7 mg, 0.10 mmol, 1.53 equivalentes). La solución resultante se agita durante 3 h a temperatura ambiente, después de lo cual se concentra bajo vacío. El residuo se purifica por CCD preparativa con acetato de etilo/éter de petróleo(1:5) para proporcionar 35 mg (87%) de 46.1 como un sólido blanco.

Síntesis del compuesto I-164. El compuesto I-164 se prepara a partir de 46.1 de una manera análoga al compuesto 2.5. Se aísla un sólido blanco con un rendimiento de 28% a partir de 46.1. Condiciones de purificación: el producto crudo (30 mg) se purifica por *HPLC* preparativa bajo las siguientes condiciones (Waters): columna: XBridge Shield RP18 OBD columna, 5 µm, 19*150 mm; fase móvil: agua ($NH_4HCO_3$50 mM) y CH_3CN (CH_3CN 6.0% hasta 50.0% en 14 min); detector: UV 254/220 nm. La purificación proporciona 9 mg del compuesto I-164 (tR = 7.86 min) como un sólido blanco. EM (ES): *m/z* 554 $(M+H)^+$, 576 $(M+Na)^+$, 617 $(M+Na+CH_3CN)^+$.

Ejemplo 47: Síntesis del ácido 2-(1-((R)-2-

(((1r,4R)-4-aminociclohexil)oxi)-2-feniletil)-5-metil-6-(oxazol-2-il)-2,4-dioxo-1,2-dihidrotieno[2,3-d]pirimidin-3(4H)-il)-2-metilpropanoico (I-166) y Ejemplo 48: Síntesis del ácido 2-(1-((R)-2-(((1s,4S)-4-aminociclohexil)oxi)-2-feniletil)-5-metil-6-(oxazol-2-il)-2,4-dioxo-1,2-dihidrotieno[2,3-d]pirimidin-3(4H)-il)-2-metilpropanoico (I-167).



Síntesis del compuesto 47.1. En un matraz de fondo redondo de 50 ml se coloca el intermediario 45.2 (40 mg, 0.07 mmol, 1.00 equivalentes), 10 ml de metanol/NH_3, ácido acético (4 mg, 0.07 mmol, 1.01 equivalentes) y $NaBH_3CN$ (8 mg, 0.13 mmol, 1.93 equivalentes). La solución resultante se agita durante la noche a temperatura ambiente, después de lo cual se concentra bajo vacío. El residuo se purifica por CCD

preparativa con DCM/metanol (1:20) para proporcionar 26 mg (65%) de 47.1 como un sólido blanco.

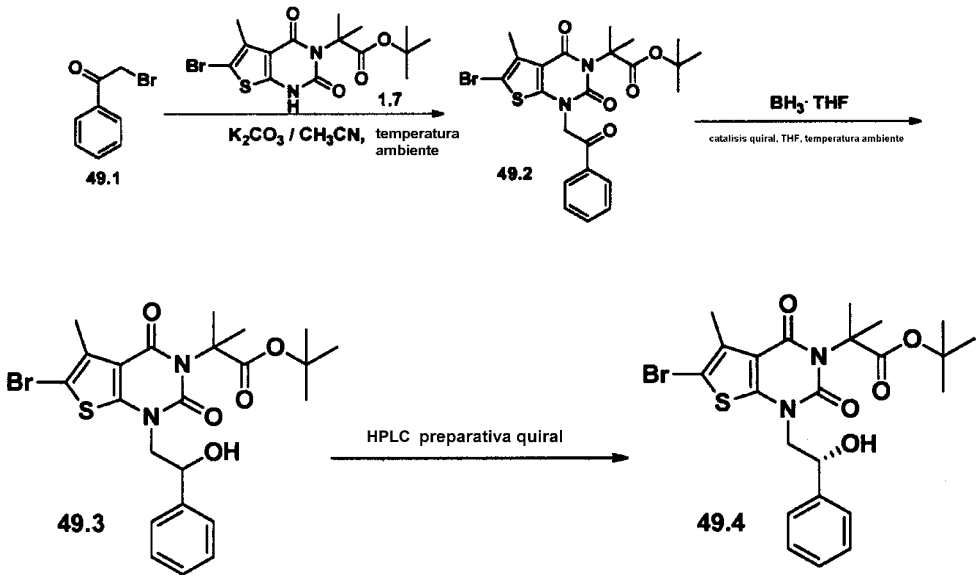
Síntesis del compuesto 47.2. Se prepara el compuesto 47.2 a partir de 47.1 de una manera análoga al compuesto 2.5. Se aísla un sólido blanco con un rendimiento de 64%.

Síntesis de los compuestos I-166 y I-167. Los enantiómeros de 47.2 (15 mg) se separaron por *HPLC* preparativa bajo las siguientes condiciones (Waters): columna: XBridge Shield RP18 OBD columna, 5 µm, 19*150 mm; fase móvil: agua (con NH_4HCO_3 50 mM) y CH_3CN (CH_3CN 20.0% hasta 80.0% en 25 min); detector: UV 254/220 nm. Se obtienen 0.6 mg del compuesto I-166 (tR = 18.73 min; sólido blanco, 5.1% de rendimiento a partir de 47.2) y 0.5 mg del compuesto I-167 (tR = 22.06 min; sólido blanco, rendimiento de 1.9% a partir de 47.2).

Datos analíticos para el compuesto I-166: EM (ES): *m/z* 553 $(M+H)^+$. RMN ^1H (300 MHz, CD_3OD): δ 0.82-0.86 (m, 2H), 1.09-1.26 (m, 12H), 1.76-1.95 (m, 10H), 2.77 (s, 3H), 3.41-3.70 (m, 2H), 4.96-5.01 (m, 2H), 7.23-7.47 (m, 6H), 7.93 (s, 1H).

Datos analíticos para el compuesto I-167: EM (ES): *m/z* 553 $(M+H)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.18 -1.78 (m, 14H), 1.90-1.95 (m, 1H), 2.79 (s, 3H), 2.86-2.91 (m, 1H), 3.45-3.51 (m, 1H), 3.92-3.96 (m, 1H), 4.23 (m, 1H), 4.85-5.04 (m, 1H), 7.25-7.57 (m, 6H), 7.95 (s, 1H).

Example 49: Síntesis del intermediario 49.4.



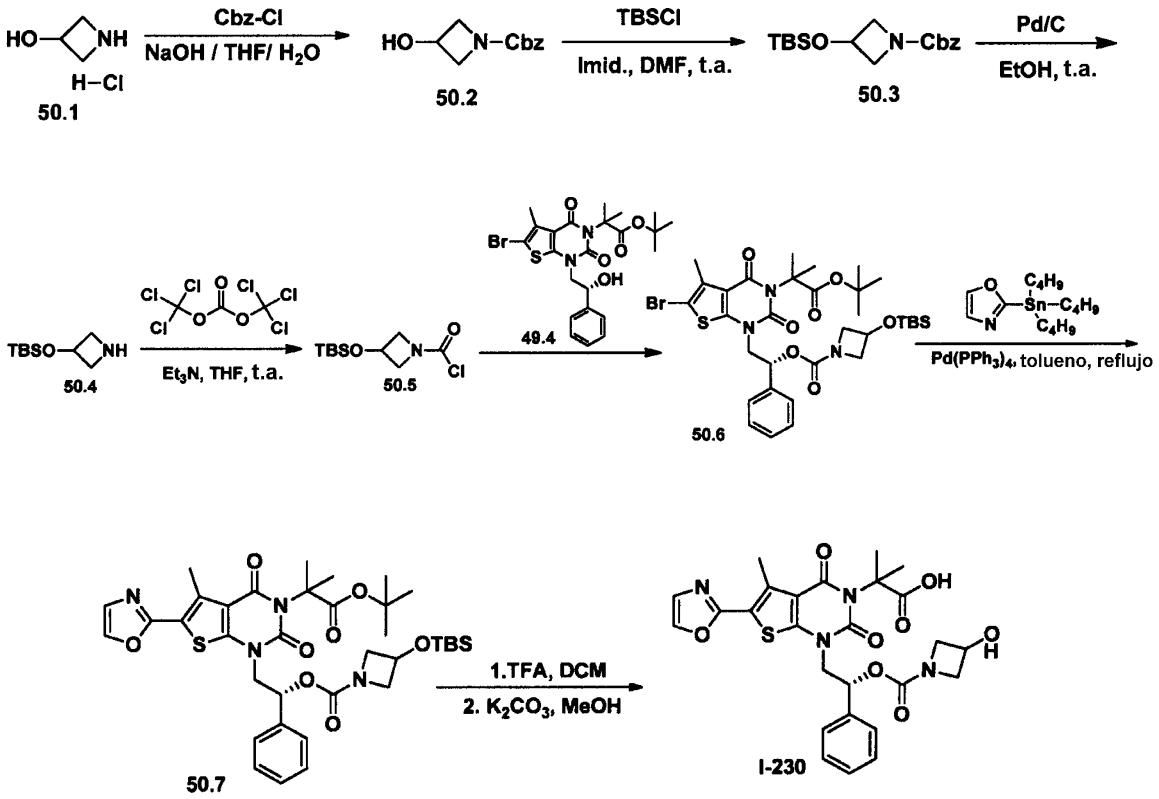
Síntesis del compuesto 49.2. A una solución de 1.7 (1.5 g, 3.72 mmol, 1.00 equivalentes) en 20 ml de CH_3CN se agrega carbonato de potasio (1.54 g, 11.14 mmol, 3.00 equivalentes) y 2-bromo-1-feniletan-1-ona (770 mg, 3.87 mmol, 1.05 equivalentes). La solución resultante se agita durante 3 h a temperatura ambiente. La reacción después se suspende por la adición de 20 ml de agua. La mezcla se extrae con 3 x 30 ml de acetato de etilo y las capas orgánicas se combinan, se lavan con 2 x 40 ml de cloruro de sodio saturado, se secan sobre sulfato de sodio anhidro y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo(1:5). La purificación proporciona 1.8 g (93%) de 49.2 como un sólido blanco.

Síntesis del compuesto 49.3. En un matraz de fondo redondo de 50 ml se coloca una solución de 49.2 (1.5 g, 2.88 mmol, 1.00 equivalentes) y (R)-CBS (239 mg, 0.86 mmol, 0.30 equivalentes) en 15 ml de tetrahidrofurano. Esto es seguido por la adición de una solución de BH_3-TF (4 ml, 1.50 equivalentes) en 5 ml de tetrahidrofurano a gotas, con agitación en h. La solución resultante se agita durante la noche a temperatura ambiente. La reacción después se suspende por la adición de 15 ml de NH_4Cl acuoso saturado. La mezcla se extrae con 3 x 20 ml de acetato de etilo y las capas orgánicas se combinan y se lavan con 2 x 30 ml de cloruro de sodio saturado. El sólido se seca en un horno bajo presión reducida. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo(1:15). La purificación proporciona 1.4 g (93%) de 49.3 como un sólido blanco.

Síntesis del compuesto 49.4. Los enantiómeros de 49.3 (1.4 g, 2.67 mmol, 1.00 equivalentes) Se separan por SFC preparativa bajo las siguientes condiciones: columna: Phenomenex Lux 5u Cellulose-3, 5*25 cm, 5 µm; fase móvil: CO_2 (80%), metanol (20%); detector: UV 254 nm. La purificación proporciona 0.98 g de 49.4 como un sólido blanco así como 0.3 g de 2-[6-bromo-1-[(2S)-2-hidroxi-2-feniletil]-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoato de terbutilo, también como un sólido blanco.

Example 50: Síntesis del ácido 2-[1-[(2R)-2-[(3-

hidroxiazetidin-1-il)carboniloxi]-2-feniletil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-230).



Síntesis del compuesto 50.2. A una solución de clorhidrato de azetidin-3-ol (2 g, 18.26 mmol, 1.0 equivalentes) e hidróxido de sodio (1.53 g, 38.25 mmol, 2.10 equivalentes) en 10 ml de agua y 25 ml de tetrahidrofurano se agrega a gotas Cbz-Cl (3.27 g, 19.17 mmol, 1.05 equivalentes) con agitación a 0°C durante 30 min. La solución resultante se agita durante 3 h a temperatura ambiente. La reacción después se suspende por la adición de 20

ml de agua. La mezcla se extrae con 3 x 30 ml de acetato de etilo y las capas orgánicas se combinan. La mezcla resultante se lava con 2 x 40 ml de cloruro de sodio saturado. La mezcla se seca sobre sulfato de sodio anhidro y se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:1). La purificación proporciona 2.0 g (53%) de 3-hidroxiazetidin-1-carboxilato de bencilo (50.2) como un líquido amarillo claro.

Síntesis del compuesto 50.3. En un matraz de fondo redondo de 50 ml se coloca 3-hidroxiazetidin-1-carboxilato de bencilo (2.15 g, 10.38 mmol, 1.00 equivalentes), TBSCl (2.34 g, 15.60 mmol, 1.50 equivalentes), imidazol (1.27 g, 18.68 mmol, 1.80 equivalentes) y 15 ml de N,N-dimetilformamida. La solución resultante se agita durante la noche a temperatura ambiente. La reacción después se suspende por la adición de 30 ml de agua. La mezcla se extrae con 3 x 40 ml de acetato de etilo y las capas orgánicas se combinan. La mezcla resultante se lava con 2 x 50 ml de cloruro de sodio saturado. La mezcla se seca sobre sulfato de sodio anhidro y se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo(1:5). La purificación proporciona 3.0 g (90%) del 3-[(terbutildimetilsilil)oxi]azetidin-1-carboxilato de bencilo (50.3) como un líquido amarillo claro.

Síntesis del compuesto 50.4. En una solución de 3-

[(terbutildimetilsilil)oxi]azetidin-1-carboxilato de bencilo (4.2 g, 13.06 mmol, 1.00 equivalentes) en 15 ml de etanol se agrega carbono en paladio (1.3 g, 0.30 equivalentes) a 0°C en un baño de agua/hielo. La solución resultante se agita durante la noche a temperatura ambiente. Los sólidos se separan por filtración. La mezcla resultante se concentra bajo vacío para proporcionar 2.2 g (90%) de 3-[(terbutildimetilsilil)oxi]azetidina (50.4) como un líquido amarillo claro.

Síntesis del compuesto 50.5. A una solución de carbonato de ditriclorometilo (2.38 g, 8.02 mmol, 1.50 equivalentes) 20 ml de diclorometano se agrega una solución de 3-[(terbutildimetilsilil)oxi]azetidina (1 g, 5.34 mmol, 1.00 equivalentes) en 5 ml de diclorometano a gotas con agitación a 0°C durante 30 min. La agitación continúa durante 30 min, después de los cual se agrega a gotas una solución de trietilamina (810 mg, 8.00 mmol, 1.50 equivalentes) en 5 ml de diclorometano, con agitación a 0°C en 30 min. La solución resultante se agita durante la noche a temperatura ambiente. La reacción después se suspende por la adición de 20 ml de bicarbonato de sodio saturado. La solución resultante se extrae con 3 x 20 ml de acetato de etilo y las capas orgánicas se combinan, se lavan con 2 x 40 ml de cloruro de sodio saturado, se secan sobre sulfato de sodio anhidro y se concentran bajo vacío. El residuo se aplica sobre una columna

de gel de sílice con acetato de etilo/éter de petróleo(1:15). La purificación proporciona 1.3 g (97%) de clorhidrato de 3-[(terbutildimetilsilil)oxi]azetidin-1-carbonilo como un líquido amarillo claro.

Síntesis del compuesto 50.6. En un matraz de fondo redondo de 3 cuellos de 50 ml se coloca una solución de 49.4 (200 mg, 0.38 mmol, 1.00 equivalentes) en 10 ml de tetrahidrofurano. Esto es seguido por la adición de hidruro de sodio (46 mg, 1.15 mmol, 3.00 equivalentes, 60%) a 0°C. La solución resultante se agita durante 0.5 h a 0°C. A esto se agrega una solución de cloruro de 3-[(terbutildimetilsilil)oxi]azetidin-1-carbonilo (142 mg, 0.57 mmol, 1.50 equivalentes) e 3 ml de tetrahidrofurano a gotas, con agitación, a 0°C. Se permite que la solución resultante reaccione, con agitación, durante la noche a temperatura ambiente. La reacción después se suspende por la adición de 10 ml de agua. La solución resultante se extrae con 3 x 20 ml de acetato de etilo y las capas orgánicas se combinan. La mezcla resultante se lava con 2 x 20 ml de salmuera. La mezcla se seca sobre sulfato de sodio y se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con PE/EA (6/1). La purificación proporciona 220 mg (78%) de 50.6 como un sólido blanco.

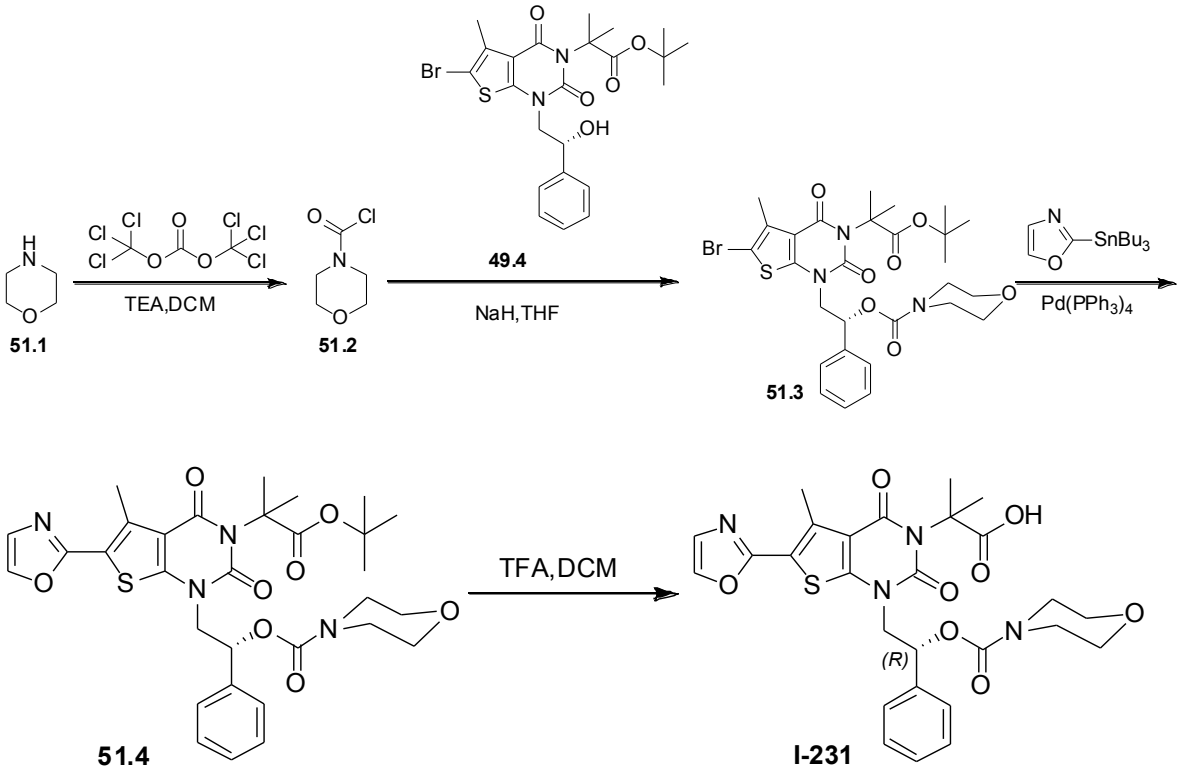
Síntesis del compuesto 50.7. En un matraz de fondo redondo de 50 ml purgado con nitrógeno se colocan 10 ml de

tolueno, 50.6 (310 mg, 0.42 mmol, 1.00 equivalentes), $Pd(PPh_3)_4$ (97 mg, 0.08 mmol, 0.20 equivalentes) y 2-(tributilestanil)-1,3-oxazol (181 mg, 0.51 mmol, 1.20 equivalentes). La solución resultante se calienta a reflujo durante la noche en un baño de aceite. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo(1:10). La purificación proporciona 0.190 g (62%) de 50.7 como un sólido blanco.

Síntesis of Compound I-230. En un matraz de fondo redondo de 50 ml se colocan 20 ml de diclorometano, 50.7 (190 mg, 0.26 mmol, 1.00 equivalentes) y 4 ml de ácido trifluoroacético. La solución resultante se agita durante 4 h a temperatura ambiente, después de lo cual se concentra bajo vacío. El residuo se disuelve en 5 ml de metanol. El valor de pH de la solución se ajusta a 10 con carbonato de potasio. La mezcla resultante se concentra bajo vacío. Se purifican 150 mg del producto crudo por *HPLC* preparativa bajo las siguientes condiciones (Waters): columna: XBridge Prep C18 OBD, 5 µm, 19*150 mm; fase móvil: agua ($NH4HCO_3$ 50 mM) y CH_3CN (CH_3CN 5% hasta 23% en 3 min, se mantiene en 23% durante 11.5 min, después aumenta hasta 95% en 2 min, después disminuye a 5% en 2 min); detector: UV 254/220 nm. Se obtienen 56.5 mg (39.5%) de I-230 como un sólido blanco. EM (ES): *m/z* 555 $(M+H)^+$. RMN ^1H (300MHz, CD_3OD): δ 1.72-1.75 (d, 6H), 2.79 (s, 3H), 3.37-3.80

(m, 2H), 3.97-4.41 (m, 4H), 6.05-6.09 (m, 1H), 7.24 (s, 1H), 7.29-7.46 (m, 5H), 7.95 (s, 1H).

Ejemplo 51: Síntesis del ácido 2-metil-2-[5-metil-1-[(2R)-2-[(morfolin-4-il)carboniloxi]-2-feniletil]-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-231).

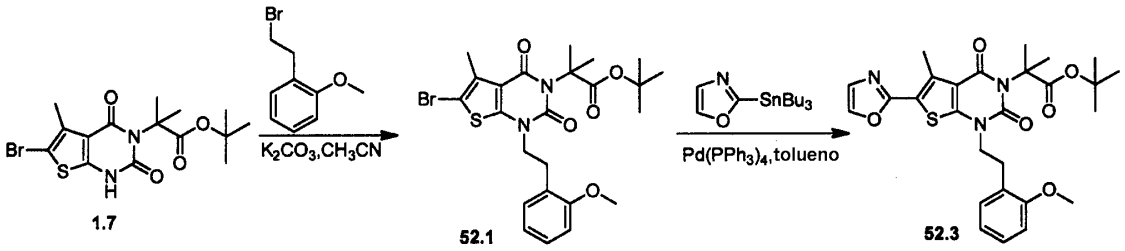


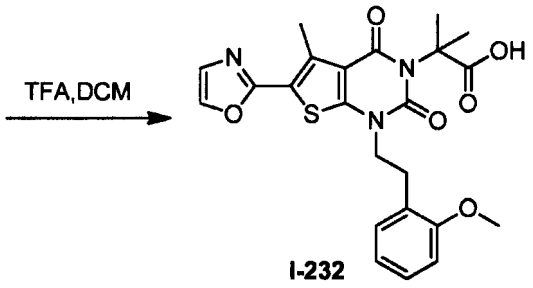
Síntesis del compuesto 51.2. En un matraz de fondo redondo de 500 ml se coloca carbonato de ditriclorometilo (10.2 g, 34.37 mmol, 1.50 equivalentes) y 100 ml de diclorometano (100 ml). Esto es seguido por la adición de morfolina (2 g, 22.96 mmol, 1.00 equivalentes) a gotas con agitación a 0°C en 2 min. A esto se agrega TEA (4.2 g, 41.51 mmol, 1.81 equivalentes) a gotas con agitación a 0°C en

3 min. La solución resultante se agita durante 3 h a temperatura ambiente. La reacción después se lava por adición de 100 ml de agua. La mezcla se seca sobre sulfato de sodio anhidro. Los sólidos se separan por filtración. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo(1:10). La purificación proporciona 2.238 g (65%) de cloruro de morfolin-4-carbonilo como un aceite amarillo claro.

Síntesis del compuesto I-231. El compuesto I-231 se prepara a partir de 51.3 y 2-(tributilestanil)-1,3-oxazol de una manera análoga a I-333 (ejemplo 9). Se aísla un sólido blanco con un rendimiento total de 9%. EM (ES): *m/z* 569 $(M+H)^+$. RMN ^1H (400 MHz , CD_3OD): δ 1.84 (d, *J* = 6 Hz), 2.87 (s, 3H), 3.15-3.64 (m, 8H), 4.11-4.17 (m, 1H), 4.41-4.45 (m, 1H), 6.27-6.30 (m, 1H), 7.32 (s, 1H), 7.38-7.52 (m, 5H), 8.03 (s, 1H).

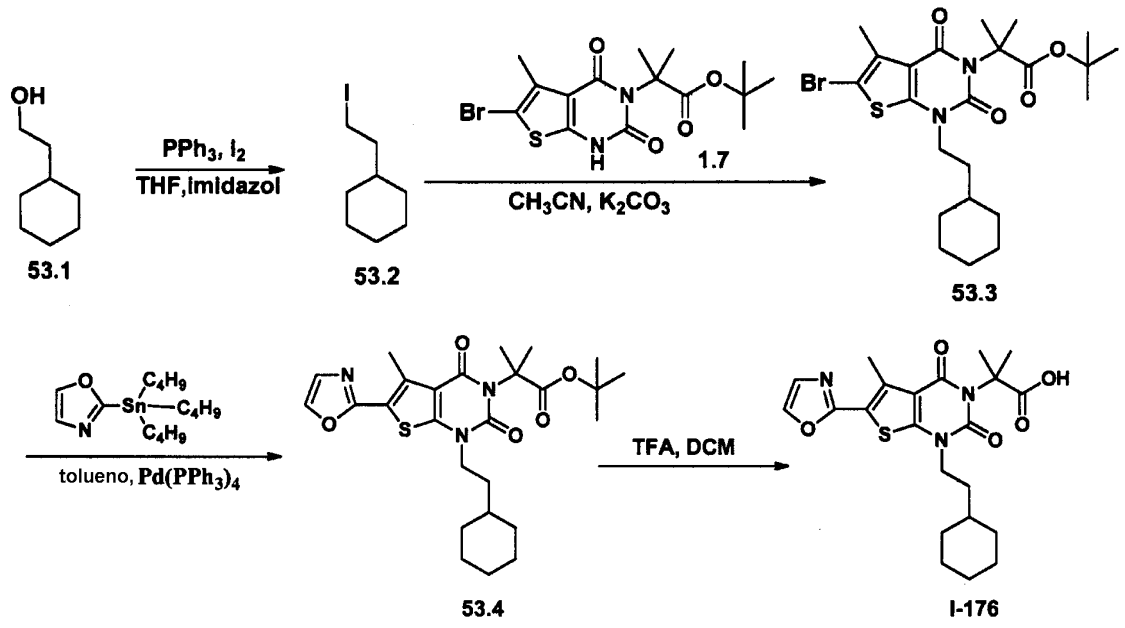
Ejemplo 52: Síntesis del ácido 2-[1-[2-(2-metoxifenil)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-232).





Se prepara el compuesto I-232 de una manera análoga a I-133 (ejemplo 9). Se aísla un sólido blanco con un rendimiento total de 33% a partir de 1.7. EM (ES): *m/z* 470 $(M+H)^+$. RMN ^1H (400 MHz, CD_3OD): δ 1.79 (s, 6H), 2.78(s, 3H), 3.11-3.16 (t, 2H), 3.84 (s, 1H), 4.16-4.19 (t, *J* = 6.8 Hz, 2H), 6.83-6.89 (m, 2H), 6.71-6.27 (m, 2H), 7.27 (s, 1H), 7.97 (s, 1H).

Ejemplo 53: Síntesis del ácido 2-[1-(2-ciclohexiletil)-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoio (I-176).

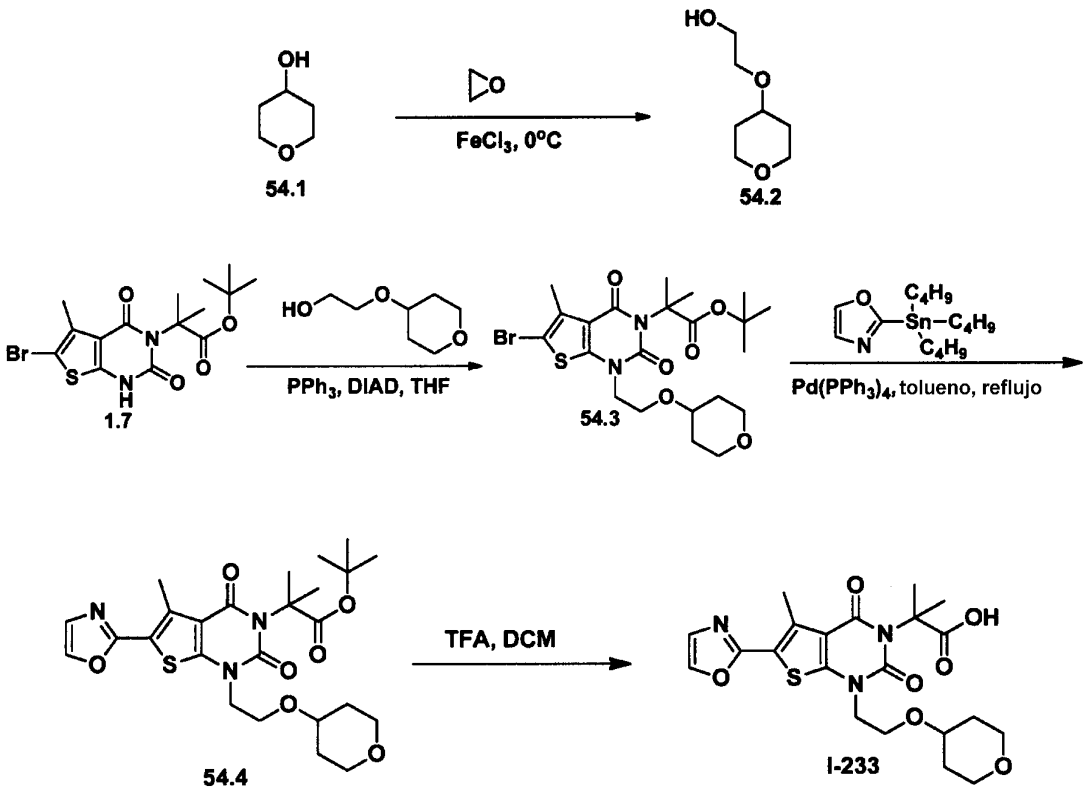


Síntesis del compuesto 53.2. En un matraz de fondo redondo de 3 cuellos de 250 ml se coloca 2-ciclohexiletan-1-ol (3 g, 23.40 mmol, 1.00 equivalentes), imidazol (2 g, 29.41 mmol, 1.26 equivalentes), PPh_3 (8 g, 30.50 mmol, 1.30 equivalentes), 60 ml de tetrahidrofurano e I_2 (7.7 g, 30.31 mmol, 1.30 equivalentes). La solución resultante se agita durante 4 h a temperatura ambiente. La reacción después se suspende por la adición de 100 ml de bicarbonato de sodio saturado. La solución resultante se extrae con 2 x 100 ml de acetato de etilo y las capas orgánicas se combinan y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con éter de petróleo. La purificación proporciona 4.4 g (79%) de (2-yodoetil)ciclohexano como un aceite incoloro.

Síntesis del compuesto I-176. El compuesto I-176 se sintetiza de una manera análoga a I-133, ejemplo 9. Se aísla un sólido blanco con un rendimiento total de 34% a partir de 1.7. EM (ES): *m/z* 446 $(M+H)^+$. RMN ^1H (DMSO-d_6, 300 MHz): δ 0.94 (m, 2H), 1.27 (m, 5H), 1.63 (m, 12H), 2.73 (s, 3H), 3.85 (t, 2H), 7.36 (s, 1H), 8.19 (s, 1H), 12.34 (s amplio, 1H).

Ejemplo 54: Síntesis del ácido 2-metil-2-[5-metil-1-[2-(oxan-4-iloxi)etil]-6-(1,3-oxazol-2-il)-2,4-dioxo-

1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-233).

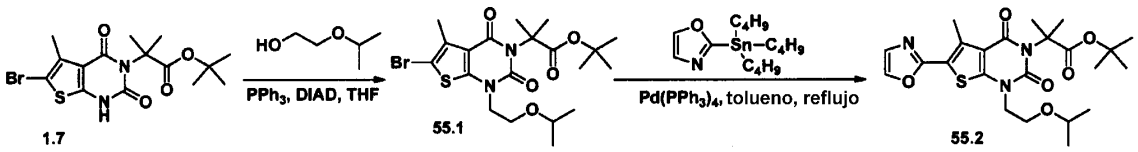


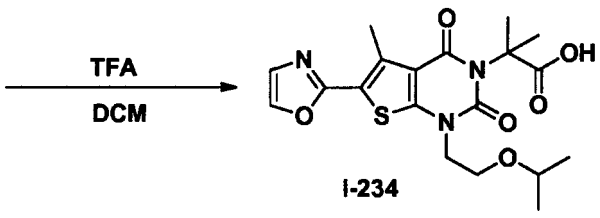
Síntesis del compuesto 54.2. En un matraz de fondo redondo de 3 cuellos de 50 ml se coloca $FeCl_3$ (800 mg, 4.94 mmol, 0.10 equivalentes). Esto es seguido por la adición de oxan-4-ol (5 g, 48.96 mmol, 1.00 equivalentes) a 0°C. A Esto se agrega a gotas 20 ml de oxirano con agitación a 0°C. La solución resultante se agita durante la noche a temperatura ambiente. La reacción después se suspende por la adición de 10 ml de agua. La solución resultante se extrae con 2 x 50 ml de acetato de etilo y las capa orgánicas se combinan. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:30-1:1). La purificación proporciona

2.25 g (crudo) de 2-(oxan-4-iloxi)etan-1-ol (54.2) como un aceite incoloro.

Síntesis del compuesto I-233. El compuesto I-233 se prepara de una manera análoga al compuesto 14.5. Se aísla un sólido blanco con un rendimiento total de 11% a partir de 1.7. Purificación: cromatografía en capa delgada revelada con diclorometano/metanol (30:1:0.15). EM (ES): *m/z* 464 $(M+H)^+$. RMN ^1H (400 MHz, CD_3OD): δ 7.99 (1H, s), 7.29 (1H, s), 4.17-4.15 (2H, t, J = 4.4 Hz), 3.87-3.85 (2H, t, J = 4.4 Hz), 3.79-3.75 (2H, m), 3.61-3.58 (1H, m), 3.50-3.33 (2H, m), 2.82 (3H, s), 1.81 (8H, s), 1.53-1.31 (2H, m).

Ejemplo 55: Síntesis del ácido 2-metil-2-[5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1-[2-(propan-2-iloxi)etil]-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-234).

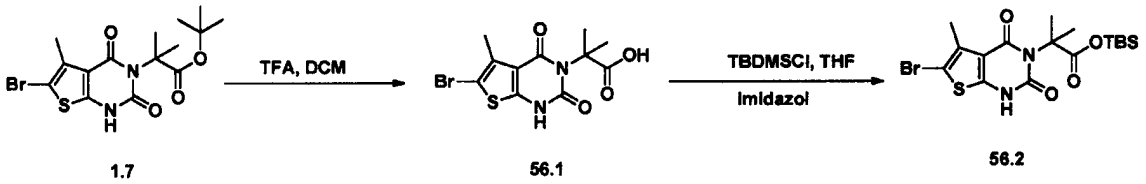




El compuesto I-234 se prepara a partir de 1.7 y 2-(propan-2-iloxi)etan-1-ol de una manera análoga al compuesto 14.5. Se aísla un sólido blanco con un rendimiento total de

12% a partir de 1.7. Purificación: CCD preparativa con diclorometano/metanol (40:1). EM (ES): *m/z* 423 $(M+H)^+$. RMN ^1H (300 MHz, $CDCl_3$): δ 1.09-1.11 (d, 6H), 1.87 (s, 6H), 2.84 (s, 3H), 3.57-3.63 (m, 1H), 3.72-3.76 (t, 2H), 4.03-4.10 (t, 2H), 7.26(s, 1H), 7.68 (s, 1H).

Ejemplo 56: Síntesis del intermediario 56.2.



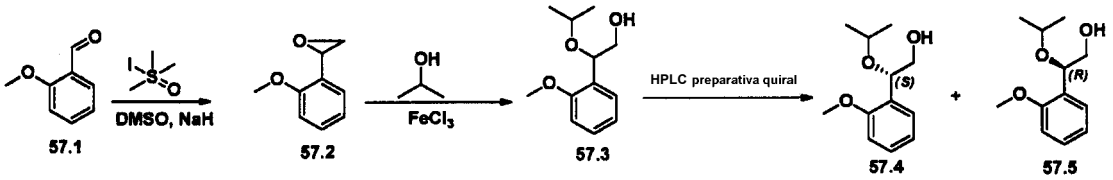
1.7 56.1 56.2

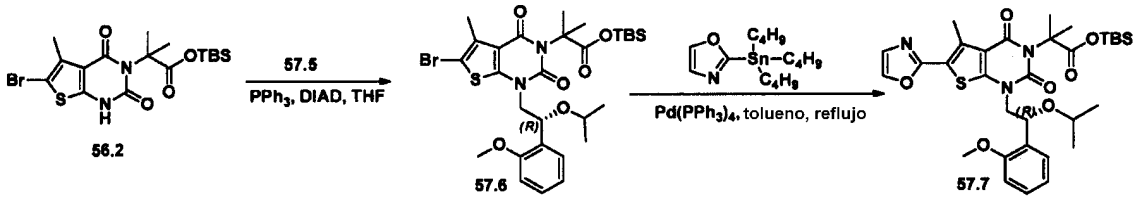
Síntesis del compuesto 56.1. En un matraz de fondo redondo de 250 ml se coloca 1.7 (4 g, 9.92 mmol, 1.00 equivalentes), 100 ml de diclorometano y 20 ml de ácido trifluoroacético. La solución resultante se agita durante la noche a temperatura ambiente. La mezcla se concentra bajo vacío. La purificación proporciona 3.3 g (crudo) de 56.1 como un sólido blanco.

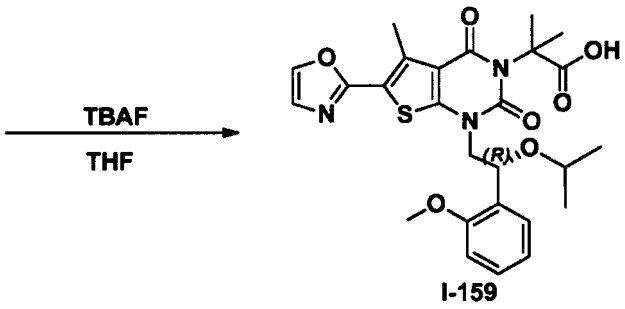
Síntesis del intermediario 56.2. En un matraz de fondo redondo de 250 ml se coloca 56.1 (3.3 g, 9.51 mmol, 1.00 equivalentes), 60 ml de tetrahidrofurano, imidazol (775 mg, 10.37 mmol, 1.2 equivalentes) y TBDMSCl (1.7 g, 11.26 mmol, 1.18 equivalentes). La solución resultante se agita durante 3 h a temperatura ambiente. Los sólidos se separan por filtración. El filtrado se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice y se eluye con PE/EA

(10/1) para proporcionar 3.9 g (89%) de 56.2 como un sólido blanco.

Ejemplo 57: Síntesis del ácido 2-[1-[(2R)-2-(2-metoxifenil)-2-(propan-2-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-159).







Síntesis del compuesto 57.2. En un matraz de fondo redondo de 3 cuellos de 1000 ml se colocan 400 ml de DMSO e hidruro de sodio (7 g, 175.00 mmol, 1.19 equivalentes, 60%). Esto es seguido por la adición de yoduro de S,S-dimetilmetansulfinilo (38 g, 172.67 mmol, 1.18 equivalentes).

La mezcla se agita durante 1 h a 40°C. A esto se agrega una solución de 2-metoxibenzaldehído (20 g, 146.90 mmol, 1.00 equivalentes) en 100 ml de DMSO a gotas con agitación a 15°C. La solución resultante se agita durante 1 h a temperatura ambiente. La reacción después se suspende por la adición de 400 ml de NH_4Cl acuoso. La solución resultante se extrae con 1000 ml de acetato de etilo y las capas orgánicas se combinan. La mezcla resultante se lava con 1000 ml de H_2O. La mezcla se seca sobre sulfato de sodio anhidro y se concentra bajo vacío. La purificación proporciona 14 g (63%) de 2-(2-metoxifenil)oxirano como un aceite amarillo.

Síntesis del compuesto 57.3. Se prepara 57.3 utilizando el mismo método que para la preparación de 54.2. Se aísla un sólido blanco con un rendimiento de 33%.

Síntesis del compuesto 57.5. Los enantiómeros de 57.3 (8.5 g) se separan por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): columna: Venusil Chiral OD-H, 21.1*25 cm, 5 µm; fase móvil: hexanos y etanol grado *HPLC* (que se mantiene en etanol 5% durante 12 min); detector: UV 220/254 nm. Se obtienen 3.3 g de 57.5 (tR = 8 min).

Síntesis del compuesto 57.6. En un matraz de fondo redondo de 3 cuellos de 500 ml se coloca 56.2 (3 g, 6.50 mmol, 1.00 equivalentes), 57.5 (2.73 g, 12.98 mmol, 2.00 equivalentes), 150 ml de tetrahidrofurano y DIAD (1.97 g, 9.74

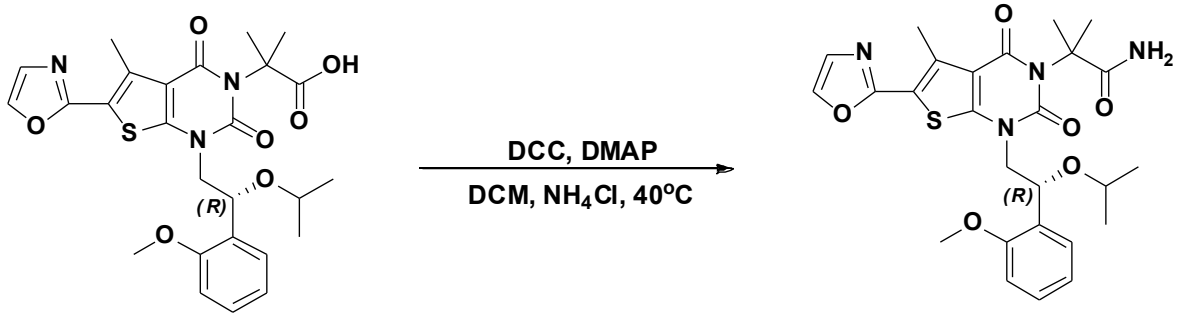
mmol, 1.50 equivalentes). Esto es seguido por la adición de una solución de PPh_3 (2.55 g, 9.72 mmol, 1.50 equivalentes) en 50 ml de tetrahidrofurano a gotas con agitación a 0°C. La solución resultante se agita durante la noche a temperatura ambiente y después se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo(1:50). La purificación proporciona 4.2 g (crudo) de 57.6 como un sólido amarillo.

Síntesis del compuesto 57.7. En un matraz de fondo redondo de 3 cuellos de 500 ml, purgado y mantenido en una atmósfera inerte de nitrógeno se coloca 57.6 (4.2 g, 6.42 mmol, 1.00 equivalentes), 100 ml de tolueno, 2-(tributilestanil)-1,3-oxazol (3.44 g, 9.61 mmol, 1.50 equivalentes) y $Pd(PPh_3)_4$ (740 mg, 0.64 mmol, 0.10 equivalentes). La solución resultante se agita durante la noche a 110°C en un baño de aceite. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo(1:25). La purificación proporciona 1.15 g (impuro) de 57.7 como un sólido amarillo.

Síntesis del compuesto I-159. En un matraz de fondo redondo de 100 ml se coloca 57.7 (1.15 g, 1.79 mmol, 1.00 equivalentes), 20 ml de tetrahidrofurano y $TBAF{\cdot}3H_2O$ (306 mg, 0.97 mmol, 0.54 equivalentes). La solución resultante se agita durante 15 min a temperatura ambiente y después se

concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:2). La purificación proporciona 583 mg (62%) del compuesto I-159 como un sólido blanco. EM (ES): *m/z* 528 $(M+H)^+$, 550 $(M+Na)^+$, 591 $(M+Na+CH_3CN)^+$. RMN ^1H (300 MHz, CD_3OD): δ 0.98 (d, 3H), 1.01 (d, 3H), 1.72 (s, 3H), 1.76 (s, 3H), 1.77 (s, 3H), 3.47 (m, 1H), 3.78 (s, 3H), 4.04 (m, 2H) , 4.84 (m, 1H), 6.95-7.93 (m, 6H).

Ejemplo 58: Síntesis de 2-[1-[(2R)-2-(2-metoxifenil)-2-(propan-2-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanamida (I-174).

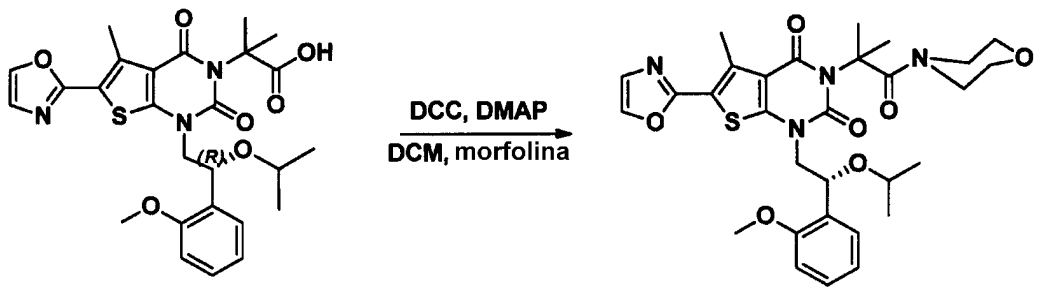


I-158 **I-174**

El compuesto I-174 se prepara a partir del compuesto I-158 utilizando el método del ejemplo 4. Purificación: cromatografía en capa delgada revelada con diclorometano/metanol (20:1). Se aísla un sólido blanco con un rendimiento de 52%. EM (ES): *m/z* 527 $(M+H)^+$, 549 $(M+Na)^+$. RMN ^1H (300 MH_Z, CD_3OD): δ 1.07 (m, 6H), 1.76-1.77 (d, 6H), 2.75

(s, 3H), 3.41-3.51 (m, 1H), 3.77 (s, 3H), 3.97-4.12 (m, 2H), 5.28-5.33 (m, 1H) , 6.85-6.88 (d, 1H), 6.94-6.99 (t, 1H), 7.19-7.24 (m, 2H), 7.47-7.50 (d, 1H), 7.93 (s, 1H).

Ejemplo 59: Síntesis de 1-[(2R)-2-(2-metoxifenil)-2-(propan-2-iloxi)etil]-5-metil-3-[2-metil-1-(morfolin-4-il)-1-oxopropan-2-il]-6-(1,3-oxazol-2-il)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-2,4-diona (I-235).



I-158 I-235

El compuesto I-235 se prepara a partir del compuesto I-158 y morfolina utilizando el método del ejemplo 4. Purificación: *HPLC* preparativa (Waters) bajo las siguientes condiciones: columna: XBridge Prep Fenil OBD, 5 µm, 19*150 mm; fase móvil, agua (NH_4HCO_3 50 mM) y CH_3CN (CH_3CN 5.0% hasta 95.0% en 10 min, se mantiene en 95.0% en 2 min, disminuye a 5.0% en 2 min); detector: UV 254, 220 nm. Se obtienen 34.2 mg (60%) del compuesto I-235. RMN ^1H (400 MHz, CD_3OD): δ 1.03-1.08 (m, 6H), 1.77 (s, 6H), 2.82 (s, 3H), 3.44-3.66 (m, 9H), 3.85 (s, 3H), 4.08-4.24 (m, 2H), 5.38 (m, 1H), 6.89-7.03 (m, 2H) , 7.29 (m, 2H), 7.51 (m,1H), 7.99 (s, 1H). EM (ES): *m/z* 619 $(M+Na)^+$.

Ejemplo 60: Síntesis de N-etil-2-[1-[(2R)-2-(2-metoxifenil)-2-(propan-2-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanamida (I-236).

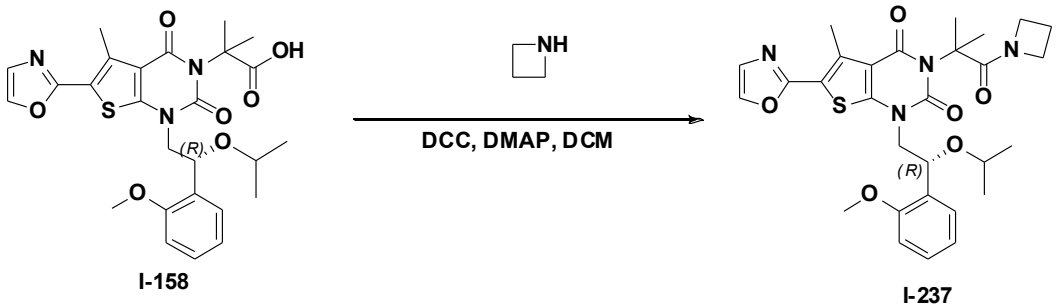


I-158 I-236

Se prepara el compuesto I-236 a partir del compuesto I-158 y clorhidrato de etilamina utilizando el método del ejemplo 4. Purificación: *HPLC* preparativa (Waters) bajo las siguientes condiciones: columna: XBridge Prep Fenil OBD, 5 µm, 19*150 mm; fase móvil, agua ($NH_4HCO_3$50 mM) y CH_3CN (CH_3CN 5.0% hasta 95.0% en 10 min, se mantiene 95.0% en 2 min, disminuye a 5.0% en 2 min); detector: UV 254, 220 nm. EM (ES): *m/z* 577 $(M+Na)^+$. RMN ^1H (400 MHz, CD_3OD): δ 1.13-1.15 (m, 9H), 1.77 (d, 6H), 2.79 (s, 3H), 3.26 (m, 2H), 3.52 (m, 1H), 3.81 (s, 3H), 4.10 (m, 2H), 5.34 (m, 1H), 6.89-7.01 (m, 2H), 7.29 (m, 2H), 7.51 (m, 1H), 7.97 (s, 1H).

Ejemplo 61: Síntesis de 3-[1-(azetidin-1-il)-2-metil-1-oxopropan-2-il]-1-[(2R)-2-(2-metoxifenil)-2-(propan-2-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-1H,2H,3H,4H-tieno[2,3-

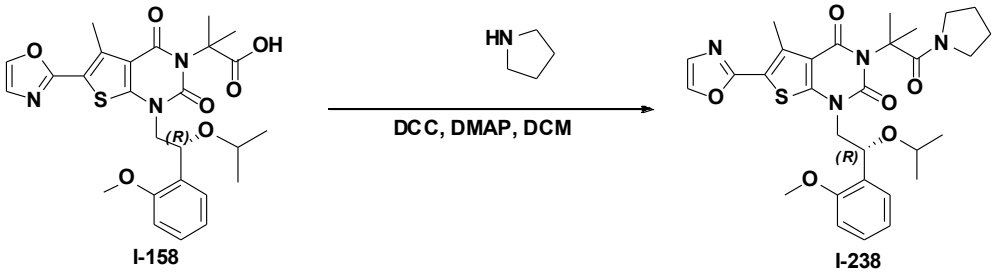
d]pirimidin-2,4-diona (I-237).



I-158 I-237

El compuesto I-237 se prepara a partir del compuesto I-158 y azetidina utilizando el método del ejemplo 4. Purificación: la mezcla de reacción se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con diclorometano/metanol (40:1). La purificación proporciona 38.3 mg (48%) del compuesto I-237 como un sólido blanco. EM (ES): *m/z* 568 $(M+H)^+$, 589 $(M+Na)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.05 (t, 6H), 1.76 (s, 6H), 2.19-2.27 (m, 2H), 2.83 (s, 3H), 3.41-3.55 (m, 1H), 3.85 (s, 3H), 4.06-4.17 (m, 6H), 5.35-5.39 (t, 1H), 6.94-7.04 (m, 2H), 7.26-7.32 (m, 2H), 7.50-7.51 (d, 1H), 7.99 (s, 1H).

Ejemplo 62: Síntesis de 1-[(2R)-2-(2-metoxifenil)-2-(propan-2-iloxi)etil]-5-metil-3-[2-metil-1-oxo-1-(pirrolidin-1-il)propan-2-il]-6-(1,3-oxazol-2-il)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-2,4-diona (I-238).

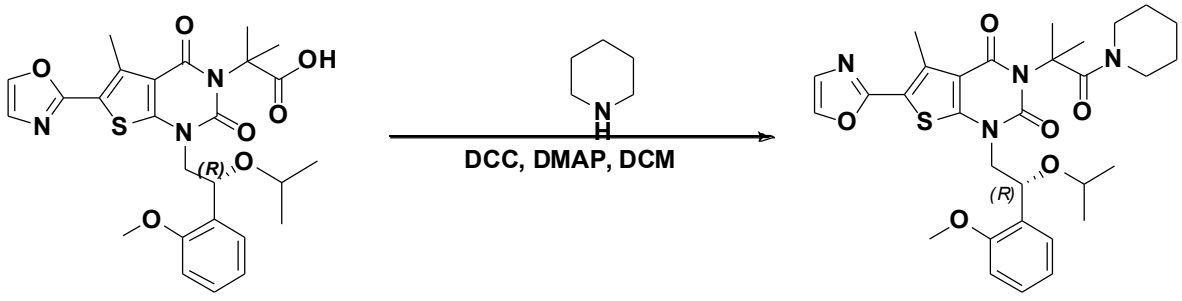


I-158 I-238

El compuesto I-238 se prepara a partir del compuesto

I-158 y pirrolidina utilizando el método del ejemplo 4. Purificación: la mezcla de reacción se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con diclorometano/metanol (40:1). La purificación proporciona 41.6 mg (50%) del compuesto I-238 como un sólido blanco. EM (ES): *m/z* 603 $(M+Na)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.03-1.07 (m, 6H), 1.77-1.82 (m, 10H), 2.80 (s, 3H), 3.09-3.15 (m, 2H), 3.46-3.56 (m, 3H), 3.86 (s, 3H), 4.15 (s amplio, 2H), 5.35-5.39 (t, 1H), 6.95-7.04 (m, 2H), 7.26-7.32 (m, 2H), 7.50-7.52 (d, 1H), 7.99 (s, 1H).

Ejemplo 63: Síntesis de 1-[(2R)-2-(2-metoxifenil)-2-(propan-2-iloxi)etil]-5-metil-3-[2-metil-1-oxo-1-(piperidin-1-il)propan-2-il]-6-(1,3-oxazol-2-il)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-2,4-diona (I-239).



I-158 I-239

El compuesto I-239 se prepara a partir del compuesto I-158 y piperidina utilizando el método del ejemplo 4. Purificación: La mezcla de reacción se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con diclorometano/metanol (40:1). La purificación proporciona 41.6

mg (49%) del compuesto I-239 como un sólido blanco. EM (ES): *m/z* 617 $(M+Na)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.02 (m, 6H), 1.29-1.41 (m, 2H), 1.41-1.95 (m, 10H), 2.81 (s, 3H), 3.45-3.61 (m, 3H), 3.87 (s, 3H), 4.10-4.24 (m, 1H), 5.38-5.39 (m, 1H) , 6.95-7.04 (m, 2H), 7.27-7.32 (m, 2H), 7.43-7.65 (m, 1H), 8.03 (s, 1H).

Ejemplo 64: Síntesis de N-metansulfonil-2-[1-[(2R)-2-(2-metoxifenil)-2-(propan-2-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanamida (I-240).

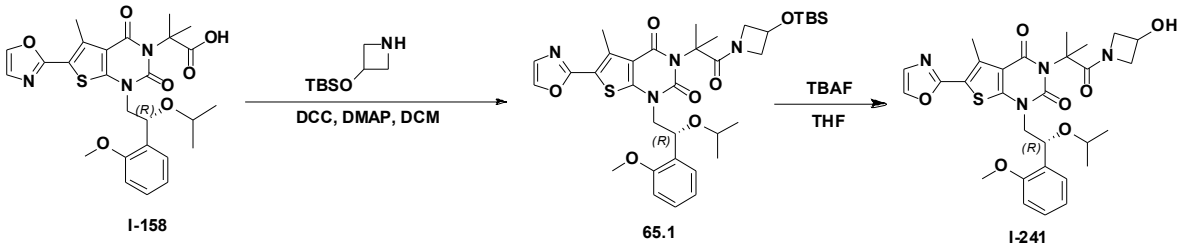


I-158 I-240

El compuesto I-240 se prepara a partir del compuesto I-158 y metansulfonamida utilizando el método del ejemplo 4. Purificación: La mezcla de reacción se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con diclorometano/metanol (40:1). La purificación proporciona 13.6 mg (16%) del compuesto I-240 como un sólido blanco. EM (ES): *m/z* 605 $(M+H)^+$, 627 $(M+Na)^+$. RMN ^1H (300 MHz, CD_3OD): δ 0.80-0.94 (m, 6H), 1.67-1.68 (d, 6H), 2.75 (s, 3H), 3.15 (s, 3H), 3.35-3.43 (m, 1H), 3.70 (s, 3H), 3.97-3.99 (m, 1H), 5.20-5.26

(m, 1H), 6.79-6.82 (d, 1H), 6.88-6.93 (t, 1H), 7.13-7.17 (m, 2H), 7.41-7.43 (d, 2H), 7.87(s, 1H).

Ejemplo 65: 3-[1-(3-hidroxiazetidin-1-il)-2-metil-1-oxopropan-2-il]-1-[(2R)-2-(2-metoxifenil)-2-(propan-2-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-2,4-diona (I-241).

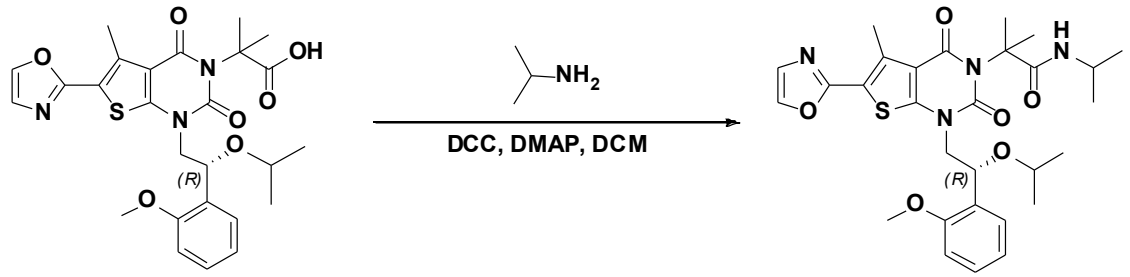


Síntesis del compuesto 65.1. El compuesto 65.1 se prepara a partir del compuesto I-158 y 3-[(terbutildimetilsilil)oxi]azetidina utilizando el método del ejemplo 4, excepto que la fuente de calor es irradiación por microondas a 50°C. Purificación: la mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:2). La purificación proporciona 100 mg (50%) del compuesto 65.1 como un sólido blanco.

Síntesis del compuesto I-241. En un matraz de fondo redondo de 50 ml se coloca 65.1 (100 mg, 0.14 mmol, 1.00 equivalentes), 10 ml de oxolano y TBAF (37.4 mg, 0.14 mmol, 1.00 equivalentes). La solución resultante se agita durante 2 h a temperatura ambiente y después se concentra bajo

vacío. El residuo se aplica sobre una columna de gel de sílice con diclorometano/metanol (30:1). La purificación proporciona 53.6 mg (64%) del compuesto I-241 como un sólido blanco. EM (ES): *m/z* 605 $(M+Na)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.03-1.07 (m, 6H), 1.74-1.75 (d, 6H), 2.83 (s, 3H), 3.47-3.55 (m, 1H), 3.76-3.80 (m, 2H), 3.85 (s, 3H), 4.16-4.24 (m, 4H), 4.47-4.55 (m, 1H), 5.35-5.39 (t, 1H), 6.94-7.04 (m, 2H), 7.26-7.32 (m, 2H), 7.50-7.53 (d, 1H), 7.99 (s, 1H).

Ejemplo 66: Síntesis de 2-[1-[(2R)-2-(2-metoxifenil)-2-(propan-2-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metil-N-(propan-2-il)propanamida (I-242).

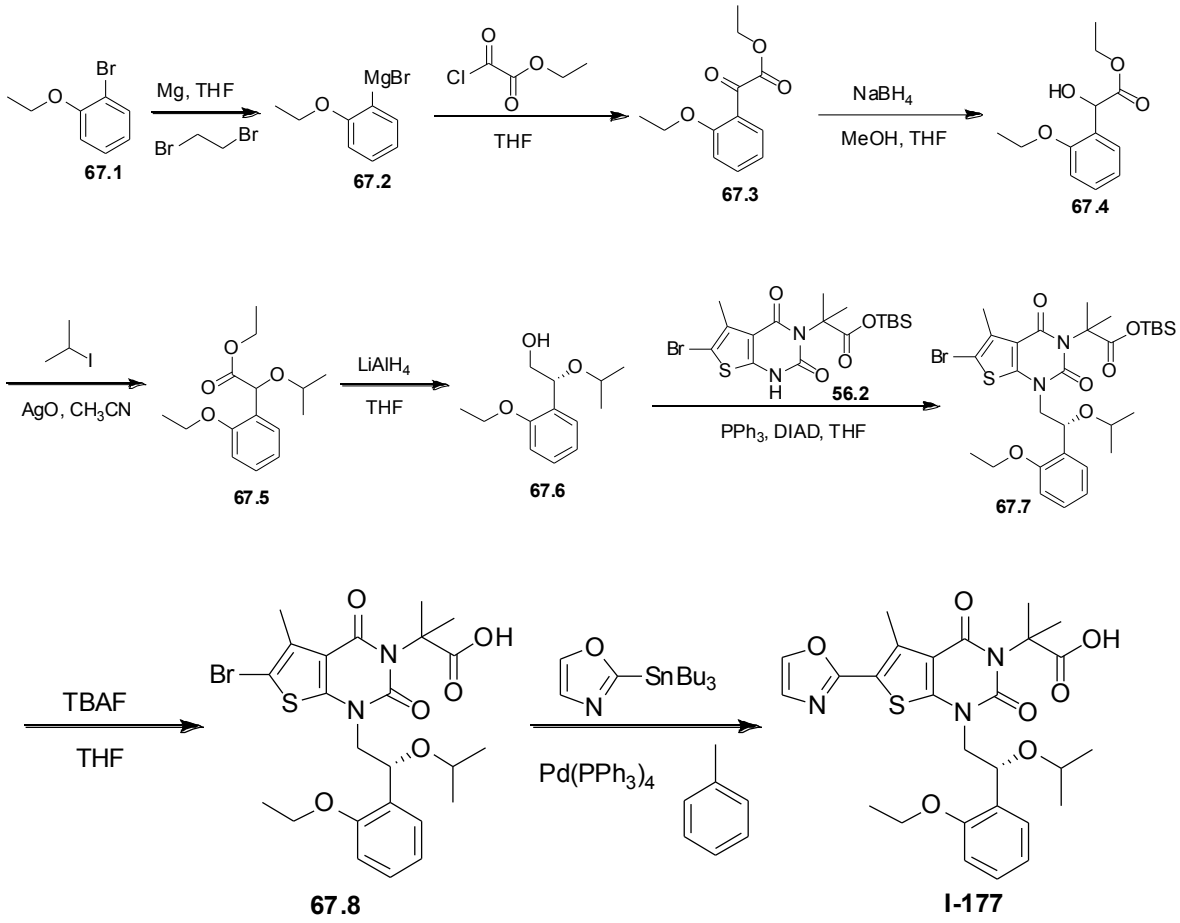


I-158 I-242

El compuesto I-242 se prepara a partir del compuesto I-158 y propan-2-amina utilizando el ejemplo 4. Purificación: la mezcla de reacción de concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con diclorometano/metanol (40:1). La purificación proporciona 31.5 mg (39%) del compuesto I-242 como un sólido blanco. EM (ES): *m/z* 591 $(M+Na)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.03-1.07 (m, 6H), 1.10-1.20 (m, 6H), 1.77-1.83 (d, 6H), 2.85 (s, 3H), 3.46-3.56

(m, 1H), 3.81 (s, 3H), 3.97-4.10 (m, 3H), 5.33-5.38 (t, 1H), 6.89-6.92 (d, 1H), 6.99-7.04 (t, 1H), 7.23-7.32 (m, 2H), 7.52-7.55 (m, 1H), 7.98 (s, 1H).

Ejemplo 67: Síntesis del ácido 2-[1-[(2R)-2-(2-etoxifenil)-2-(propan-2-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-177).



Síntesis del compuesto 67.2. En un matraz de fondo redondo de 3 cuellos de 100 ml se coloca Mg (1.55 g) y 10 ml de tetrahidrofurano. Después se agrega para iniciar la

reacción 1 g de 1-bromo-2-etoxibenceno y 1,2-dibromoetano (100 mg, 0.53 mmol, 0.01 equivalentes). Después se agrega a gotas un segundo lote de 9 g de 1-bromo-2-etoxibenceno disuelto en 40 ml de TF. La solución resultante se agita durante 2 h a temperatura ambiente. La mezcla se utiliza directamente en la siguiente etapa.

Síntesis del compuesto 67.3. En un matraz de fondo redondo de 3 cuellos de 100 ml se colocan 20 ml de tetrahidrofurano y 2-cloro-2-oxoacetato de etilo (17 g, 124.51 mmol, 2.51 equivalentes). Esto es seguido por la adición de bromo(2-etoxifenil)magnesio (20 ml, 1.00 equivalentes) a gotas con agitación a -80°C. La solución resultante se agita durante 30 min a -80°C. La reacción después se suspende por la adición de 50 ml de agua. La solución resultante se extrae con 3 x 100 ml de acetato de etilo y las capas orgánicas se combinan y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:20). La purificación proporciona 8.5 g (77%) de 67.3 como un aceite incoloro.

Síntesis del compuesto 67.4. En un matraz de fondo redondo de 3 cuellos de 100 ml se colocan 10 ml de metanol, 2-(2-etoxifenil)-2-oxoacetato de etilo (8.5 g, 38.25 mmol, 1.00 equivalentes) y 50 ml de tetrahidrofurano. Esto es seguido por la adición de $NaBH_4$ (730 mg, 19.30 mmol, 0.50 equivalentes), en porciones, a 0°C. La solución resultante se agita durante

30 min a temperatura ambiente. La reacción después se suspende por la adición de 50 ml de agua. La solución resultante se extrae con 3 x 100 ml de acetato de etilo y las capas orgánicas se combinan y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:20). La purificación proporciona 7.1 g (83%) de 67.4 como u aceite incoloro.

Síntesis del compuesto 67.5. En un matraz de fondo redondo de 250 ml se coloca 2-(2-etoxifenil)-2-hidroxiacetato de etilo (7.1 g, 31.66 mmol, 1.00 equivalentes), 50 ml de CH_3CN, 22.1 g de Ag_2O y 2-yodopropano (27 g, 158.83 mmol, 5.02 equivalentes). La solución resultante se agita durante la noche a 40°C. Los sólidos se separan por filtración. El filtrado se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:100). La purificación proporciona 1.3 g (15%) de 67.5 como un aceite incoloro.

Síntesis del compuesto 67.6. En un matraz de fondo redondo de 3 cuellos de 50 ml se colocan 20 ml de tetrahidrofurano y 67.5 (1.3 g, 4.88 mmol, 1.00 equivalentes). Después se agrega $LiAlH_4$ (186 mg, 4.90 mmol, 1.00 equivalentes) a 0°C. La solución resultante se agita durante 30 min a 0°C. La reacción después se suspende por la adición de 20 ml de NH_4Cl acuoso. La solución resultante se extrae con 3 x 100 ml de acetato de etilo y las capas orgánicas se

combinan y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:20). El producto crudo se purifica por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): columna: Venusil Chiral OD-H, 21.1*25 cm, 5 µm; fase móvil: hexanos y etanol (que se mantiene en etanol 2.0% durante 11 min); detector: UV 220/254 nm. La purificación proporciona 0.35 g (32%) de 67.6 como un sólido amarillo.

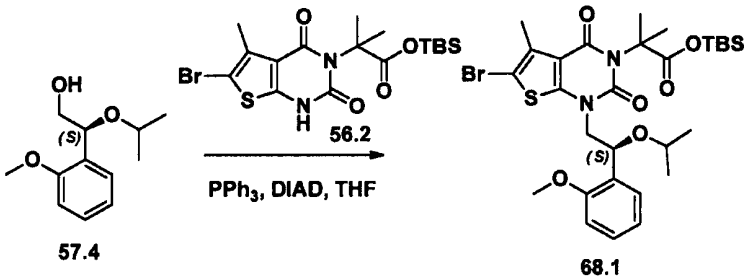
Síntesis del compuesto 67.7. En un matraz de fondo redondo de 50 ml se coloca Ph_3P (545 mg, 2.08 mmol, 2.00 equivalentes), 67.6 (350 mg, 1.56 mmol, 1.50 equivalentes), 10 ml de tetrahidrofurano, 56.2 (480 mg, 1.04 mmol, 1.00 equivalentes) y DIAD (420 mg, 2.08 mmol, 2.00 equivalentes). La solución resultante se agita durante la noche a temperatura ambiente y después se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:50). La purificación proporciona 400 mg (crudo) de 67.7 como un aceite amarillo.

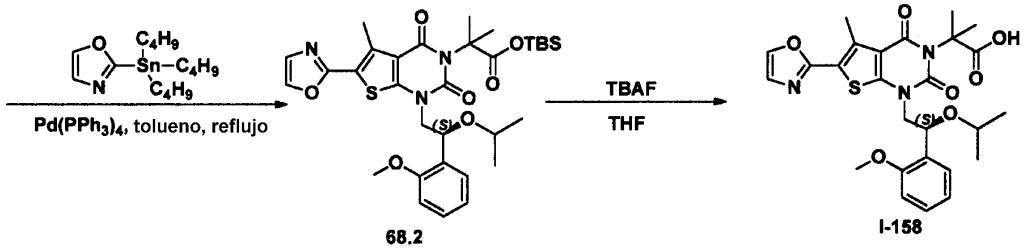
Síntesis del compuesto 67.8. En un matraz de fondo redondo de 50 ml se colocan 5 ml de tetrahidrofurano, 67.7 (400 mg, 0.60 mmol, 1.00 equivalentes) y TBAF (172 mg, 0.66 mmol, 1.10 equivalentes). La solución resultante se agita durante 2 h a temperatura ambiente. La reacción después se suspende por la adición de 0.5 ml de agua. La

mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:10). La purificación proporciona 350 mg (crudo) de 67.8 como un aceite amarillo.

Síntesis del compuesto I-177. El compuesto I-177 se prepara a partir de 67.8 y 2-(tributilestanil)-1,3-oxazol de acuerdo con el método del ejemplo 2. Purificación: El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:10). La purificación proporciona 106.1 mg (31%) del compuesto I-177 como un sólido blanco. EM (ES): *m/z* 542 $(M+H)^+$, 564 $(M+Na)^+$. RMN ^1H (400 MHz, CD_3OD): δ 0.99-1.04 (m, 6H), 1.44 (t, *J* = 7.2, 3H), 1.75-1.76 (m, 6H), 2.83 (s, 3H), 3.43-3.51 (m, 1H), 4.05-4.13 (m, 4H), 5.37-5.41 (m, 1H), 6.93 (d, *J* = 8.4, 1H), 7.00 (t, *J* = 7.2, 1H), 7.23-7.28 (m, 2H), 7.53 (d, *J* = 7.6, 1H), 7.97 (s, 1H).

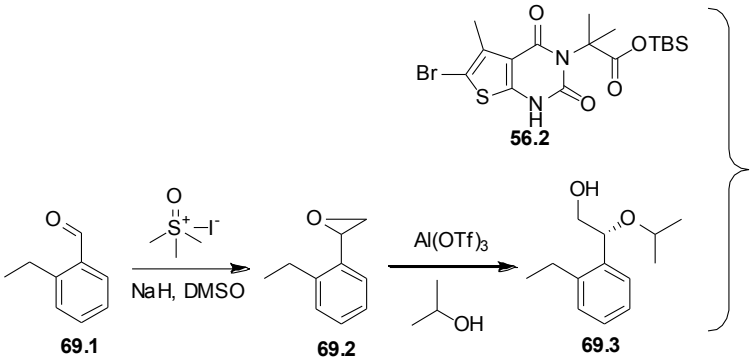
Ejemplo 68: Síntesis del ácido 2-[1-[(2S)-2-(2-metoxifenil)-2-(propan-2-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-158).

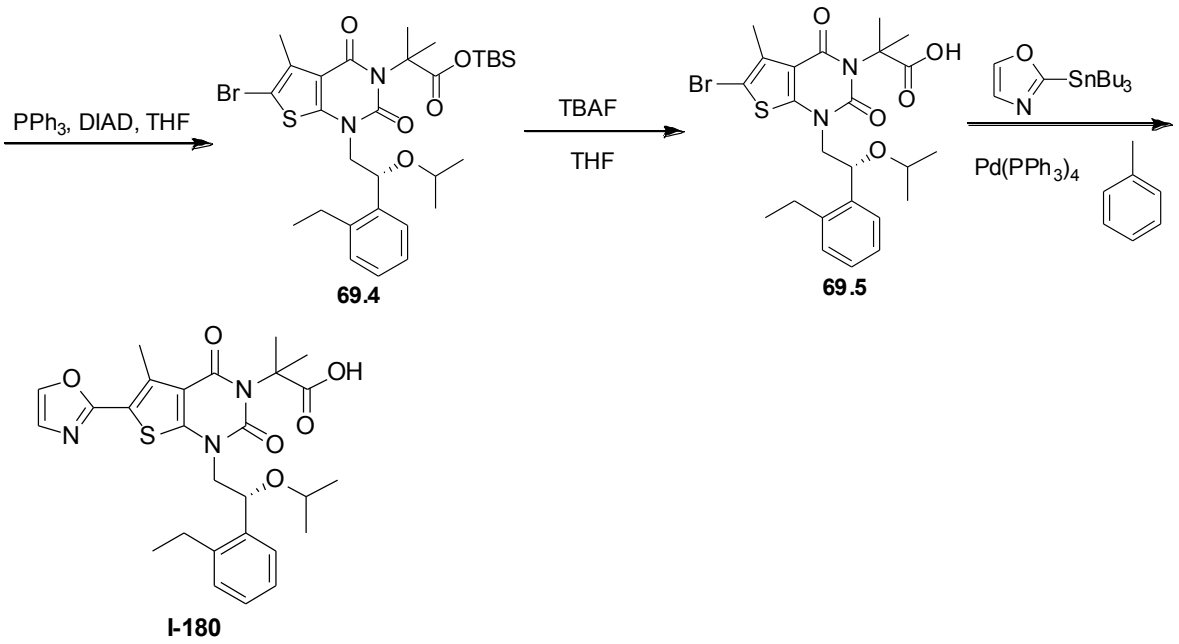




El compuesto I-158 se prepara a partir de 57.4 y el intermediario 56.2 utilizando el mismo procedimiento que para el ejemplo 57. Purificación: columna de gel de sílice con acetato de etilo/éter de petróleo (1:5). Se aíslan 541 mg (20%) del compuesto I-158 como un sólido blanco. EM (ES): *m/z* 528 $(M+H)^+$, 550 $(M+Na)^+$, 591 $(M+Na+CH_3CN)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.02 (d, 3H), 1.05 (d, 3H), 1.76 (s, 3H), 1.81 (s, 3H), 2.80 (s, 3H), 3.46 (m, 1H), 3.83 (s, 3H), 4.09 (m, 2H) , 5.32 (m, 1H), 6.91-7.04 (m, 2H), 7.25 (m, 2H), 7.53 (d, 1H), 7.97 (s, 1H).

Ejemplo 69: Síntesis del ácido 2-[1-[(2R)-2-(2-etilfenil)-2-(propan-2-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-180).





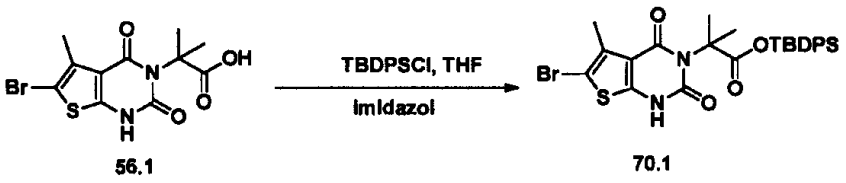
Síntesis del compuesto 69.2. El compuesto 69.2 se prepara a partir de 69.1 utilizando el mismo método que para la síntesis de 57.2. Se aísla un aceite incoloro con un rendimiento cuantitativo.

Síntesis del compuesto 69.3. En un matraz de fondo redondo de 50 ml se coloca $Al(OTf)_3$ (641 mg, 1.35 mmol, 0.05 equivalentes), 20 ml de propan-2-ol y 69.2 (4 g, 26.99 mmol, 1.00 equivalentes). La solución resultante se agita durante 1 h a temperatura ambiente. La reacción después se suspende por la adición de 1 ml de agua. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:100). A partir del racemato purificado se aísla el enantiómero deseado por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson GX 281): columna: Venusil Chiral OD-H, 21.1*25 cm, 5

µm; fase móvil: hexanos (TEA 0.2%) e IPA (que mantiene en IPA 2.0% en 11 min); detector: UV 220/254 nm. El segundo pico para eluir es el que se recolecta. La concentración proporciona 1.2 g (21%) de 69.3 como un aceite amarillo.

Síntesis del compuesto I-180. El compuesto I-180 se prepara de una manera análoga al ejemplo 67. Purificación: columna de gel de sílice con acetato de etilo/éter de petróleo (1:10). Se aíslan 47.8 mg (11% de rendimiento total a partir de 56.2) del compuesto I-180 como un sólido blanco. EM (ES): *m/z* 526 $(M+Na)^+$, 589 $(M+H+CH_3CN)^+$. RMN ^1H (300 MHz, CD_3OD): δ 0.95 (t, *J* = 6.3 Hz, 6H), 1.25 (t, *J* = 7.5Hz, 3H), 1.78-1.80 (m, 6H), 2.68-2.75 (m, 1H), 2.79 (s, 3H), 2.89-2.94 (m, 1H), 3.37-3.45 (m, 1H), 3.65-3.70 (m, 1H), 4.18-4.24 (m, 1H), 5.14-5.18 (m, 1H), 7.19-7.27 (m, 4H), 7.57-7.60 (m, 1H), 7.95 (s, 1H).

Ejemplo 70: Síntesis del intermediario 70.1.

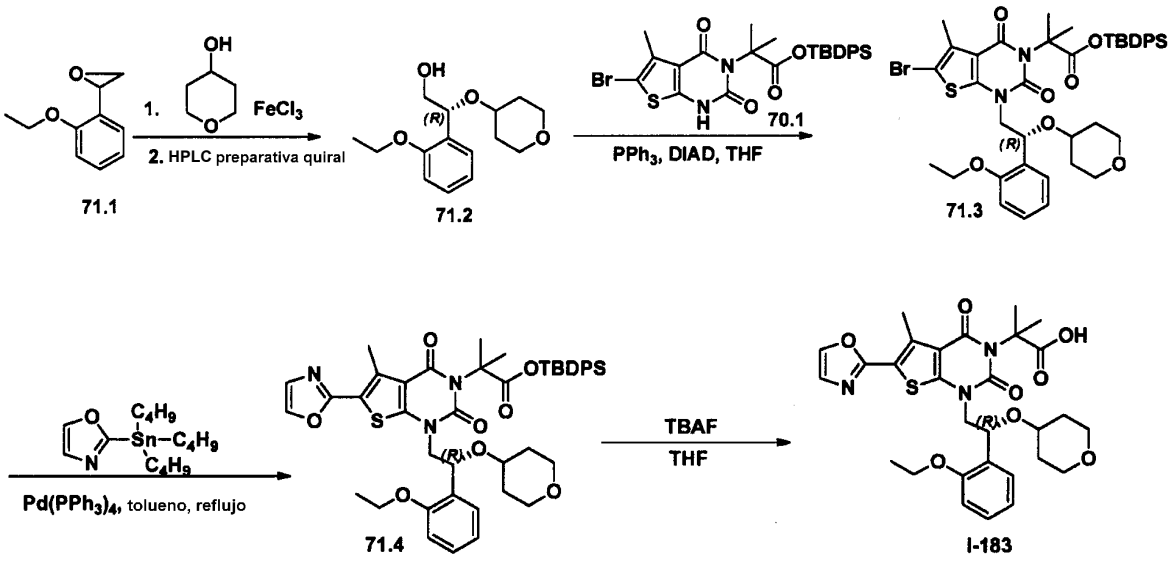


56.1 70.1

El intermediario 70.1 se prepara de una manera análoga al intermediario 56.2. Se aísla un sólido blanco en 84%.

Ejemplo 71: Síntesis del ácido 2-[1-[(2R)-2-(2-etoxifenil)-2-(oxan-4-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-

2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-183).

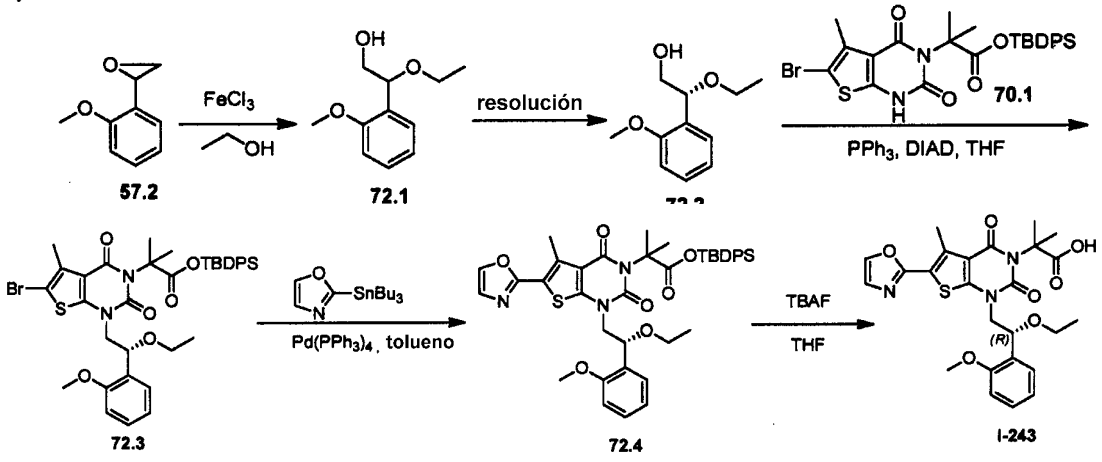


Síntesis del compuesto 71.2. El compuesto 71.2 se sintetiza utilizando el método para la síntesis de 20.1. Purificación: El residuo obtenido después del tratamiento se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:10) para obtener un producto racémico puro. Los enantiómeros después se separan por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): columna: Lichrom OD-H 2*25 cm, 5 µm; fase móvil: hexanos e IPA (que se mantiene en IPA 5% durante 15 min); detector: UV 220/254 nm. Se obtienen 0.870 g (8%) de 71.2 como un aceite incoloro.

Síntesis del compuesto I-183. El compuesto I-183 se prepara siguiendo el mismo procedimiento que para el ejemplo 57. Purificación: El material crudo se aplica sobre una

columna de gel de sílice con acetato de etilo/éter de petróleo (1:2, 0.5%, AcOH). El producto (100 mg) obtenido de esta manera se purifica adicionalmente por *HPLC* preparativa bajo las siguientes condiciones (Waters): columna: XBridge Prep C18 OBD columna, 5 µm, 19*150 mm; fase móvil: agua (con NH_4HCO_3 50 mM) y CH_3CN (CH_3CN 20.0% hasta 50.0% en 10 min, hasta 95.0% en 2 min, disminuye a 20.0% en 2 min); detector: UV 254, 220 nm. La purificación proporciona 0.046 g (12% de 70.1) del compuesto I-183 como un sólido blanco. EM (ES): *m/z* 606 $(M+Na)^+$ 606. RMN ^1H (CD_3OD, 300 MHz): δ 1.41 (m, 5H), 1.73 (m, 8H), 2.77 (s, 3H), 3.34 (m, 2H), 3.41 (m, 1H), 3.50-3.70 (m, 2H), 3.90 (m, 1H), 4.02 (m, 2H), 4.20 (m, 1H), 5.40 (dd, *J* = 4.2 Hz, 9.0 Hz, 1H), 6.95 (m, 2H), 7.23 (m, 2H), 7.49 (dd, *J* = 1.5 Hz, 7.5 Hz, 1H), 7.93 (s, 1H).

Ejemplo 72: Síntesis del ácido 2-[1-[(2R)-2-etoxi-2-(2-metoxifenil)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-243).

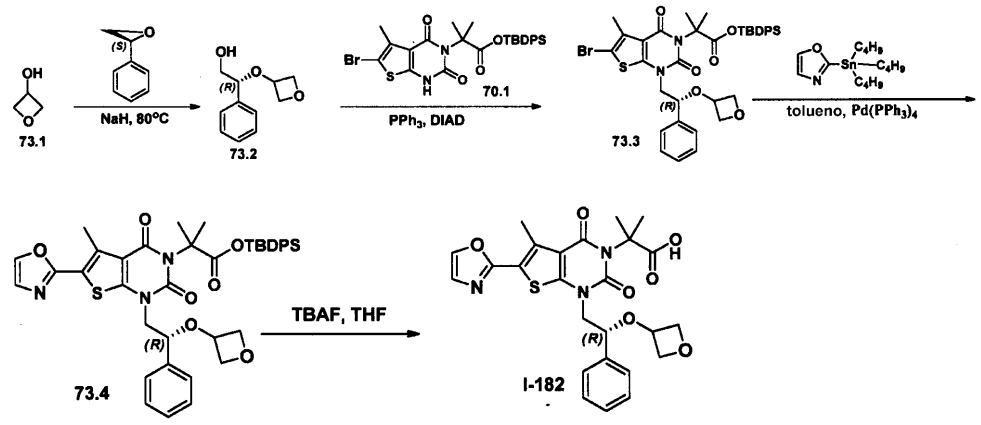


Síntesis del compuesto 72.2. El compuesto 72.2 se prepara de una manera análoga al compuesto 57.5, sustituyendo etanol por isopropanol en la etapa de abertura de epóxido. Purificación: Se purifican 1.5 g del producto crudo por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): Columna: Venusil Chiral OD-H, 21.1 *25 cm, 5 µm; fase móvil: hexanos y etanol (retenida en etanol 5.0% por 12 min); detector: UV 220/254 nm. El segundo pico se recolecta. Se obtienen 0.59 g (36% de 57.2) de 72.2 como un sólido blanco.

Síntesis de compuesto 1-243. Se prepara el compuesto 1-243 de una manera análoga a la síntesis del compuesto 1-158 (Ejemplo 57). Purificación: columna de gel de sílice con diclorometano/metanol (100:1). Se aísla un sólido blanco en 37% de rendimiento total a partir de 70.1. EM (ES): m/z 514 $(M+H)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.13 (t, *J* = 6.9 Hz, 3H), 1.75 (s, 3H), 1.79 (s, 3H), 2.79 (s, 3H), 3.32-3.53 (m, 2H), 3.80 (s, 3H), 4.06-4.10 (m, 1H), 4.21-4.28 (m, 1H), 5.21-5.26 (m, 1 H), 6.91 (d, *J* = 8.4 Hz, 1 H), 7.02 (t, *J* = 7.8, 1 H), 7.24-7.29 (m, 2H), 7.46-7.49 (m, 1 H), 7.97 (s, 1 H).

Ejemplo 73: Síntesis del ácido 2-metil-2-[5-metil-6-(1,3-oxazol-2-il)-1-[(2R)-2-(oxetan-3-iloxi)-

2-feniletil]-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-182).

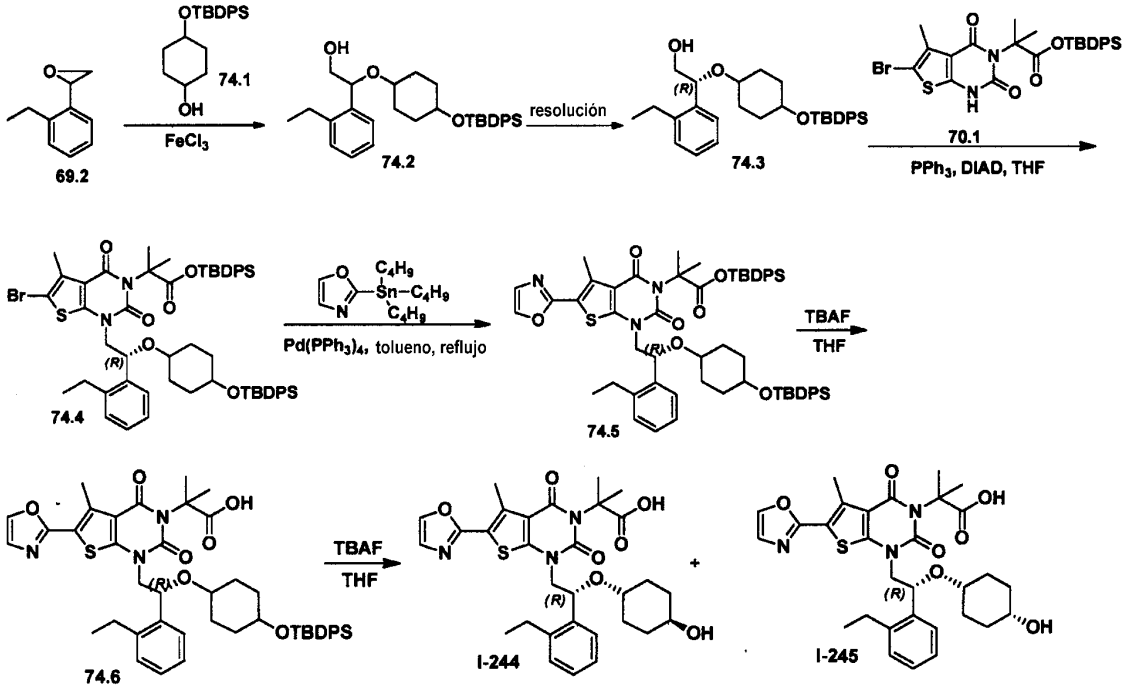


Síntesis del compuesto 73.2. En un matraz de fondo redondo de 50 ml se coloca (2S)-2-feniloxirano (4 g, 33.29 mmol, 1.00 equivalentes) y 16 ml de oxetan-3-ol. Esto es seguido por la adición de hidruro de sodio (1.3 g, 32.50 mmol, 1.00 equivalentes, 60%) en varios lotes. La solución resultante se agita durante 1 h a 80 °C en un baño de aceite. La reacción después se suspende por adición de 50 ml de NH_4Cl acuoso saturado. La solución resultante se extrae con 2 x 50 ml de acetato de etilo y las capas orgánicas se combinan y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con PE/EA (8:1). La purificación proporciona 1.6 g (25%) de (2R)-2-(oxetan-3-iloxi)-2-feniletan-1-ol (73.2) como un aceite amarillo.

Síntesis de compuesto I-182. El compuesto I-182 se prepara de una manera análoga al Ejemplo 57. Purificación: El producto crudo se aplica sobre una columna de gel de sílice

con diclorometano/metanol (20:1). Se obtienen 23.6 mg (27%) del compuesto I-182 como un sólido blanco. EM (ES): m/z 512 $(M+H)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.83 (s, 6H), 2.85 (8, 3H), 3.41-3.45 (t, 1H), 3.47-3.56 (t, 1H), 3.89-3.99 (m, 2H), 4.07-4.23 (m, 3H), 4.57-4.61 (m, 1 H), 7.27-7.38 (m, 6H) 7.99 (s, 1 H).

Ejemplo 74: Síntesis del ácido 2-(1-((R)-2-(2-etilfenil)-2-(((1r,4R)-4-hidroxiciclohexil)oxi)etil)-5-metil-6-(oxazol-2-il)-2,4-dioxo-1,2-dihidrotieno[2,3-d]pirimidin-3(4H)-il)-2-metilpropanoico (I-244) y Ejemplo 75: Síntesis del ácido 2-(1-((R)-2-(2-etilfenil)-2-(((1s,4S)-4-hidroxiciclohexil)oxi)-etil)-5-metil-6-(oxazol-2-il)-2,4-dioxo-1,2-dihidrotieno[2,3-d]pirimidin-3(4H)-il)-2-metilpropanoico (I-245).



Síntesis del compuesto 74.1. En un matraz de fondo redondo de 3 cuellos de 1000 ml se coloca ciclohexano-1,4-diol (20 g, 172.18 mmol, 1.00 equivalentes), 500 ml de 1,4-dioxano y 1H-imidazol (17.58 g, 258.24 mmol, 1.50 equivalentes) Esto es seguido por la adición de una solución de ter-butil(cloro)difenilsilano (49.69 g, 180.78 mmol, 1.05 equivalentes) en 100 ml de dioxano a gotas con agitación a 15°C. La solución resultante se agita durante 15 h a 15-20°C. Los sólidos se separan por filtración. El filtrado se diluye con 200 ml de agua. La solución resultante se extrae con 3 x 200 ml de acetato de etilo y las capas orgánicas se combinan y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (0:1-1:60-1:50-1:30-1:20). La purificación proporciona 32.98 g (54%) de 4-[(ter-butildifenilsilil)oxi]ciclohexan-1-ol (74.1) como un semisólido blanco.

Síntesis del compuesto 74.2. Se prepara el compuesto 74.2 de una manera análoga al compuesto 57.4 y 57.5, sustituyendo a 74.1 por isopropanol en la etapa de abertura del epóxido: Purificación: Se aplica el producto crudo sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1/10). El material obtenido de esta manera (1.8 g) se vuelve a purificar por *HPLC* preparativa instantánea bajo las siguientes condiciones (IntelFlash-1): Columna: gel de sílice C18; fase móvil: acetonitrilo/agua = 3/1 que incrementa

acetonitrilo/agua= 19/1 en los siguientes 30 min; detector: UV 220 nm. 1.64 g de 74.2 se obtienen como un aceite incoloro.

Resolución del compuesto 74.3. Se separan los enantiómeros de 74.2 (2.09 g) por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): Columna: Venusil Chiral OD-H, 21.1 *25 cm, 5 µm; fase móvil: hexanos e IPA.

Síntesis del compuesto 74.4. El compuesto 74.4 se prepara de una manera análoga al compuesto 57.7. Se aísla un aceite amarillo claro con un rendimiento de 54% a partir de 70.1.

Síntesis del compuesto 74.6. En un matraz de fondo redondo de 100 ml se colocan 74.5 (486 mg, 0.46 mmol, 1.00 equivalentes), 10 ml de tetrahidrofurano y TBAF (120 mg, 0.46 mmol, 1.00 equivalentes) La solución resultante se agita durante la noche a temperatura ambiente y después se concentra bajo vacío. El residuo se purifica por cromatografía en capa delgada revelado con DCM/MeOH/HOAc (30/1/0.15). Se obtienen 78 mg (21 %) de 74.7 como un sólido blanco.

Síntesis de los compuestos I-244 e I-245. En un matraz de fondo redondo de 25-ml se coloca el compuesto 74.7 (78 mg, 0.10 mmol, 1.00 equivalentes), en 2 ml de tetrahidrofurano y TBAF (100 mg, 0.38 mmol, 4.02 equivalentes) La solución resultante se agita durante 4 días a temperatura ambiente y después se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con DCM/MeOH/HOAc

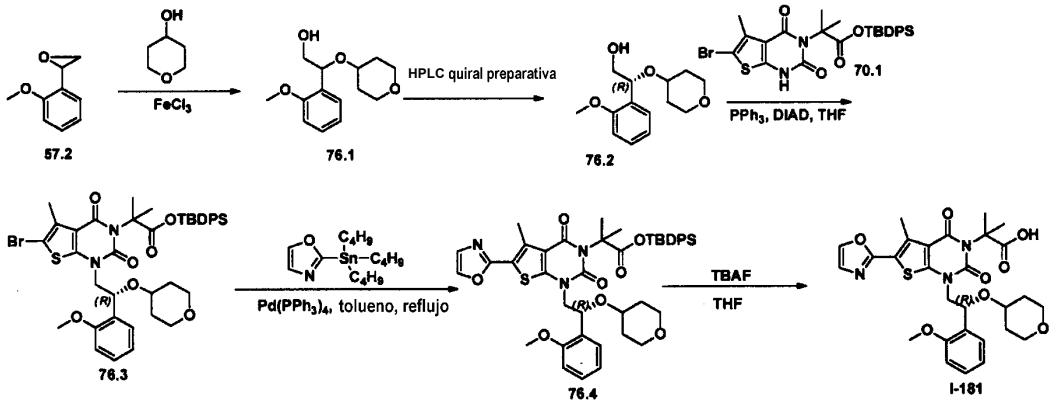
(1:16:0.1). El producto (70 mg) obtenido de esta manera se purifica adicionalmente por *HPLC* preparativa bajo las siguientes condiciones (Waters): Columna: SunFire Prep C18, 19* 150 mm 5 µm; fase móvil: agua (con NH_4CO_3 50 mM) y CH_3CN (CH_3CN 5.0% hasta 42.0% en 10 min, hasta 95.0% en 2 min, disminuye a 5.0% en 2 min); detector: UV 254/220 nm. 10.5 mg (38%) del compuesto I-244 y 4.6 mg (16%) del compuesto I-245 se obtienen, ambos como sólidos blancos. EM (ES): m/z 582 $(M+H)^+$.

Datos analíticos para el compuesto I-244: RMN ^1H (CD_3OD, 300 MHz) δ 7.99 (1H, s), 7.63-7.60 (1H, m), 7.23-7.22 (4H, m), 5.26-5.22 (1H, dd, J_1 = 9.0 Hz, J_2 = 3.0 Hz), 4.30-4.25 (1H, d, J = 12.0 Hz), 3.70-3.62 (1H, t, J = 12.0 Hz), 3.50-3.47 (1H, m), 3.20-3.19 (1H, m), 3.08-2.90 (1H, m), 2.82 (3H, s), 2.80-2.69 (1H, m), 1.83 (3H, s), 1.81 (3H, s), 1.73-1.62 (4H, m), 1.46-1.31 (4H, m), 1.25-1.10 (3H, m).

Datos analíticos para el compuesto I-245: EM (ES): m/z 582 $(M+H)^+$; 604 $(M+Na)^1$. RMN ^1H (CD_3OD, 300 MHz): δ 7.97 (1H, s), 7.65-7.62 (1H, m), 7.32-7.25 (4H, m), 5.29-5.26 (1H, m), 4.30-4.26 (1H, m), 3.70-3.63 (1H, m), 3.54-3.45 (1H, m), 3.19-2.96 (1H, m), 2.82 (EH, s), 2.76-2.63 (1H, m), 1.94 (3H, s), 1.91 (3H, s), 1.81-1.67 (2H, m), 1.53-1.38 (9H, m).

Ejemplo 76: Síntesis del ácido 2-[1-[2-(2-metoxifenil)-2-oxan-4-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-

metilpropanoico (I-181).



Síntesis del compuesto 76.1. En un matraz de fondo redondo de 3 cuellos de 250 ml, purgado y mantenido con una atmósfera inerte de nitrógeno, se coloca oxan-4-ol (86 g, 842.05 mmol, 2.01 equivalentes) y 10 g de $FeCl_3$. Esto es seguido por la adición de 57.2 (63 g, 419.51 mmol, 1.00 equivalentes) a gotas con agitación a 0°C. La solución resultante se agita durante 3 h a temperatura ambiente. La solución resultante se diluye con 500 ml de H_2O. La solución resultante se extrae con 3 x 100 ml de acetato de etilo y las capas orgánicas se combinan. La solución resultante se extrae con 3 x 300 ml de cloruro de sodio saturado y las capas orgánicas se combinan y se secan sobre sulfato de sodio anhidro. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:10). Esto resulta en 22 g (21 %) de 76.1 como un sólido blanco.

Síntesis del compuesto 76.2. Los enantiómeros de 76.1 (22 g) se resuelven por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): Columna: Venusil Chiral OD-H, 21.1 *25 cm, 5 µm; fase móvil: hexanos (TEA 0.2%) y etanol (TEA 0.2%) (retenida en 10% etanol (TEA 0.2%) durante 13 min); detector: UV 220/254 nm. Se obtienen 11.4 g (52%) de 76.2 como un sólido blanco.

Síntesis del compuesto 76.3. En un matraz de fondo redondo de 3 cuellos de 500 ml, purgado y mantenido en una atmósfera inerte de nitrógeno, se coloca 70.1 (12 g, 20.49 mmol, 1.00 equivalentes), 200 ml de tetrahidrofurano, 76.2 (6.2 g, 24.57 mmol, 1.20 equivalentes) y DIAD (6.5 g, 32.18 mmol, 1.57 equivalentes). Esto es seguido por la adición de una solución de trifenilfosfano (8.4 g, 32.03 mmol, 1.56 equivalentes) en 100 ml de tetrahidrofurano a gotas con agitación a 0°C en 60 min. La solución resultante se agita durante la noche a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:5). Esto resulta en 17 g (crudo) de 76.3 como un sólido blanco.

Síntesis del compuesto 76.4. En un matraz de fondo redondo de 3 cuellos de 500 ml, purgado y

mantenido con una atmósfera inerte de nitrógeno, se coloca 76.3 (17 g, crudo), 300 ml de tolueno, $Pd(PPh_3)_4$ (1.7 g, 1.47 mmol, 0.07 equivalentes) y 2-(tributilestanil)-1,3-oxazol (8.6 g, 24.02 mmol, 1.16 equivalentes) La solución resultante se agita durante la noche a 110°C. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:10). La purificación proporciona 6 g de 76.4 como un sólido blanco.

Síntesis del compuesto I-181. En un matraz de fondo redondo de 3 cuellos de 250 ml se coloca 76.4 (6 g, 7.43 mmol, 1.00 equivalentes),100 ml de tetrahidrofurano, TBAF (2.3 g, 8.80 mmol, 1.18 equivalentes) La solución resultante se agita durante 1 h a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con diclorometano/metanol (50:1). Esto resulta en 3.4 g (80%) del compuesto I-181 como un sólido blanco.

Purificación: EM (ES): m/z 570 $(M+H)^+$, 592 $(M+Na)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 1.22-1.36 (m, 2H), 1.62 (m, 8H), 2.75 (s, 3H), 3.20-3.39 (m, 3H), 3.48-3.58 (m, 2H), 3.80 (s, 3H), 3.85-4.20 (m, 2H), 5.30 (m, 1H), 7.03 (m, 2H), 7.33-7.50 (m, 3H), 8.2 (s, 1H).

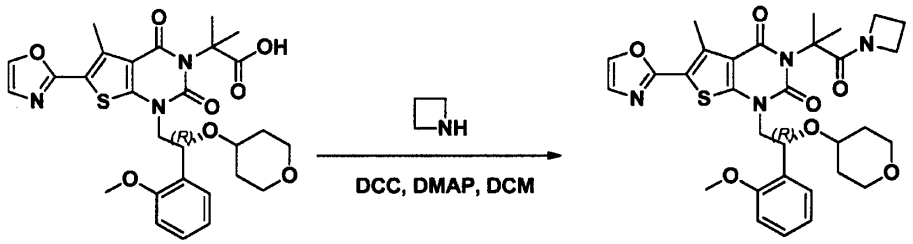
Ejemplo 77: Síntesis de 2-[1-[(2R)-2-(2-metoxifenil)-2-(oxan-4-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanamida (I-246).



I-181 I-246

Se prepara el compuesto I-246 a partir del compuesto I-181 de acuerdo con el método del Ejemplo 4. Purificación: columna de gel de sílice con diclorometano/metanol (40:1). Se aísla un sólido blanco con un rendimiento de 37%. EM (ES): m/z 591 $(M+Na)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.29-1.36 (m, 2H), 1.65-1.67 (m, 8H), 2.75 (s, 3H), 3.20-3.26 (m, 2H), 3.50-3.59 (m, 2H), 3.79 (s, 3H), 3.95-4.09 (m, 2H), 5.26-5.31 (t, 1H), 6.78 (s amplio, 1H), 6.97-7.10 (m, 3H), 7.27-7.33 (M, 1H), 7.39 (s, 1H),7.47-7.49 (m, 1H), 8.22 (s, 1H).

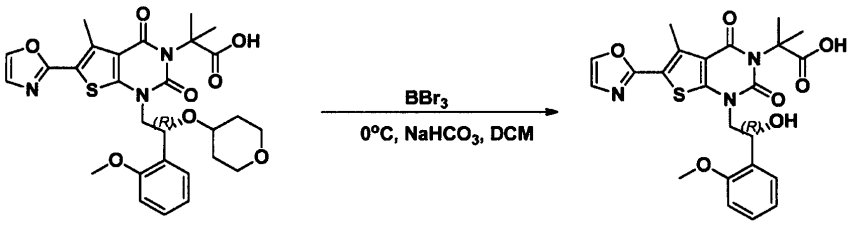
Ejemplo 78: Síntesis de 3-[1-(azetidin-1-il)-2-metil-1-oxopropan-2-il]-1-[(2R)-2-(2-metoxifenil)-2-(oxan-4-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-1H,2H,3H,4H-tieno[2,3-dipirimidin-2,4-diona (I-247).



I-181 I-247

Se prepara el compuesto I-247 a partir del compuesto I-181 y azetidina de acuerdo con el método del Ejemplo 4. Purificación: EM (ES): m/z 609 $(M+H)^+$, RMN ^1H (DMSO-d_6, 300 MHz): δ 8.24 (1H, s), 7.48-7.46 (1H, d), 7.40 (1H, s), 7.31-7.29 (1H, t), 7.06-7.00 (2H, m), 5.31-5.29 (1H, m), 3.91-3.89 (2H, m), 3.86-3.81 (4H, m), 3.81 (3H, s), 3.70-3.58 (2H, m), 3.38-3.24 (1H, m), 3,23-3.21 (2H, m), 2.78 (3H, s), 2.14-2.09 (2H, t), 1.64-1.63 (8H, m), 1.40-1.15 (2H, m).

Ejemplo 79: Síntesis de ácido 2-[1-[(2R)-2-hidroxi-2-(2-metoxifenil)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-248).

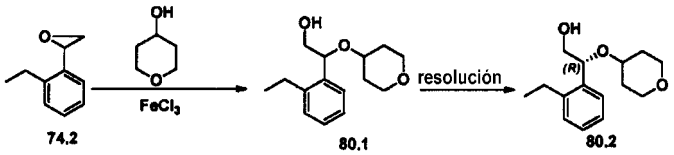


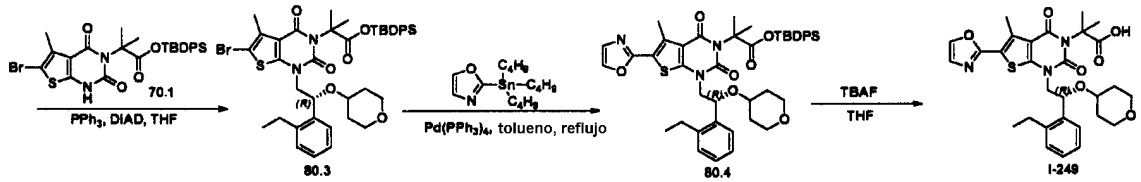
I-181 I-248

En un matraz de fondo redondo de 50 ml se coloca I-181 (100 mg, 0.18 mmol, 1.00 equivalentes), bicarbonato de sodio (798 mg, 9.50 mmol, 50.11 equivalentes) y 10 ml diclorometano. Esto es seguido por la adición de BBr_3 (476 mg, 10.03 equivalentes) a gotas con agitación a 0°C. La solución resultante se agita durante 0.5 h a temperatura ambiente y después se concentra bajo vacío. El residuo se purifica por cromatografía en capa delgada revelado con metanol/DCM (1:20).

Se obtienen 9.6 mg (11 %) del compuesto I-248 como un sólido blanco. EM (ES): m/z 586 (M+H). RMN ^{1}H (400 MHz, CD_3OD): δ 1.79-1.82 (d, 6H), 2.78 (s, 3H), 3.33 (s, 3H), 4.00-4.05 (m, 1H), 4.25-4.31 (m, 1H), 5.14-5.17 (t, 1H), 6.71-6.73 (d, 1H), 6.87-6.90 (t, 1H), 7.07-7.11 (t, 1H), 7.25 (s, 1H), 7.35-7.36 (d, 1H), 7.96 (s, 1H).

Ejemplo 80: Síntesis del ácido 2-[1-[(2R)-2-(2-etilfenil)-2-(oxan-4-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-249).



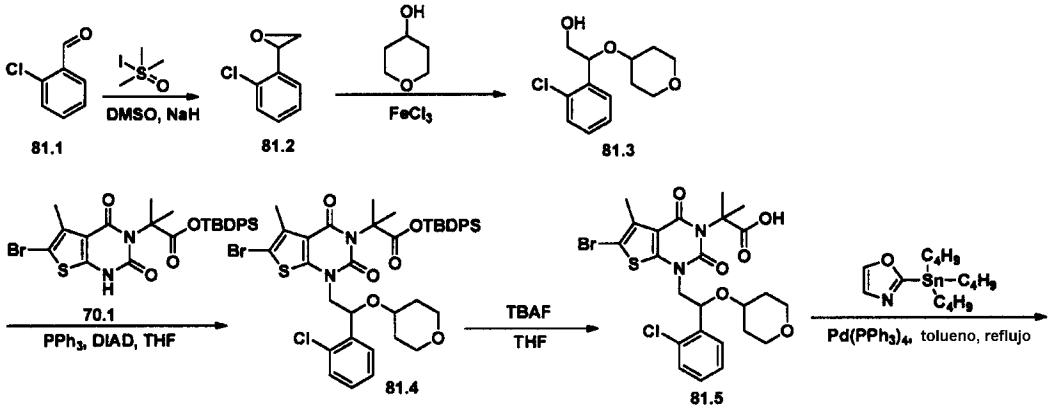


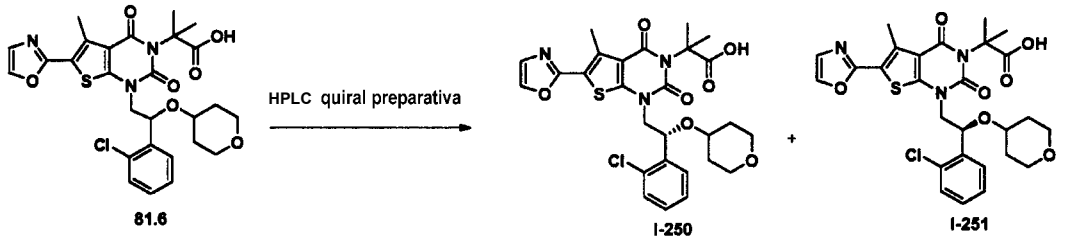
Síntesis del compuesto 80.2. Se prepara el compuesto 80.2 de acuerdo con el método para la preparación del compuesto 57.5. Purificación: Los enantiómeros del producto racémico (550 mg) se separan por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): columna: Venusil Chiral OD-H, 21.1 *25 cm, 5 µm; fase móvil: hexanos y etanol (que se mantiene en etanol 5% durante 7 min); detector: UV 220/254 nm. Se obtienen 300 mg de

producto (0.05% de rendimiento a partir de 74.2).

Síntesis de compuesto 1-249. Se prepara el compuesto I-249 de acuerdo con el método del Ejemplo 57. Purificación: columna de gel de sílice con diclorometano/metanol (40:1). Se obtienen 56.6 mg (80%) del compuesto I-249 como un sólido blanco. EM (ES): m/z 568 $(M+H)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.23-1.28 (t, 3H), 1.40-1.42 (m, 2H), 1.64-1.68 (m, 2H), 1.77-1.81 (d, 6H), 2.72-2.76 (m, 1H), 2.80 (s, 3H), 2.89-2.94 (m, 1H), 3.32-3.62 (m, 6H), 4.26-4.27 (d, 1H), 5.22-5.26 (d, 1H), 7.22-7.27 (m, 4H), 7.59-7.62 (m, 1H), 7.96(s, 1H).

Ejemplo 81: Síntesis de ácido 2-[1-[(2R)-2-(2-clorofenil)-2-(oxan-4-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-250) y Ejemplo 82: Síntesis de ácido 2-[1-[(2S)-2-(2-clorofenil)-2-(oxan-4-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (1-251).





Síntesis del compuesto 81.3. Se prepara el compuesto 81.3 de acuerdo con el método utilizado para la preparación de 57.3, sustituyendo 4-hidroxipirano por isopropanol en la etapa de abertura de epóxido. Se aísla un líquido amarillo claro con un rendimiento general de 5%.

Síntesis del compuesto 81.6. Se prepara el compuesto 81.6 a partir de 81.3 y 70.1 siguiendo el procedimiento del Ejemplo 67. Purificación: El residuo obtenido después del tratamiento se aplica sobre una columna de gel de sílice y se eluye con DCM/MeOH = 100:1. El producto obtenido de esta manera se vuelve a purificar por *HPLC* preparativa instantánea bajo las siguientes condiciones (IntelFlash-1): Columna: C18 gel de sílice; fase móvil: acetonitrilo : agua = 0 : 100 incrementara a acetonitrilo : agua = 100 : 0 dentro de 16 min; detector: UV 220 nm. Se obtienen 40 mg (23%) de 81.6 como un aceite incoloro.

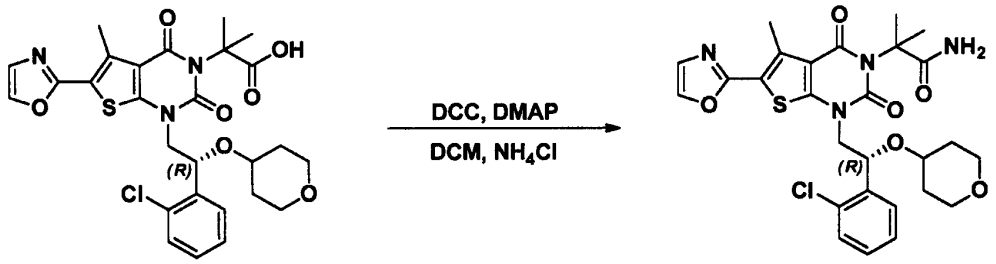
Síntesis de compuestos I-250 y I-251. Los enantiómeros 81.6 se separan por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): Columna: Chiralpak IA, 2*25 cm, 5 µm; fase móvil: hexanos e IPA (se mantiene a

20% de IPA durante 22 min); detector: UV 220/254 nm. 2.8 mg (7%) del compuesto I-250 y 3.5 mg (9%) de I-251 se obtienen como sólidos blancos.

Los datos analíticos para el compuesto I-250: EM (ES): m/z 574 $(M+H)^+$. RMN 1H (300 MHz, CD_3OD): δ 8.00 (s, 1H), 7.75 (d, 1H, *J* = 6.0 Hz), 7.45 (m, 2H), 7.35 (d, 1H, *J*= 5.1 Hz), 7.29 (s, 1H), 5.49 (c, 1H, *J* = 5.1 Hz), 4.32 (m, 1H), 3.99 (m, 1H), 3.70 (m, 2H), 3.50 (m, 1H), 3.40 (m, 2H), 2.83 (s, 3H), 1.82 (s, 3H), 1.80 (s, 3H), 1.75 (m, 2H), 1.52 (m, 2H).

Los datos analíticos para el compuesto I-251: EM (ES): m/z 574 $(M+H)^+$. RMN 1H (300 MHz, CD_3OD): δ 7.99 (s, 1H), 7.75 (d, 1H, *J* = 6.0 Hz), 7.45 (m, 3 H), 7.29 (s, 1H), 5.49 (c, 1H, *J* = 3.3 Hz), 4.32 (m, 1H), 3.99 (m, 1H), 3.71-3.49 (m, 3H), 3.38 (m, 2H), 2.83 (s, 3H), 1.82(s, 3H), 1.80 (s, 3H), 1.74 (m, 2H), 1.50 (m, 2H).

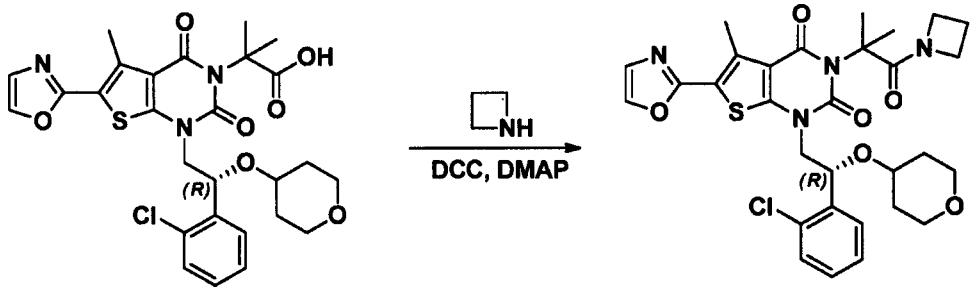
Ejemplo 83: Síntesis de 2-[1-[(2R)-2-(2-clorofenil)-2-(oxan-4-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanamida (I-252).



I-250 I-252

Se prepara el compuesto I-252 a partir del compuesto I-250 (Ejemplo 81) y cloruro de amonio, de acuerdo con el método del Ejemplo 4. Se aísla un sólido blanco con un rendimiento de 60%. EM (ES): m/z 595 $(M+Na)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 8.22 (1H, s), 7.70-7.67 (1H, d), 7.49-7.37 (4H, m), 7.30-6.70 (2H, m), 5.35-5.30 (1H, m), 4.30-4.15 (1H, m), 3.90-3.80 (1H, m), 3.54-3.52 (2H, m), 3.40-3.36 (1H, m), 3.32-3.21 (2H, m), 2.75 (3H, s), 1.66-1.60 (8H, m), 1.32-1.24 (2H, m).

Ejemplo 84: Síntesis de 3-[1-(azetidin-1-il)-2-metil-1-oxopropan-2-il]-1-[(2R)-2-(2-clorofenil)-2-(oxan-4-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-2,4-diona (1-253).

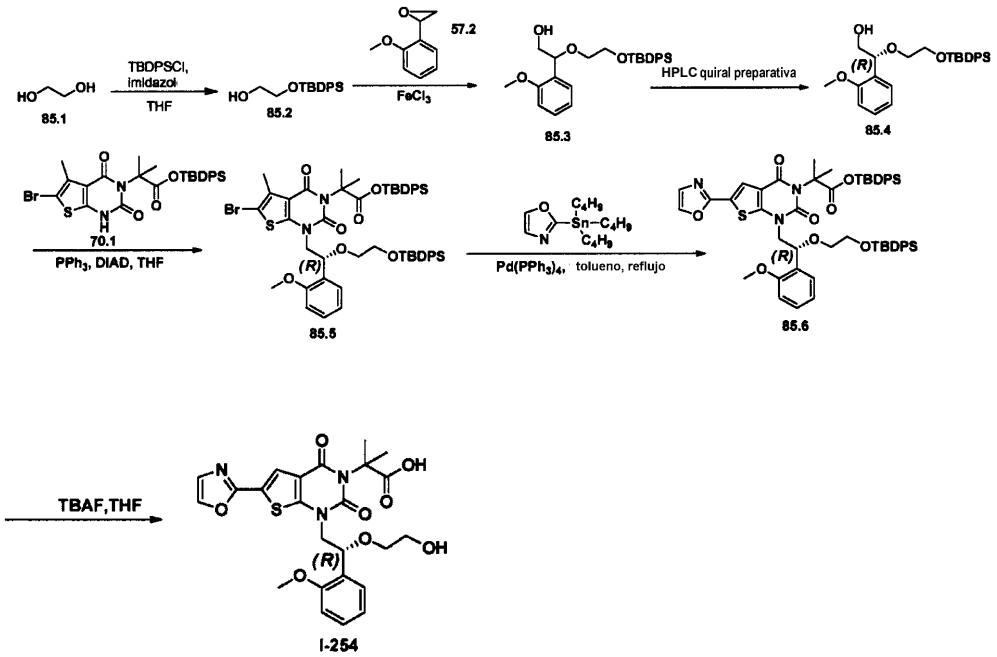


I-250 I-253

Se prepara el compuesto I-253 a partir del compuesto I-250 (Ejemplo 81) y azetidina de acuerdo con el método del Ejemplo 4. Se aísla un sólido blanco con un rendimiento de 49%. EM (ES): m/z 613 $(M+H)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 8.24 (1H, s), 7.69-7.66 (1H, d), 7.48-7.38 (4H, m), 5.35-5.30 (1H, m), 4.30-4.21 (1H, m), 3.90-3.88 (4H, m), 3.57-3.48 (2H, m),

3.33-3.30 (1H, m), 3.27-3.24 (3H, m), 2.77 (3H, s), 2.12 (2H, m), 1.70-1.61 (8H, m), 1.38-1.25 (2H, m).

Ejemplo 85*:* Síntesis de 2-[1-[(2R)-2-(2-hidroxietoxi)-2-(2-metoxifenil)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-254).



Síntesis del compuesto 85.2. En un matraz de fondo redondo de 3 cuellos de 2 l se colocan 800 ml de tetrahidrofurano, etano-1,2-diol (40 g, 644.46 mmol, 1.00 equivalentes) e imidazol (61.4 g, 901.92 mmol, 1.40 equivalentes). Esto es seguido por la adición de 186.3 g de TBDPSCI a gotas con agitación a 0°C durante 30 min. La solución resultante se agita durante la noche a temperatura ambiente. Los sólidos se separan por filtración y la torta de

filtro se lava con 200 ml de EA. La mezcla resultante se lava con 200 ml de salmuera y se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:25). La purificación proporciona 83 g (43%) de 2-[(ter-butildifenilsili)oxi]etan-1-ol (85.2) como un aceite incoloro.

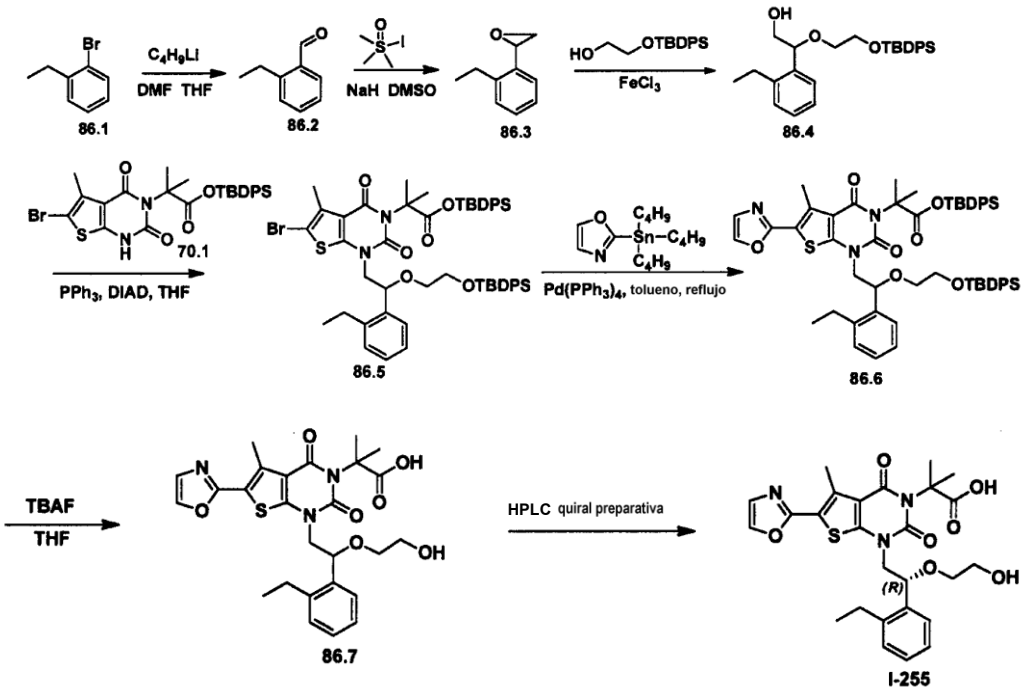
Síntesis del compuesto 85.3. Se prepara el compuesto 85.3 de acuerdo con el método utilizado para la síntesis de 57.3, sustituyendo 85.2 por isopropanol. Se aísla un aceite amarillo con un rendimiento de 5%.

Síntesis del compuesto 85.4. Los enantiómeros de 85.3 se separan por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): Columna: Venusil Chiral OD-H, 21.1 *25 cm, 5 µm; fase móvil: hexanos e IPA (que se mantiene en IPA 2.0% durante 16 min); detector: UV 220/254 nm. Se obtienen 270 mg (39%) de 85.4 como un aceite amarillo.

Síntesis del compuesto I-254. Se prepara el compuesto I-254 de acuerdo con el método del Ejemplo 57. Purificación: El residuo obtenido después del tratamiento se aplica sobre una columna de gel de sílice con diclorometano/metanol (40:1). La purificación proporciona 14 mg (4% de 70.1) del compuesto I-254 como un sólido blanco. EM (ES): m/z 468 $(M-C_2H_5O_2)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.65-1.67 (d, 6H), 2.69 (s, 3H), 3.20-3.39 (m, 1H), 3.41-3.49 (m, 1H), 3.51-3.57 (m, 2H), 3.68 (s, 3H), 3.88-3.95 (m, 1H), 4.20-4.27

(m, 1H), 5.16-5.21 (t, 1H), 6.78-6.81 (d, 1H), 6.88-6.93 (t, 1H), 7.13-7.18 (m, 2H), 7.41-7.44 (d, 1H), 7.95 (s, 1H).

Ejemplo 86: Síntesis de 2-[1-[(2R)-2-(2-etilfenil)-2-(2-hidroxietoxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-255).



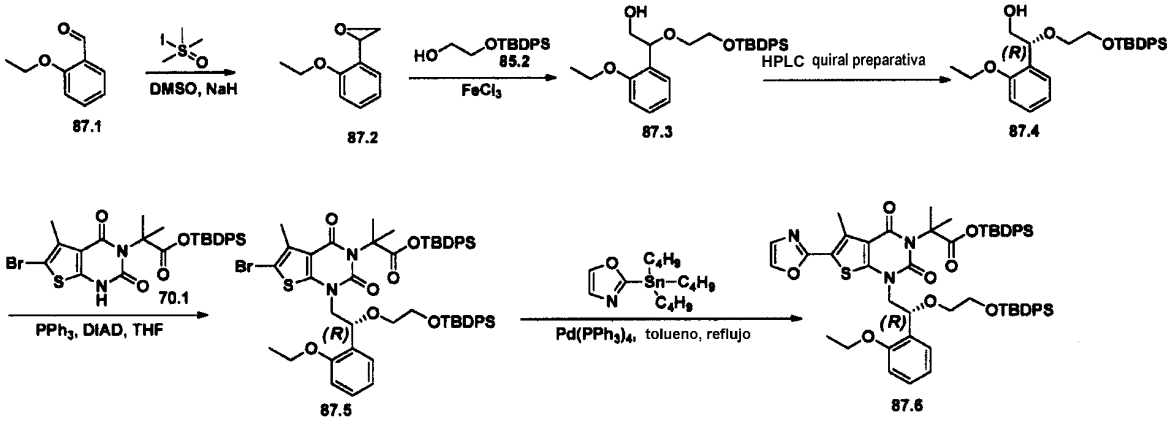
Síntesis del compuesto 86.5. Se prepara el compuesto 86.5 de una manera análoga al compuesto 85.3. Se aísla un aceite incoloro con un rendimiento de 2%.

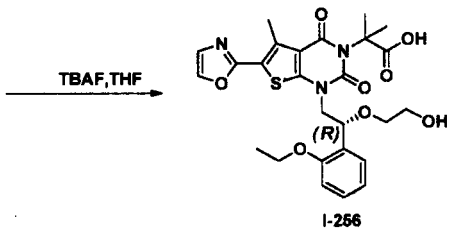
Síntesis del compuesto 86.7. Se prepara el compuesto 86.7 de acuerdo con el método del Ejemplo 57. Purificación: El residuo obtenido después del tratamiento se aplica sobre una placa de CCD con diclorometano/metanol/HOAc (40:1:0.1). La purificación proporciona 406 mg (57% de 70.1) de 86.7 como un

polvo blanco.

Síntesis de compuesto I-255. El enantiómero (R) se aísla de 406 mg de 86.7 por *HPLC* preparativa quiral bajo las siguientes condiciones: Columna: CHIRALPAK IA; fase móvil: hexanos (ácido acético 0.1%) : IPA = 75 : 25; detector: UV 254 nm. Se obtienen 44.5 mg del compuesto I-255 como un sólido blanco. EM (ES): m/z 528 (M+H). RMN ^{1}H (CD_3OD, 300 MHz): δ 7.98 (H, d, J = 0.6 Hz), 7.62-7.59 (1H, m), 7.31-7.21 (4H, m), 5.19-5.15 (1 H, dd, J, = 9 Hz, J_2 = 3.3 Hz), 4.26-4.20 (1H, dd, J_1 = 14.7 Hz, J_2 = 3.3 Hz), 3.93 -3.85 (1H, dd, J_1 = 14.7 Hz, J_2 = 9Hz), 3.57-3.53 (2H, m), 3.49-3.40 (1H, m), 2.96-2.87 (1H, m), 2.80-2.70 (4H, m), 1.81 (3H, s), 1.80 (3H, s), 1.30-1.25 (3H, t, J = 7.5 Hz).

Ejemplo 87: Síntesis del ácido 2-[1-[(2R)-2-(2-etoxifenil)-2-(2-hidroxietoxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-256).

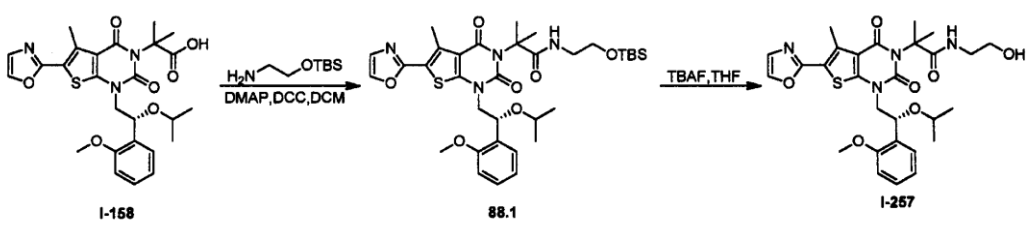




Síntesis del compuesto 87.4. Se prepara el compuesto 87.4 a partir de 87.1 de una manera análoga al compuesto 57.5. Se aísla un aceite amarillo con un rendimiento total de 2%.

Síntesis de compuesto I-256. Se prepara el compuesto I-256 a partir de 87.4 y 70.1 de una manera análoga a la síntesis del compuesto I-158 (Ejemplo 57). EM (ES): m/z 482 $(M-C_2H_5O_2)^+$. 544 $(M+H)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.31-1.41 (t, 3H), 1.72-1.74 (d, 2H), 2.77-2.81 (s, 3H), 3.32-3.68 (m, 4H), 4.02-4.11 (m, 2H), 4.21-4.23 (m, 2H), 5.30-5.35 (t, 1H), 6.93-7.31 (m, 2H), 7.24-7.30 (m, 2H), 7.52-7.54 (d, 1H), 7.98 (s, 1H).

Ejemplo 88: Síntesis de N-(2-hidroxietil)-2-[1-[(2R)-2-(2-metoxifenil)-2-(propan-2-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3d]pirimidin-3-il]-2-metilpropanamida (I-257).

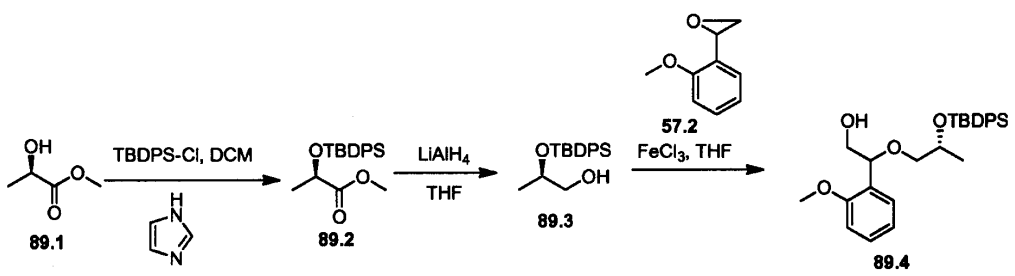


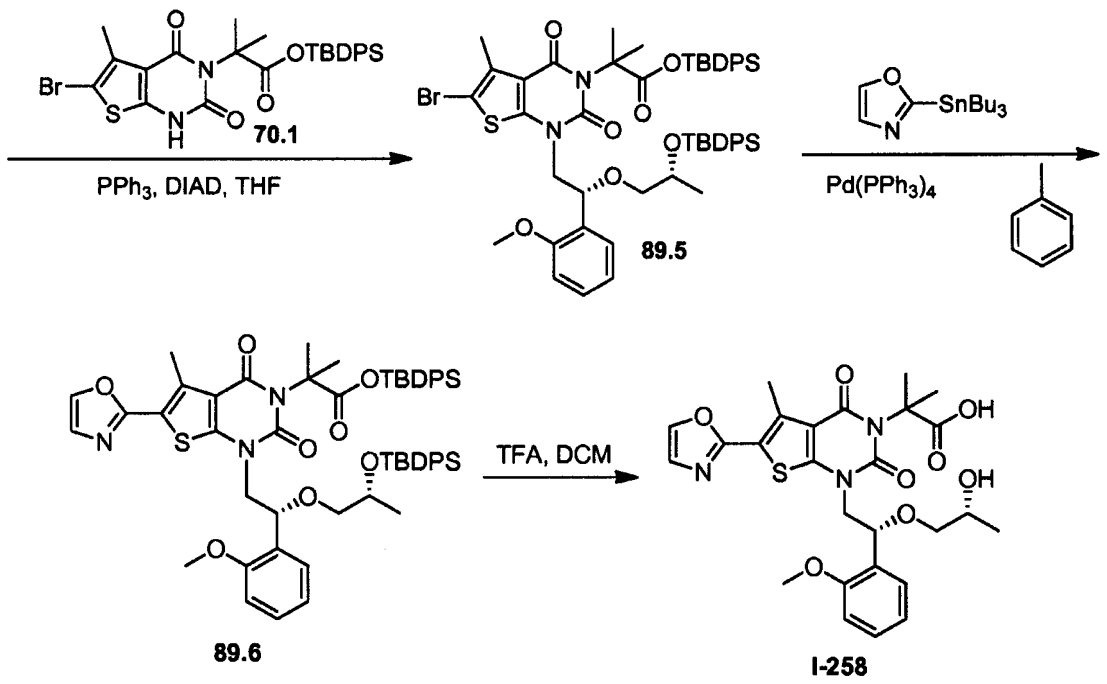
Síntesis de 88.1. Se prepara el compuesto 88.1 a partir del compuesto I-158 (Ejemplo 57) de una manera análoga

al Ejemplo 4. Se aísla un sólido blanco con un rendimiento de 48%.

Síntesis de compuesto 1-257. En un matraz de fondo redondo de 50 ml se coloca 88.1 (50 mg, 0.07 mmol, 1.00 equivalentes), TBAF (20 mg, 0.08 mmol, 1.05 equivalentes) y 5 ml de tetrahidrofurano. La solución resultante se agita durante 3 h a temperatura ambiente y después se concentra bajo vacío. El residuo se purifica por CCD con acetato de etilo/éter de petróleo (1:1) para proporcionar 8 mg (19%) del compuesto I-257 como un sólido amarillo claro. EM (ES): m/z 571 (M+H). RMN ^{1}H (400 MHz, CD_3OD): δ 1.14-1.15 (m, 6H), 1.71-1.96 (m, 6H), 2.41 (s, 3H), 3.33 (m, 1H), 3.46 (m, 1H), 3.56 (m, 1H), 3.74 (m, 4H), 3.93 (s, 3H), 5.13 (s, 1H), 7.00 (t, J = 7.6 Hz, 2H), 7.19 (s, 1H), 7.28-7.33 (t, *J* = 7.2 Hz, 1H), 7.46-7.48 (d, *J*= 7.6 Hz, 1H), 7.87 (s, 1H).

Ejemplo 89: Síntesis del ácido 2-[1-[(2R)-2-[(2R)-2-hidroxipropoxi]-2-(2-metoxifenil)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-258).





Síntesis del compuesto 89.2. En un matraz de fondo redondo de 3 cuellos de 250 ml, se colocan 100 ml de diclorometano, (2R)-2-hidroxipropanoato de metilo (10 g, 96.06 mmol, 1.00 equivalentes) y 1H-imidazol (9.8 g, 143.95 mmol, 1.50 equivalentes) Esto es seguido por la adición de TBDPSCI (29.1 g, 112.45 mmol, 1.17 equivalentes) a gotas con agitación a 0°C. La solución resultante se agita durante 2 h a temperatura ambiente y después se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:50). La purificación proporciona 32 g (97%) de 89.2 como un aceite incoloro.

Síntesis del compuesto 89.3. En un matraz de fondo redondo de 3 cuellos de 500 ml se colocan 200 ml de tetrahidrofurano y 89.2 (28 g, 81.75 mmol, 1.00 equivalentes)

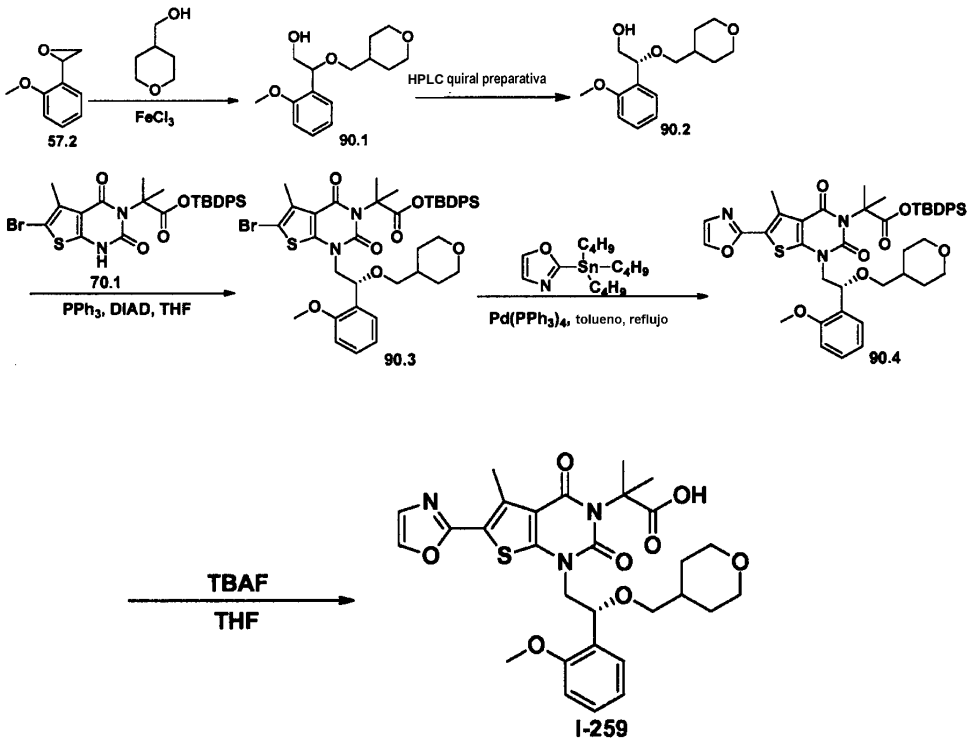
Esto es seguido por la adición de $LiAlH_4$ (1.56 g, 41.11 mmol, 0.50 equivalentes) en porciones a -30°C. La solución resultante se agita durante 30 min a -30°C. La reacción después se suspende por la adición de 100 ml de NH_4Cl acuoso saturado. La solución resultante se extrae con 3 x 200 ml de acetato de etilo y las capas orgánicas se combinan y concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:30). Esto resulta en 11.8 g (46%) de (2R)-2-[(ter-butildifenilsilil)oxi]propan-1-ol (89.3) como un aceite incoloro.

Síntesis del compuesto 89.4. Se prepara el compuesto 89.4 a partir de 57.2 y el compuesto 89.3 de una manera análoga al compuesto 57.3. Se aísla un aceite incoloro con un rendimiento de 1%.

Síntesis de compuesto I-258. Se prepara el compuesto I-258 a partir de 89.4 y 70.1 de una manera análoga a la preparación del compuesto 14.5. Se aísla un sólido blanco con un rendimiento de 22% a partir de 70.1. EM (ES): m/z 544 $(M+H)^+$. RMN ^1H (400 MHz, CD_3OD): δ 1.05 (d, J = 7.2 Hz, 3H), 1.79-1.80 (m, 6H), 2.81 (s, 3H), 3.13-3.18 (m, 1H), 3.83-3.87 (m, 4H), 4.01-4.06 (m, 1H), 4.28-4.34 (m, 1 H), 5.27-5.31 (m, 1 H), 6.94 (d, *J* = 8.4, 1 H), 7.03 (t, *J* = 7.6, 1 H), 7.26-7.30 (M, 2H), 7.54 (d, *J* = 7.6, 1 H), 7.98 (s, 1 H).

Ejemplo 90: Síntesis del ácido 2-[1-[(2R)-2-(2-

metoxifenil)-2-(oxan-4-ilmetoxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-259).

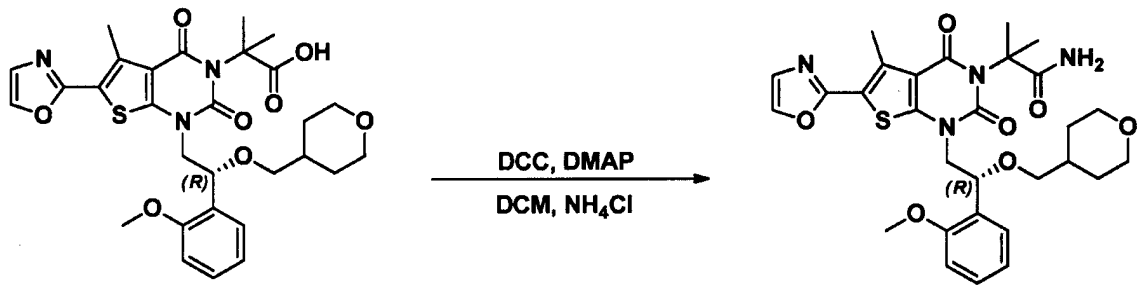


Síntesis del compuesto 90.2. Se prepara el compuesto 90.2 a partir de 57.2 y (tetrahidro-2H-piran-4-il)metanol de una manera análoga a la síntesis de 57.5. Separación quiral: Gitson Gx 281; Columna: Venusil Chiral OD-H, 0.46*25 cm, 5 µm; fase móvil: hexanos y EtOH (que se mantiene en EtOH 5.0% durante 18 min); detector: UV 254 nm. Se aíslan 970 mg (12%) de un aceite incoloro

Síntesis de compuesto I-259. Se prepara el compuesto I-259 a partir de 90.2 y 70.1 de una manera análoga a la

preparación del compuesto I-158, Ejemplo 57. EM (ES): m/z 584 (M+H). RMN ^{1}H (300 MHz, CD_3OD): δ 1.13-1.46 (m, 2H), 1.51-1.57 (m, 2H), 1.62-1.80 (m, 7H), 2.76-2.81 (s, 3H), 3.07-3.12 (t, 1H), 3.25-3.56 (m, 3H), 3.82-3.92 (m, 5H), 4.09-4.21 (m, 2H, 5.21-5.26 (t, 1H), 6.95-7.05 (m, 2H), 7.32-7.32 (m, 2H), 7.44-7.47 (m, 1H), 8.00 (s, 1H).

Ejemplo 91: Síntesis de 2-[1-[(2R)-2-(2-metoxifenil)-2-(oxan-4-ilmetoxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanamida (I-260).

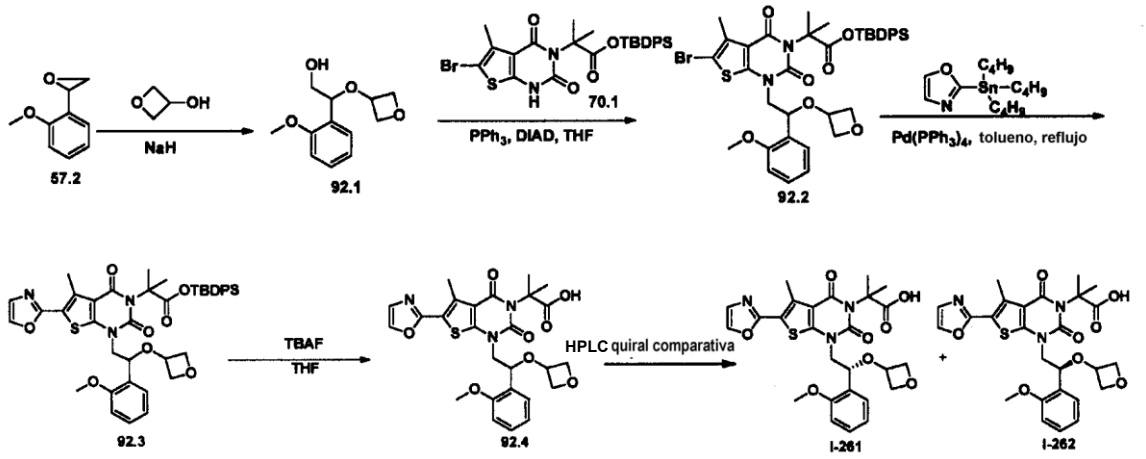


I-259 I-260

Se prepara el compuesto I-260 a partir del compuesto I-259 (Ejemplo 90) de acuerdo con el método del Ejemplo 4. Se aísla un sólido blanco con un rendimiento de 43%. EM (ES): m/z 583 $(M+H)^+$, 605 $(M+Na)^+$. RMN ^{1}H (DMSO-d_6, 300 MHz): δ 8.22 (1H, s), 7.39-7.26 (3H, m), 7.05-6.97 (3H, m), 6.70 (1H, s amplio), 5.12-5.08 (1H, m), 4.07-3.94 (2H, m), 3.78-3.70 (5H, m), 3.19-3.00 (4H, m), 2.73 (3H, s), 1.65-1.64 (7H, m), 1.44-1.36 (2H, m), 1.20-0.99 (2H,

m).

Ejemplo 92: Síntesis del ácido (R)-2-(1-(2-(2-metoxifenil)-2-(oxetan-3-iloxi)etil)-5-metil-6-(oxazol-2-il)-2,4-dioxo-1,2-dihidrotieno[2,3-d]pirimidin-3(4H)-il)-2-metilpropanoico (I-261) y el Ejemplo 93: Síntesis del ácido (S)-2-(1-(2-(2-metoxifenil)-2-(oxetan-3-iloxi)etil)-5-metil-6-(oxazol-2-il)-2,4-dioxo-1,2-dihidrotieno[2,3-dipirimidin-3(4H)-il)-2-metilpropanoico (I-262).



Síntesis del compuesto 92.1. Se prepara el compuesto 92.1 a partir de 57.2 de una manera análoga a la preparación de 73.2. Se aísla un aceite amarillo con un rendimiento de 8%.

Síntesis del compuesto 92.4. Se prepara el compuesto 92.4 a partir de 92.1 y 70.1 de una manera análoga a la síntesis del compuesto I-158, Ejemplo 57. Se

aísla un sólido blanco con un rendimiento de 15% a partir de 70.1

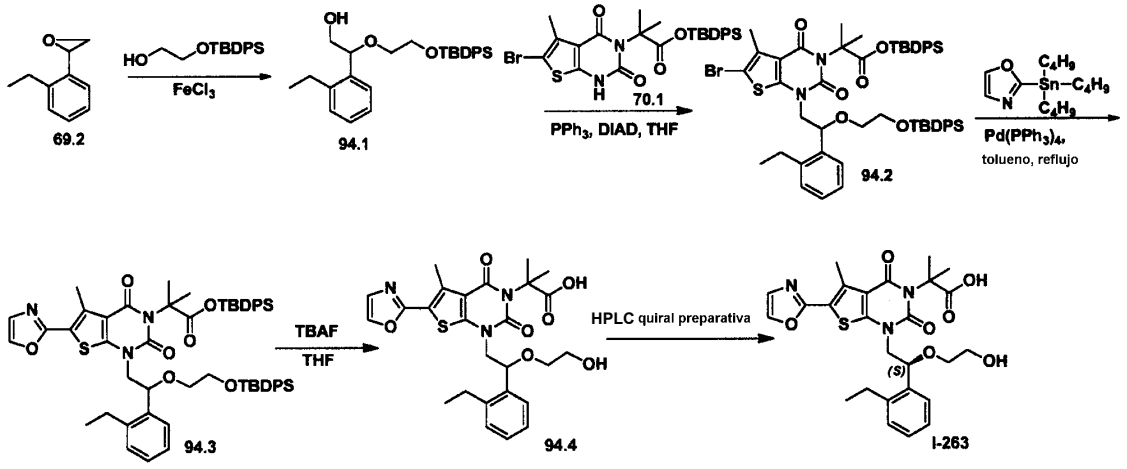
Síntesis de los compuestos I-261 y 1-262. Los enantiómeros de 92.4 (100 mg) se separan por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): Columna: Chiralpak IC, 2*25 cm, 5 µm; fase móvil: hexanos (DEA 0.1%) y etanol (DEA 0.2%) (se mantiene a 25.0% de etanol (DEA 0.2%) durante 8 minutos); detector: UV 220/250 nm. Se obtienen 11.1 mg del compuesto I-261 y 10.2 mg del compuesto I-262.

Datos analíticos para el compuesto I-261: EM (ES): m/z 542 $(M+H)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.68-1.69 (d, 6H), 2.73 (s, 3H), 3.70 (s, 3H), 4.10-4.16 (m, 1H), 4.26-4.38 (m, 3H), 4.61-4.71 (m, 3H), 6.02 (s amplio, 1H), 7.00-7.08 (m, 2H), 7.32 (s, 1H), 7.37-7.40 (m, 1H), 7.42-7.56 (m, 1H), 8.17 (s, 1H), 12.4 (s amplio, 1H).

Datos analíticos para el compuesto I-262: EM (ES): m/z 542 $(M+H)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.68-1.69 (d, 6H), 2.73 (s, 3H), 3.70 (s, 3H), 4.10-4.16 (m, 1H), 4.26-4.38 (m, 3H), 4.61-4.71 (m, 3H), 6.01 (s amplio, 1H), 7.00-7.08 (m, 2H), 7.32 (s, 1H), 7.37-7.40 (m, 1H), 7.42-7.56 (m, 1 H), 8.17 (s, 1 H), 12.40 (s amplio, 1 H).

Ejemplo 94: Síntesis de 2-[1-[(2S)-2-(2-etilfenil)-2-(2-hidroxietoxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-

2-metilpropanoico (I-263).



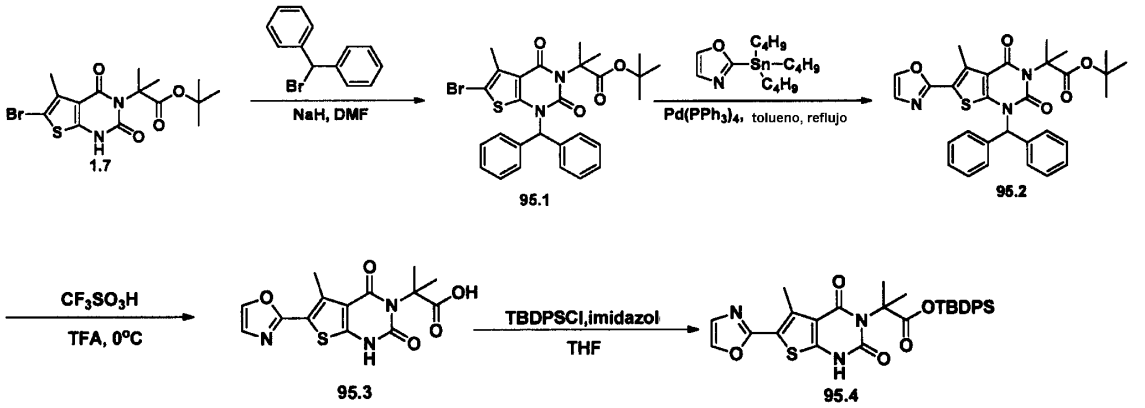
Síntesis del compuesto 94.1. El compuesto 94.1 se prepara a partir de 69.2 utilizando el mismo método que para 57.3. Se aísla un aceite incoloro con un rendimiento de 2%.

Síntesis del compuesto 94.4. El compuesto 94.4 se prepara a partir de 94.1 y 70.1 utilizando el mismo método que para el compuesto I-158, Ejemplo 57. Se aísla un polvo blanco con 57% de rendimiento.

Aislamiento del compuesto I-263. Los enantiómeros de 94.4 (406 mg) se separan por *HPLC* preparativa quiral bajo las siguientes condiciones: Columna: CHIRAPLAK IA; fase móvil: hexanos (ácido acético 0.1%);IPA = 75:25; detector: UV 254 nm. Se obtienen 34.2 mg del compuesto I-263 como un sólido blanco. EM (ES): *m/z* 528 $(M+H)^+$. RMN ^1H (300 MHz, CD_3OD): 7.98 (1H, d, *J*=0.6 Hz), 7.62-7.59 (1H, m), 7.31-7.21 (4H, m), 5.19-5.15 (1H, dd, J_1=9 Hz, J_2=3.3 Hz), 4.26-4.20 (1H, dd, J_1=14.7 Hz, J_2=3.3 Hz), 3.93-3.85 (1H, dd, J_1=14.7 Hz, J_2=9 Hz), 3.57-3.53

(2H, m), 3.49-3.40 (1H, m), 2.96-2.87 (1H, m), 2.80-2.70 (4H, m), 1.81 (3H, s), 1.80 (3H, s), 1.30-1.25 (3H, t, *J*=7.5 Hz).

Ejemplo 95: Síntesis del intermediario 95.4



Síntesis del compuesto 95.1. En un matraz de fondo redondo de 3 cuellos de 250 ml, se coloca 1.7 (5 g, 12.40 mmol, 1.00 equivalentes), 60 ml de N,N-dimetilformamida, [bromo(fenil)metil]benceno (3.966 g, 16.05 mmol, 1.29 equivalentes) e hidruro de sodio (644.8 mg, 16.12 mmol, 1.30 equivalentes, 60%). La solución resultante se agita durante la noche a temperatura ambiente. La reacción después se suspende por la adición de 300 ml de agua. La solución resultante se extrae con 4 x 200 ml de acetato de etilo y las capas orgánicas se combinan, se lavan con 200 ml de salmuera, se secan sobre sulfato de sodio anhidro y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:30). La purificación proporciona 1.93 g (27%) de 95.1 como un sólido amarillo.

Síntesis del compuesto 95.2. En un matraz de fondo

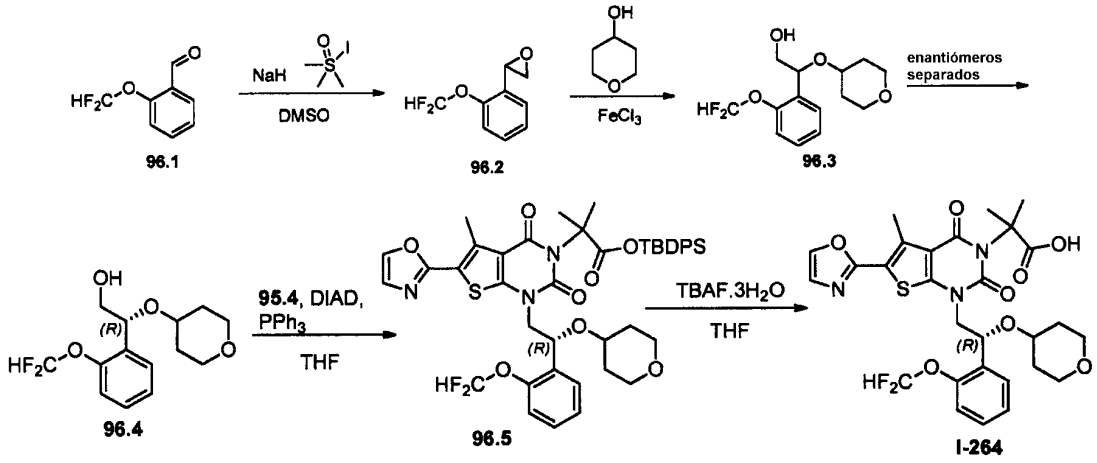
redondo de 3 cuellos de 250 ml, purgado y mantenido con una atmósfera inerte de nitrógeno, se coloca 95.1 (8.15 g, 14.31 mmol, 1.00 equivalentes), 40 ml de tolueno, 2-(tributilestannil)-1,3-oxazol (10.024 g, 27.99 mmol, 1.96 equivalentes) y $Pd(PPh_3)_4$ (2.426 g, 2.10 mmol, 0.15 equivalentes). La solución resultante se agita bajo una atmósfera de N_2 durante la noche a 110°C en un baño de aceite y después se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:20). La purificación proporciona 5.5 g (69%) de 95.2 como un sólido café.

Síntesis del compuesto 95.3. En un matraz de fondo redondo de 3 cuellos de 250 ml, se coloca 95.2 (5.5 g, 9.86 mmol, 1.00 equivalentes), 30 ml de ácido trifluoroacético y 2.97 g de CF_3SO_3H. La solución resultante se agita durante 3 h a 0°C en un baño de agua/hielo y después se diluye con 300 ml de agua. Los sólidos se recolectan por filtración y después se disuelven en 100 ml de etanol. La mezcla resultante se concentra bajo vacío. Los sólidos se recolectan por filtración para proporcionar 2.5 g (76%) de 95.3 como un sólido blanco.

Síntesis del compuesto 95.4. En un matraz de fondo redondo de 3 cuellos de 100 ml se coloca 95.3 (2.556 g, 7.58 mmol, 1.00 equivalentes), 20 ml de tetrahidrofurano, ter-butil(cloro)difenilsilano (4.181 g, 15.21 mmol, 2.00 equivalentes) e imidazol (1.038 g, 15.26 mmol, 2.01

equivalentes). La solución resultante se agita durante la noche a temperatura ambiente y después se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:30). La purificación proporciona 4 g (92%) de 95.4 como un sólido blanco.

Ejemplo 96: Síntesis del ácido 2-[1-[(2R)-2-[2-(difluorometoxi)fenil]-2-(oxan-4-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-264).

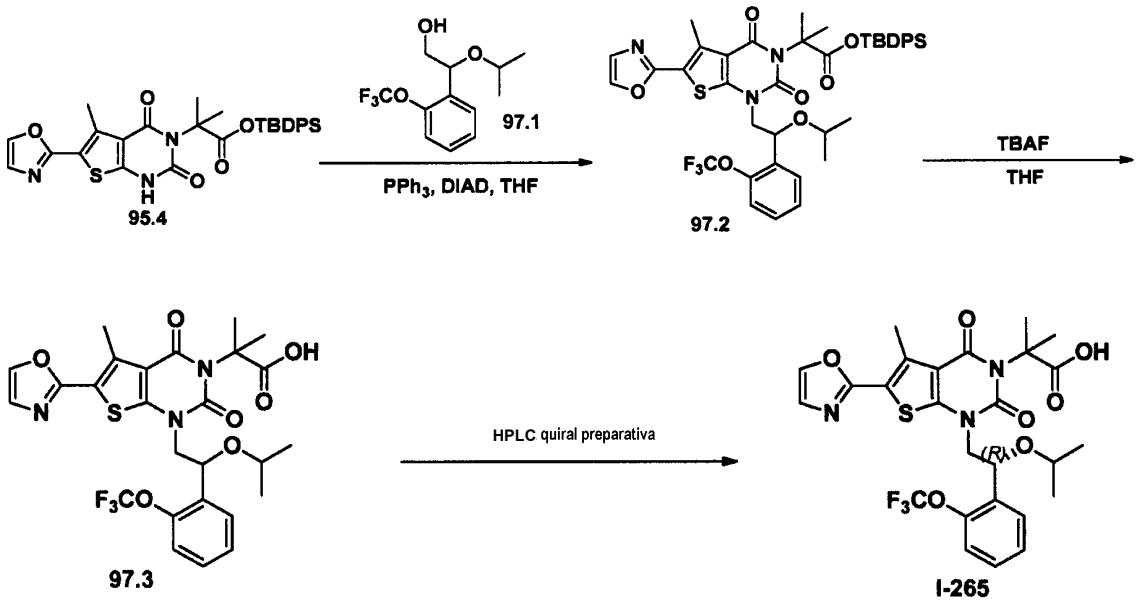


Síntesis del compuesto 96.4. El compuesto 96.4 se prepara a partir 2-(difluorometoxi)benzaldehído de acuerdo con el procedimiento para la síntesis de 57.5. Separación quiral: Gilson Gx 281; columna: Venusil Chiral OD-H, 21.1*25 cm, 5 µm; fase móvil: hexanos y etanol (que se mantiene en etanol 2% durante 13 min); detector: UV 254/220 nm. Se aíslan 248 mg (2% de rendimiento general a partir 96.1) de un aceite incoloro.

Síntesis de compuesto I-264. El compuesto I-264 se

prepara a partir del intermediario 95.4 y 96.4 de una manera análoga al compuesto 67.8. Se aísla un sólido blanco con un rendimiento de 20% a partir de 95.4. EM (ES): *m/z* 607 $(M+H)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 1.23-1.30 (m, 2H), 1.65 (m, 8H), 2.75 (s, 3H), 3.24-3.27 (m, 2H), 3.50-3.53 (m, 2H), 3.96-4.18 (m, 2H), 5.26-5.27 (m, 1H), 7.00-7.65 (m, 5H), 8.24 (s, 1H), 12.42 (s, 1H).

Ejemplo 97: Síntesis del ácido (R)-2-(1-(2-isopropoxi-2-(2-(trifluorometoxi)fenil)etil)-5-metil-6-(oxazol-2-il)-2,4-dioxo-1,2-dihidrotieno[2,3-d]pirimidin-3(4H)-il)-2-metilpropanoico (I-265).



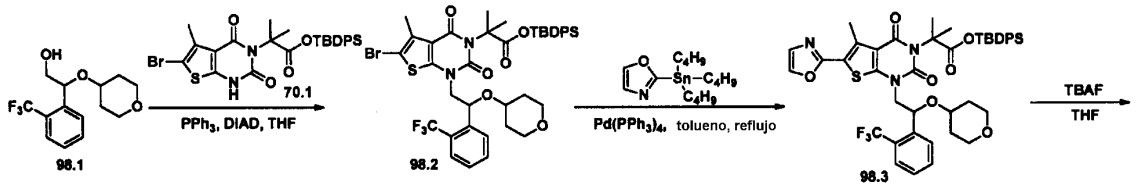
Síntesis del compuesto 97.1. El compuesto 97.1 se prepara a partir de 2-(trifluorometoxi)benzaldehído e isopropanol utilizando el mismo método que para el compuesto 57.3. Se aísla un aceite incoloro con un rendimiento general

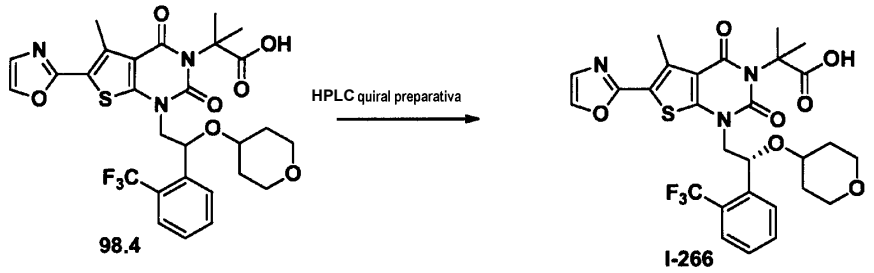
de 17%.

Síntesis del compuesto 97.3. Se prepara el compuesto 97.3 a partir de 95.4 y 97.1 de una manera análoga al Ejemplo 96. Se aísla un sólido blanco con un rendimiento de 23% a partir de 95.4.

Síntesis de compuesto I-265. Se aísla el enantiómero R a partir de 390 mg de 97.3 por *HPLC* preparativa quiral bajo las siguientes condiciones: Gilson Gx 281; columna: Chiralpak IC, 2*25 cm, 5 µm; fase móvil: hexanos (TFA 0.1%) e IPA (TFA 0.1%) (se mantiene en IPA 4% (TFA 0.1%) en 10 min); detector: UV 254/220 nm. Se obtienen 56.2 mg de un sólido blanco. EM (ES): *m/z* 582 $(M+H)^+$. RMN ^1H (300 MHz, CD_3OD): δ 8.23 (s, 1H), 7.72-7.68 (m, 1H), 7.52-7.45 (m, 2H), 7.38-7.34 (m, 2H), 5.16 (t, 1H, *J* = 6.6 Hz), 4.06-3.97 (m, 2H), 3.46-3.32 (m, 1H), 2.74 (s, 3H), 1.65 (d, 6 H, *J* = 1.2 Hz), 0.95 (t, 6 H, *J* = 6.0 Hz).

Ejemplo 98: Síntesis del ácido 2-metil-2-[5-metil-1-[(2R)-2-(oxan-4-iloxi)-2-[2-(trifluorometil)fenil]etil]-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-266).

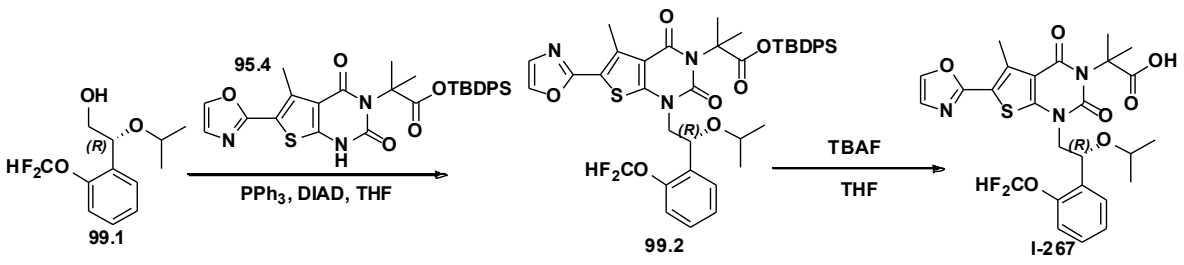




Síntesis del compuesto 98.1. El compuesto 98.1 se prepara a partir de 2-(trifluorometoxi)benzaldehído y oxan-4-ol utilizando el mismo método que para el compuesto 57.3. Se aísla un aceite incoloro con un rendimiento de 5% a partir de 2-(trifluorometoxi)benzaldehído.

Síntesis de compuesto I-266. compuesto I-266 se prepara a partir de 98.1 y 70.1 de una manera análoga al Ejemplo 97. EM (ES): *m/z* 608 $(M+H)^+$. RMN ^1H (CD_3OD, 300 MHz): 7.90 (2H, m), 771-7.63 (2H, m), 7.48-7.43 (1H, m), 7.20 (1H, s), 5.35-5.34 (1H, m), 4.30-4.24 (1H, m), 3.89-3.70 (1H, m), 3.55-3.34 (2H, m), 3.33-3.20 (2H, m), 2.73 (3H, s), 1.71-1.50 (8H, m), 1.37-1.20 (2H, m).

Ejemplo 99: Síntesis del ácido 2-[1-[(2R)-2-[2-(difluorometoxi)fenil]-2-(propan-2-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]-pirimidin-3-il]-2-metilpropanoico (I-267).

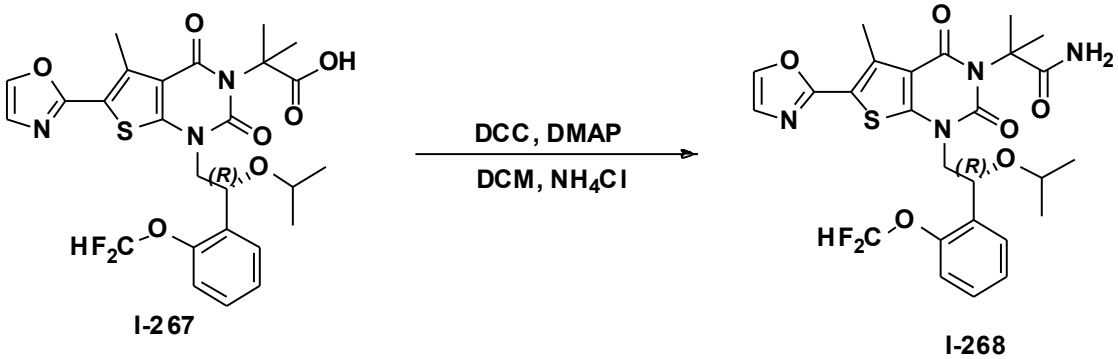


Síntesis del compuesto 99.1. El compuesto 99.1 se prepara a partir de 2-(difluorometoxi)benzaldehído e isopropanol utilizando el mismo método que para el compuesto 57.5.

Purificación: Columna Venusil chiral OD-H, 0.46*25 cm, 5 µm; fase móvil: hexanos:IPA = 98:2; detector: UV 220 nm. Se aísla un sólido blanco con un rendimiento de 13% a partir de 2-(difluorometoxi)benzaldehído.

Síntesis de compuesto I-267. El compuesto I-267 se prepara a partir de 99.1 y 95.4 de una manera análoga al compuesto I-264 (Ejemplo 96). Se aísla un sólido blanco con un rendimiento de 37% a partir de 95.4. EM (ES): *m/z* 564 $(M+H)^+$. RMN ^1H (DMSO-d_6, 300 MHz): δ 12.38 (1H, s amplio), 8.23 (1H, s), 7.62-7.61 (1H, d, *J* = 1.8 Hz), 7.60-7.22 (3H, m), 7.20-6.97 (2H, m), 5.20-5.16 (1H, t), 4.04 (2H, m), 3.47-3.33 (1H, m), 2.74 (3H, s), 1.65-1.64 (6H, d, *J* = 2.1 Hz), 0.98-0.93 (6H, m).

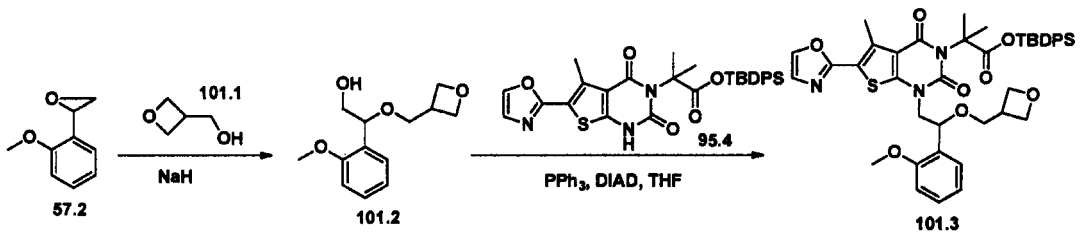
Ejemplo 100: Síntesis de 2-[1-[(2R)-2-[2-(difluorometoxi)fenil]-2-(propan-2-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanamida (I-268).

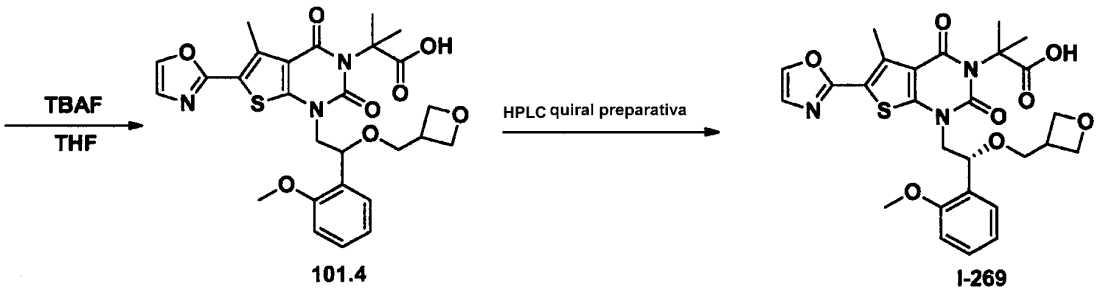


I-267 I-268

El compuesto I-268 se prepara a partir de I-267 y cloruro de amonio utilizando el mismo método que el Ejemplo 4. Se aísla un sólido blanco con un rendimiento de 80%. EM (ES): *m/z* 563 $(M+H)^+$. RMN ^1H (DMSO-d_6, 300 MHz): δ 8.22 (1H, s), 7.62-7.60 (1H, m), 7.31 (1H, m), 7.39-7.32 (3H, m), 7.21-6.96 (3H, m), 5.18 (1H, m), 4.03 (2H, m), 3.45-3.41 (1H, m), 2.73 (3H, s), 1.63 (6H, d), 0.96 (6H, d).

Ejemplo 101: Síntesis del ácido (R)-2-(1-(2-(2-metoxifenil)-2-(oxetan-3-ilmetoxi)etil)-5-metil-6-(oxazol-2-il)-2,4-dioxo-1,2-dihidrotieno[2,3-d]pirimidin-3(4H)-il)-2-metilpropanoico (I-269).

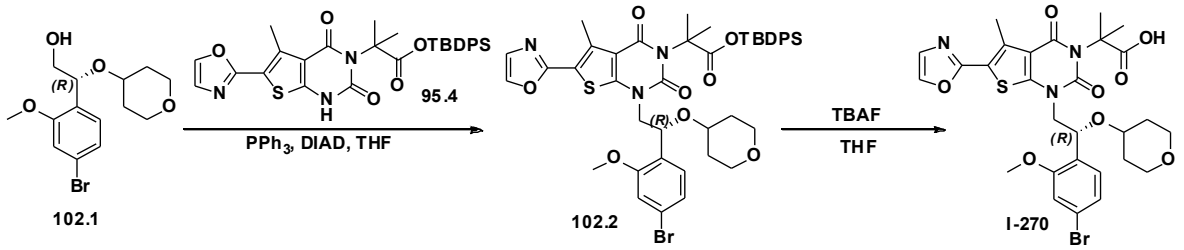




Síntesis del compuesto 101.2. El compuesto 101.1 se prepara a partir de 57.2 y 101.1 disponible comercialmente de una manera análoga a 73.2. Se aísla un aceite incoloro con un rendimiento de 38%.

Síntesis de compuesto I-269. El compuesto I-269 se prepara a partir de 95.4 y 101.2 de una manera análoga a I-265 (Ejemplo 97). Se aísla un sólido blanco con un rendimiento de 2% total a partir de 95.4.EM (ES): *m/z* 556 $(M+H)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 1.70 (d, 6H), 2.69 (s, 3H), 3.08-3.12 (m, 1H), 3.62-3.81 (m, 5H), 4.16-4.23 (m, 3H), 4.32-4.28 (m, 1H), 4.48-4.54 (m, 2H), 6.09 (m, 1H), 6.99-7.09 (m, 2H), 7.32 (s, 1H), 7.38-7.40 (m, 1H), 7.43-7.57 (m, 1H), 8.17 (s, 1H).

Ejemplo 102: ácido 2-[1-[(2R)-2-(4-bromo-2-metoxifenil)-2-(oxan-4-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-270).

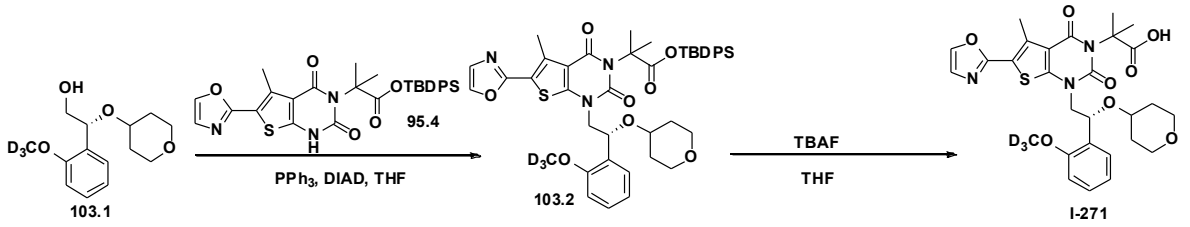


Síntesis del compuesto 102.1. El compuesto 102.1 se prepara a partir de 4-bromo-2-metoxibenzaldehído y oxan-4-ol de una manera análoga a 57.5. El enantiómero R se aísla por *HPLC* preparativa quiral bajo las siguientes condiciones: Columna: Chiralcel OJ-H: 0.46*25 cm, 5 µm; fase móvil, hexanos:EtOH = 75:25; detector: 254 nm. Se aísla un sólido blanco con un rendimiento total de 2%.

Síntesis de compuesto I-270. El compuesto I-270 se

prepara a partir de 95.4 y 102.1 de una manera análoga a I-264 (Ejemplo 96). Se aísla un sólido blanco con un rendimiento total de 27% a partir de 95.4. EM (ES): *m/z* 650 $(M+H)^+$. RMN ^1H (DMSO-d_6, 300 MHz): δ 8.24 (1H, s), 7.43-7.39 (2H, m), 7.25-7.21 (2H, m), 5.23-5.19 (1H, m), 4.07-3.95 (2H, m), 3.83 (3H, s), 3.59-3.49 (2H, m), 3.32-3.20 (2H, m), 2.75 (3H, s), 1.67-1.64 (8H, m), 1.35-1.31 (2H, m).

Ejemplo 103: Síntesis del ácido 2-[1-[(2R)-2-[2-(d_3)metoxifenil]-2-(oxan-4-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-dipirimidin-3-il]-2-metilpropanoico (I-271).

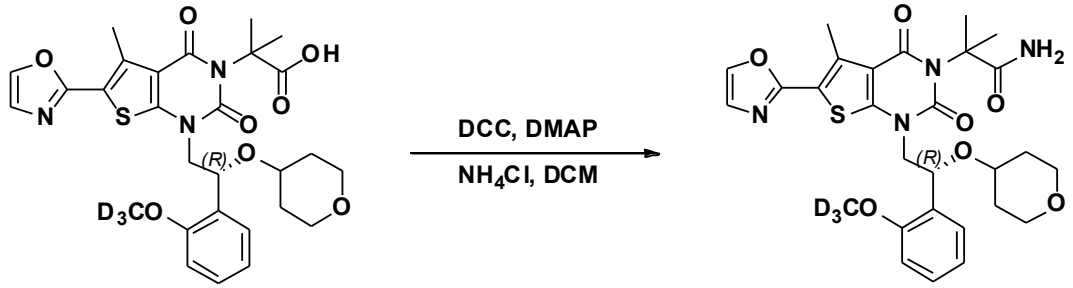


Síntesis del compuesto 103.1. El compuesto 103.1 se prepara a partir de 2-(d_3)metoxibenzaldehído y oxan-4-ol de una manera análoga a 57.5. El enantiómero R se aísla por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): Columna: Venusil Chiral OD-H: 21.1*25 cm, 5 µm; fase móvil, hexanos y EtOH (EtOH 5% por 12 min); detector: 220/254 nm. Se aísla un sólido blanco con un rendimiento total de 9%.

Síntesis de compuesto I-271. El compuesto I-271 se prepara a partir de 95.4 y 103.1 de una manera análoga al Ejemplo 96. Se aísla un sólido blanco con un rendimiento total

de 42% a partir de 95.4. EM (ES): *m/z* 573 $(M+H)^+$. RMN ^1H (DMSO-d_6, 300 MHz): δ 12.4 (1H, s amplio), 8.25 (1H, s), 7.50-7.49 (1H, d), 7.39 (1H, m), 7.34-7.28 (1H, m), 7.06-6.99 (2H, m), 5.30-5.26 (1H, m), 4.07-3.80 (2H, m), 3.59-3.48 (2H, m), 3.39-3.32 (1H, m), 3.27-3.20 (2H, m), 2.75 (3H, s), 1.69-1.67 (8H, m), 1.38-1.21 (2H, m).

Ejemplo 104: Síntesis de 2-[1-[(2R)-2-[2-(d_3)metoxifenil]-2-(oxan-4-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-dipirimidin-3-il]-2-metilpropanamida (I-272).

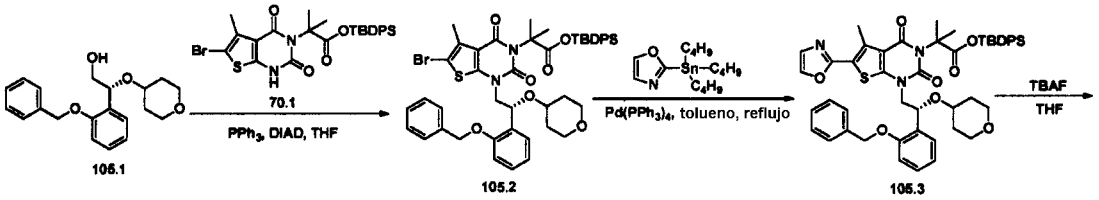


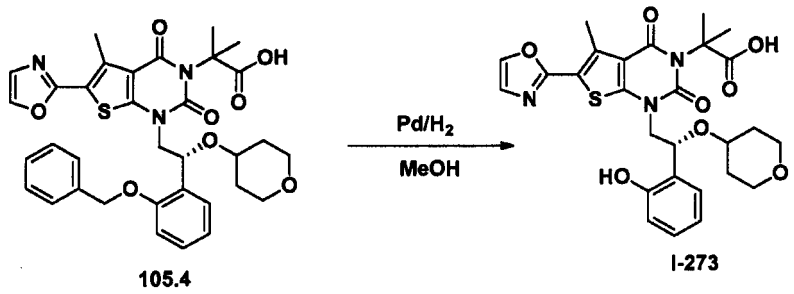
I-271 I-272

El compuesto I-272 se prepara a partir de I-271 (Ejemplo 103) y cloruro de amonio utilizando el mismo método que para el Ejemplo 4. Se aísla un sólido blanco con un rendimiento de 57%. EM (ES): *m/z* 594 $(M+Na)^+$. RMN ^1H (DMSO-d_6, 300 MHz): δ 1.20-1.33 (m, 2H), 1.65-1.67 (m, 8H), 2.75 (s, 3H), 3.20-3.26 (m, 2H), 3.33-3.37 (m, 1H), 3.50-3.58 (m, 2H), 3.94-4.04 (m, 2H), 5.26-5.31 (s, 1H), 6.99-7.06 (m, 4H), 7.27-7.29 (m, 1H), 7.32 (s, 1H), 7.47-7.50 (d, 1H), 8.22 (s, 1H).

Ejemplo 105: Síntesis del ácido 2-[1-[(2R)-2-(2-

hidroxifenil)-2-(oxan-4-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-273).





Síntesis del compuesto 105.1. El compuesto 105.1 se prepara a partir de 2-(benciloxi)benzaldehído y oxan-4-ol de una manera análoga al 57.5. El enantiómero R se aísla por SCF preparativa bajo las siguientes condiciones: Columna: Chiralpak AD-H, 2*25 cm; fase móvil: CO_2 (75%), etanol (25%); detector: UV 254 nm. Se aísla el producto con un rendimiento total de 10% a partir de 2-(benciloxi)benzaldehído.

Síntesis del compuesto 105.4. El compuesto 105.4 se prepara a partir de 70.1 y 105.1 de una manera análoga al Ejemplo 57. Se aísla un sólido blanco con un rendimiento total de 25% a partir de 70.1.

Síntesis de compuesto I-273. En un matraz de fondo

redondo de 100 ml se coloca 105.4 (100 mg, 0.15 mmol, 1.00 equivalentes) y 20 ml de metanol. Esto es seguido por la adición de 20 mg de paladio en carbono. El matraz se evacua y se purga tres veces con nitrógeno, seguido por purgado con hidrógeno. La mezcla se agita durante la noche a temperatura ambiente bajo una atmósfera de hidrógeno. Los sólidos se recolectan por filtración. El filtrado se concentra bajo vacío. El residuo se purifica por cromatografía en capa delgada revelado con diclorometano/MeOH/HOAc (30:1:0.15). Se obtienen 35.7 mg (41%) de I-273 como un sólido blanco. EM (ES): *m/z* 556 $(M+H)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 1.18-1.34 (m, 2H), 1.57-1.62 (m, 2H), 1.62 (s, 3H), 1.70 (s, 3H), 2.75 (s, 3H), 3.12-3.35 (m, 3H), 3.50-3.70 (m, 2H), 3.78 (m, 1H), 4.11-4.14 (m, 1H), 5.23-5.28 (m, 1H), 6.81-6.85 (m, 2H), 7.06-7.11 (m, 1H), 7.36-7.37 (m, 1H).

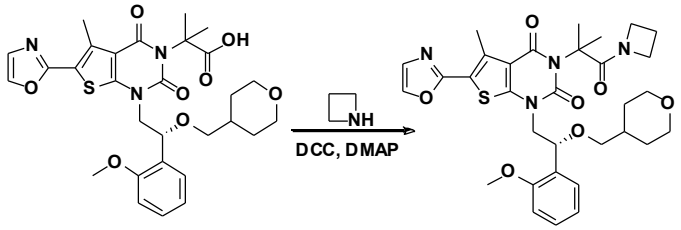
Ejemplo 106: Síntesis de 2-[1-[(2R)-2-[2-(difluorometoxi)fenil]-2-(oxan-4-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanamida (1-274).



I-264 **I-274**

El compuesto I-274 se prepara a partir de I-264 (Ejemplo 96) y cloruro de amonio de una manera análoga al Ejemplo 4. Se aísla 63.4 mg de un sólido blanco con un rendimiento de 57%. EM (ES): *m/z* 627 $(M+Na)^+$. RMN ^1H (DMSO-d_6, 300 MHz): δ 1.24-1.34 (m, 2H), 1.63-1.65 (m, 8H), 2.74 (s, 3H), 3.20-3.26 (m, 2H), 3.32 (m, 1H), 3.53 (m, 2H), 4.01-4.10 (m, 2H), 5.27 (m, 1H), 6.98 (s amplio, 1H), 6.98 (s amplio, 1H), 7.18 (s amplio, 1H), 7.21-7.32 (m, 1H), 7.34-7.47 (m, 3H), 7.62-7.64 (m, 1H), 8.22 (s, 1H).

Ejemplo 107: Síntesis de 3-[1-(azetidin-1-il)-2-metil-1-oxopropan-2-il]-1-[(2R)-2-(2-metoxifenil)-2-(oxan-4-ilmetoxi)etil]-5-metil-6-(1,3-oxazol-2-il)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-2,4-diona (I-275).

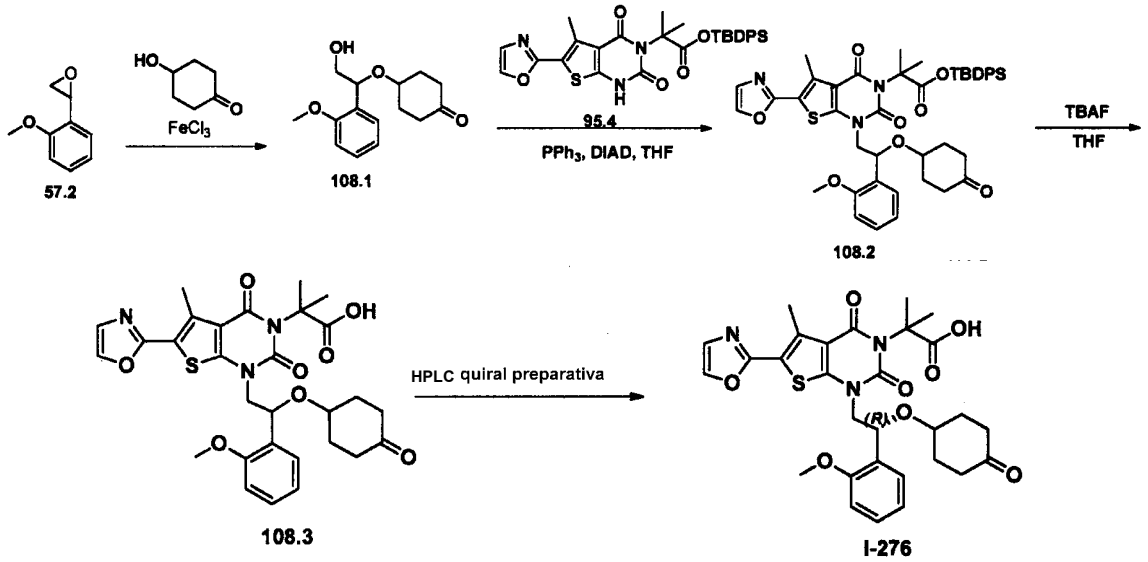


I-259 I-275

El compuesto I-275 se prepara a partir de I-259 (Ejemplo 90) y azetidina de una manera análoga al Ejemplo 4. Se utiliza un tubo sellado en vez de un matraz de fondo redondo. Se aíslan 46.8 mg de un sólido blanco con un rendimiento de 44%. EM (ES): *m/z* 623 $(M+H)^+$. RMN ^1H (DMSO-d_6, 300 MHz): δ 8.23 (1H, s), 7.40-7.28 (3H, m), 7.06-7.00 (2H, m), 5.14-5.09 (1H, t), 4.09 (1H, m), 3.87-3.84 (4H, m), 3.80

(3H, s), 3.78-3.69 (2H, m), 3.19-3.11 (3H, m), 3.06-3.00 (1H, m), 2.76 (3H, s), 2.14-2.09 (2H, m),1.63-1.61 (6H, d), 1.44-1.35 (2H, m), 1.10-1.03 (2H, m).

Ejemplo 108: Síntesis del ácido (R)-2-(1-(2-(2-metoxifenil)-2-((4-oxociclohexil)oxi)etil)-5-metil-6-(oxazol-2-il)-2,4-dioxo-1,2-dihidrotieno[2,3-d]pirimidin-3(4H)-il)-2-metilpropanoico (I-276).

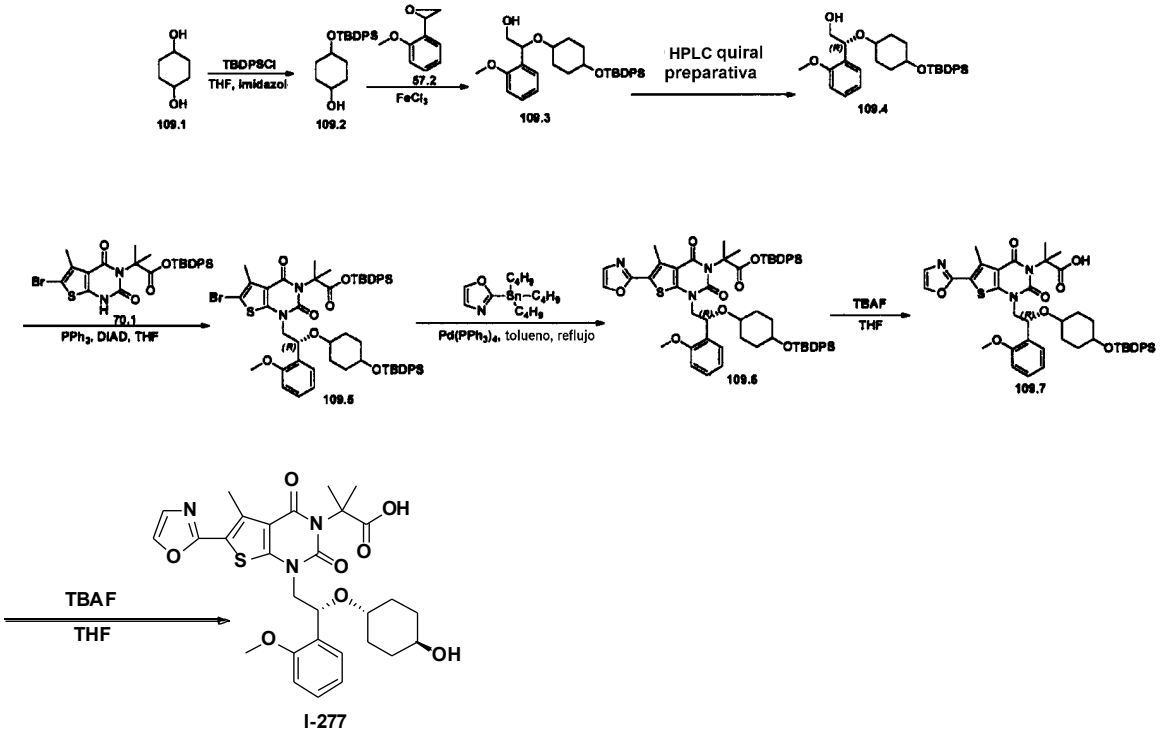


Síntesis del compuesto 108.1. El compuesto 108.1 se sintetiza a partir de 57.2 y 4-hidroxiciclohexan-1-ona utilizando el método para la síntesis del compuesto 57.3. Se aíslan 400 mg de un aceite incoloro con un rendimiento de 5%.

Síntesis de compuesto I-276. El compuesto 1-276 se prepara a partir de 108.1 y 95.4 de una manera análoga al Ejemplo 97. Se aíslan 7.7 mg (1% a partir de 95.4) de un sólido blanco. (EM (ES): *m/z* 582 $(M+H)^+$. RMN ^1H (300 MHz,

DMSO-d_6): δ 1.64-1.78 (m, 10H), 2.06-2.20 (m, 3H), 2.22-2.27 (m, 1H), 2.73 (s, 3H), 3.56 (m, 1H), 3.83 (s, 3H), 4.09 (m, 2H), 5.31-5.35 (m, 1H), 7.02-7.09 (m, 2H), 7.30-7.39 (m, 2H), 7.52-7.42 (d, 1H), 8.23 (s, 6H), 12.42 (s, 1H).

Ejemplo 109: ácido 2-[1-[(2R)-2-[(4-hidroxiciclohexil)oxi]-2-(2-metoxifenil)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-277).



Síntesis del compuesto 109.2. En un matraz de fondo redondo de 3 cuellos de 1000 ml se coloca ciclohexano-1,4-diol (20 g, 172.18 mmol, 1.00 equivalentes), 500 ml de 1,4-dioxano y 1H-imidazol (17.58 g, 258.24 mmol, 1.50 equivalentes). Esto

es seguido por la adición de una solución de ter-butil(cloro)difenilsilano (49.69 g, 180.78 mmol, 1.05 equivalentes) en 100 ml de dioxano, a gotas con agitación a 15°C. La solución resultante se agita durante 15 h a 15-20°C. Los sólidos se separan por filtración. El filtrado se diluye con 200 ml de agua. La solución resultante se extrae con 3 x 200 ml de acetato de etilo y las capas orgánicas se combinan y concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (0:1-1:60-1:50-1:30-1:20). La purificación proporciona 32.98 g (54%) de 109.2 como un semisólido blanco.

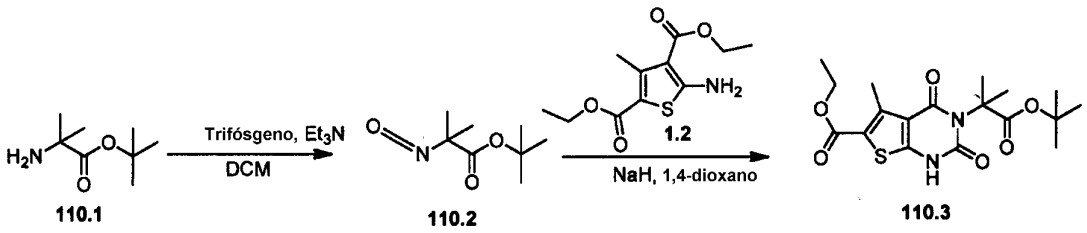
Síntesis del compuesto 109.4. El compuesto 109.4 se prepara a partir de 109.2 y 57.2 utilizando el procedimiento para la síntesis de 57.5. purificación: *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson): Columna: Venusil Chiral OD-H, 2 1.1 *25 cm, 5 µm; fase móvil: hexanos y etanol (que se mantiene a etanol 5% durante 15 min); detector: UV 220/254 nm.

Síntesis del compuesto 109.7. El compuesto 109.7 se prepara a partir de 70.1 y 109.4 de una manera análoga al Ejemplo 57. Se aísla un sólido blanco con rendimiento de 14% a partir de 70.1.

Síntesis de compuesto 1-277. En un matraz de fondo redondo de 10 ml se coloca una solución de 109.7 (100 mg, 0.12 mmol, 1.00 equivalentes) en 5 ml de tetrahidrofurano.

Se agregan 127 mg de TBAF y la solución resultante se agita durante 3 días a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se purifica por CCD preparativa eluyendo con metanol/DCM/HOAc (10:200:1). Se obtiene 7.8 mg (11%) del compuesto I-277 como un sólido blanco. EM (ES): *m/z* 584 $(M+H)^+$. RMN ^1H (300 MHz, CD_3OD): δ 0.88-0.94 (m, 1H), 1.01-1.29 (m, 3H), 1.48-1.84 (m, 10H), 2.70 (s, 3H), 2.97-3.22 (m, 1H), 3.38-3.44 (m ,1H), 3.75 (m, 3H) , 3.98 (m, 1H), 5.24-5.29 (t, 1H) , 6.83-6.94 (m, 2H), 7.15-7.20 (t, 2H) , 7.41-7.44 (d, 1H) , 7.86 (s, 1H).

Ejemplo 110: Síntesis del intermediario 110.3



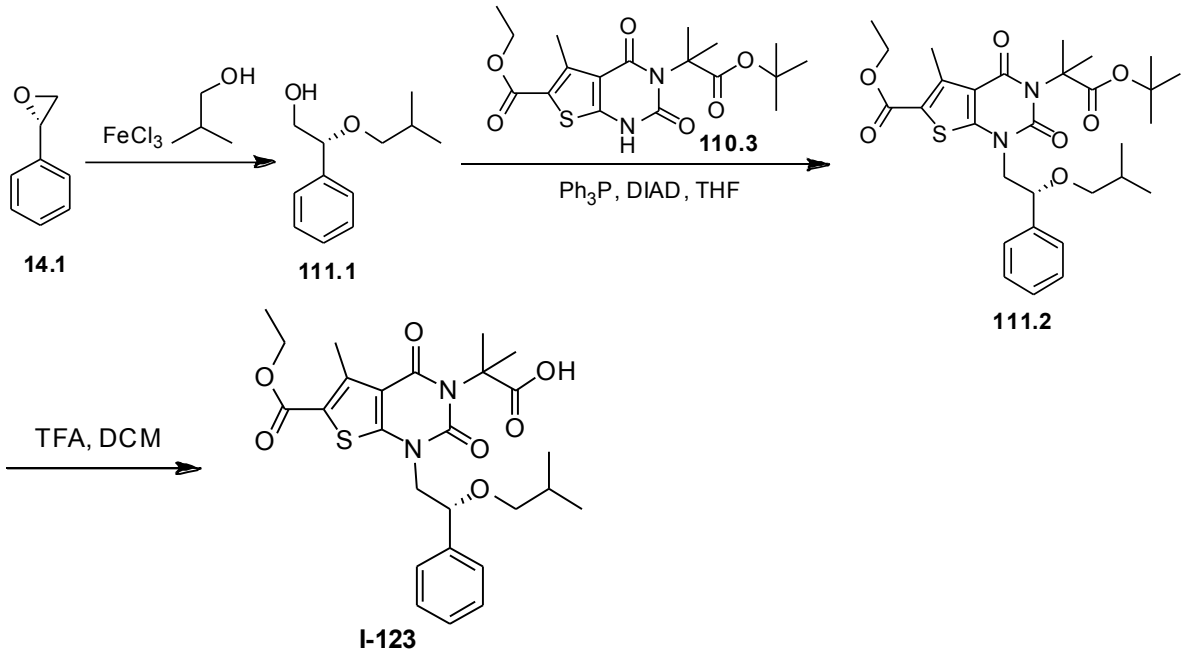
Síntesis del compuesto 110.2. En un matraz de fondo redondo de 3 cuellos de 100 ml se coloca una solución de 2-amino-2-metilpropanoato de terbutilo (1.2 g, 7.54 mmol, 1.00 equivalentes) en 20 ml de diclorometano. Esto es seguido por la adición de carbonato de ditriclorometilo (750 mg, 2.53 mmol, 0.34 equivalentes), en porciones a 0°C. Después de 30 min, se agrega a gotas con agitación trietilamina (2.3 g, 22.73 mmol, 3.02 equivalentes). La solución resultante se agita durante 5 h a temperatura ambiente y después se

concentra bajo vacío. El residuo se diluye con 20 ml de etil éter. Los sólidos se separan por filtración. El filtrado se concentra bajo vacío. La purificación proporciona 1.4 g (crudo) de 2-isocianato-2-metilpropanoato de terbutilo (1 10.2) como un aceite amarillo.

Síntesis de intermediario 110.3. En un matraz de fondo redondo de 3 cuellos de 100 ml se coloca una solución de 1.2 (1.62 g, 6.30 mmol, 1.00 equivalentes) en 20 ml de 1,4-dioxano. Esto es seguido por la adición de hidruro de sodio (280 mg, 7.00 mmol, 1.11 equivalentes, 60%) a 10°C, y la mezcla se agita a temperatura ambiente durante 15 min. A esto se agrega una solución de 110.2 (1.4 g, 7.56 mmol, 1.20 equivalentes) en 10 ml de 1,4-dioxano a gotas con agitación a 10°C. La solución resultante se agita a temperatura ambiente durante 30 min y después se calienta a 100°C con agitación durante la noche. La reacción después se suspende con la adición de 30 ml de NH_4Cl acuoso. La solución resultante se extrae con 3 x 50 ml de acetato de etilo y las capas orgánicas se combinan y se secan sobre sulfato de magnesio anhidro y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:10). La purificación proporciona 0.2 g (crudo) del intermediario 110.3 como un aceite amarillo.

Ejemplo 111: 2-[6-(etoxicarbonil)-5-metil-1-[(2R)-2-(2-metilpropoxi)-2-feniletil]-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-

d]pirimidin-3-il]-2-metilpropanoico (I-123).

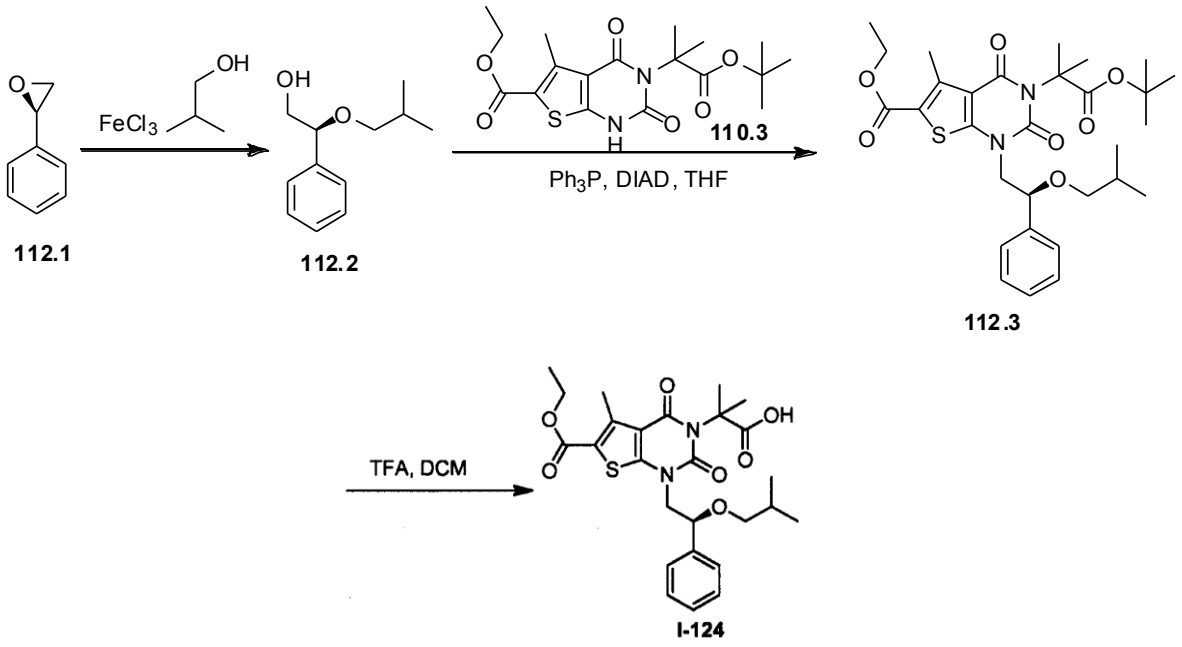


Síntesis del compuesto 111.1. El compuesto 111.1 se prepara a partir de metilpropan-1-ol y 14.1 de una manera análoga a la síntesis del compuesto 57.3. Se aísla 111.1 como un aceite incoloro con un rendimiento de 68%.

Síntesis del compuesto I-123. El compuesto 1-123 se prepara a partir de 111.1 y 110.3 de una manera análoga al compuesto 2.5. Se purifican 150 mg del producto crudo por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): Columna: Chiralpak IC, 2*25 cm, 5 µm; fase móvil: hexanos y etanol (TFA 0.1%) (que se mantiene en etanol 5.0% (TFA 0.1%) durante 15 min); detector: UV 220/254 nm. Se aíslan 33.7 mg de un sólido café claro con un rendimiento de 12% a partir de 110.3. EM (ES): *m/z* 517 $(M+H)^+$, 539 $(M+Na)^+$, 580 $(M+Na+CH_3CN)^+$. RMN ^1H (300 MHz, CD_3CN): δ 0.67-0.73 (m, 6H),

1.31 (t, *J* = 6.9, 3H), 1.60-1.67 (m, 1H), 1.70 (s, 6H), 2.71 (s, 3H), 2.93-3.09 (m, 2H), 3.79-3.87 (m, 1H), 4.08-4.13 (m, 1H), 4.28 (c, *J* = 7.2, 2H), 4.69-4.73 (m, 1H), 7.32-7.39 (m, 5H).

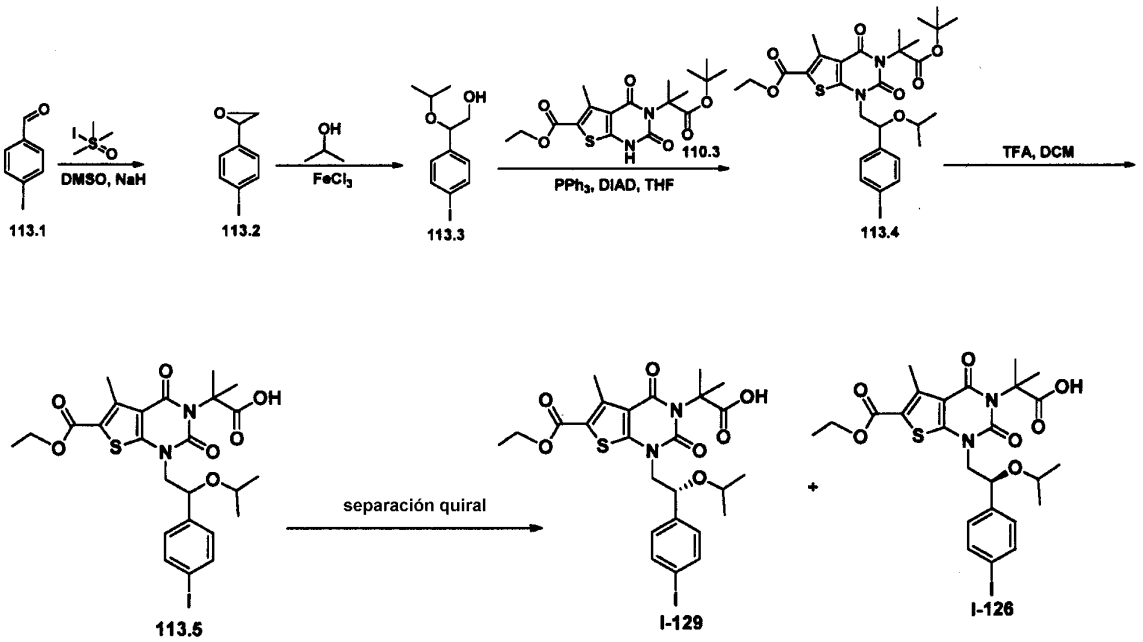
Ejemplo 112: ácido 2-[6-(etoxicarbonil)-5-metil-1-[(2S)-2-(2-metilpropoxi)-2-feniletil]-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-124).



El compuesto I-124 se prepara a partir de 112.1 y 110.3 de una manera análoga al Ejemplo 111. Se aíslan 22.2 mg (10% a partir de 110.3) como un sólido café claro. EM (ES): *m/z* 517 $(M+H)^+$, 539 $(M+Na)^+$, 580 $(M+Na+CH_3CN)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 0.64-0.72 (m, 6H), 1.31 (t, *J* = 6.9, 3H), 1.65 (s, 6H), 2.68 (s, 3H), 2.89-3.03 (m, 2H), 3.80-3.88 (m, 1H), 4.05-4.11 (m, 1H), 4.25 (C, *J* = 7.2, 2H), 4.64-4.68 (m,

1H), 7.31-7.41 (m, 5H).

Ejemplo 113: Síntesis del ácido (R)-2-(6-(etoxicarbonil)-1-(2-(4-yodofenil)-2-isopropoxietil)-5-metil-2,4-dioxo-1,2-dihidrotieno[2,3-d]pirimidin-3(4H)-il)-2-metilpropanoico (I-129) y Ejemplo 114: Síntesis del ácido (S)-2-(6-(etoxicarbonil)-1-(2-(4-yodofenil)-2-isopropoxietil)-5-metil-2,4-dioxo-1,2-dihidrotieno[2,3-d]-pirimidin-3(4H)-il)-2-metilpropanoico (I-126).



Síntesis del compuesto 113.3. El compuesto 113.3 se prepara de una manera análoga al compuesto 57.3. Se aíslan 1.036 g (59% de 113.1) como un aceite incoloro.

Síntesis del compuesto 113.5. El compuesto 113.5 se prepara de una manera análoga al compuesto 2.5. Se aísla 1.2 g de un sólido blanco con rendimiento de 79% a partir de 110.3.

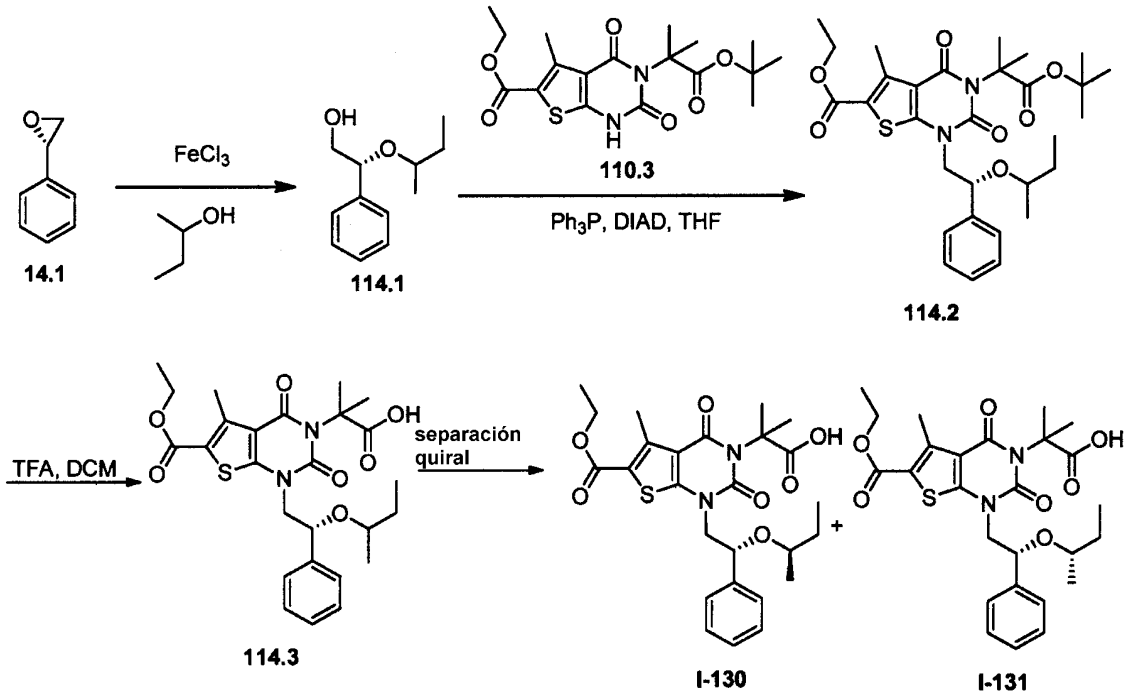
Síntesis de los compuestos I-129 y I-126. Los enantiómeros de 113.5 (1.2 g) se separan por *HPLC* preparativa quiral bajo las siguientes condiciones: (Gilson Gx 281): Columna: Chiralpak IC, 2*25 cm, 5 µm; fase móvil: hexanos y etanol (que se mantiene a 15.0% etanol por 23 min); detector: UV 220/254 nm. 325.8 mg de I-129 (tR = 18.56 min) y 325.7 mg de I-126 (tR 13.09 min) se obtienen como sólidos blancos.

Datos analíticos para el compuesto I-129: EM (ES): *m/z* 629 $(M+H)^+$, 692 $(M+Na+CH_3CN)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 0.89 (d, 3H), 0.91(d, 3H), 1.28 (t, 3H), 1.62 (s, 6H), 2.68 (s, 3H), 3.41 (m, 1H), 3.76 (m, 1H), 4.01 (d, 1H) , 4.26 (c, 2H), 4.73 (m, 1H), 7.19 (d, 2H), 7.73 (d, 2H), 12.3 (s amplio, 1H).

Datos analíticos para el compuesto I-126: EM (ES): *m/z* 629 $(M+H)^+$, 692 $(M+Na+CH_3CN)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 0.89 (d, 3H), 0.91 (d, 3H), 1.28 (t, 3H), 1.62 (s, 6H), 2.68 (s, 3H), 3.41 (m, 1H), 3.76 (m, 1H), 4.0 (d, 1H), 4.26 (c, 2H), 4.73 (m, 1H), 7.18 (d, 2H), 7.73 (d, 2H), 12.3 (s amplio, 1H).

Ejemplo 114: Síntesis del ácido 2-[1-[(2R)-2-[(2R)-butan-2-iloxi]-2-feniletil]-6-(etoxicarbonil)-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-130) y Ejemplo 115: Síntesis del ácido 2-[1-[(2R)-2-[(2R)-butan-2-iloxi]-2-feniletil]-6-

(etoxicarbonil)-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-131)



Síntesis del compuesto 114.1. El compuesto 114.1 se prepara a partir de 14.1 de una manera análoga al compuesto 57.3. Se aíslan 1.3 g (40%) de un aceite incoloro.

Síntesis del compuesto 114.3. El compuesto 114.3 se prepara de una manera análoga al 2.5. Se aíslan 320 mg de un sólido blanco con un rendimiento de 77% a partir de 110.3.

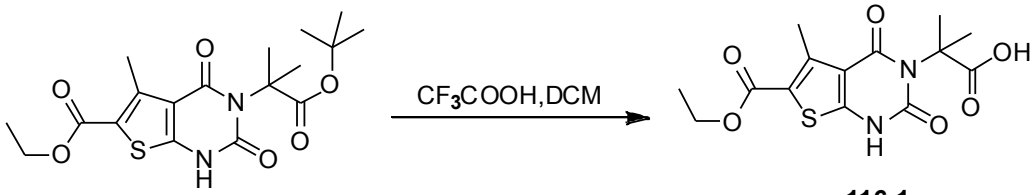
Síntesis de los compuestos I-130 y I-131. Los enantiómeros de 114.3 se separan por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson): Columna: Phenomenex Lux 5u Cellulose-4, 2.12*25, 5 µm; fase móvil: hexanos (TFA 0.1%) y etanol (que se mantiene en etanol 5.0% en 22 min);

detector: UV 220/254 nm. El compuesto I-130 es el primer compuesto en eluir y se aísla con un rendimiento de 65% (117.4 mg) como un sólido blanco. El compuesto I-131 es el segundo en eluir y se aísla con un rendimiento de 54% (97.2 mg) como un sólido blanco.

Datos analíticos para el compuesto I-130: EM (ES): *m/z* 517 $(M+H)^+$, 539 $(M+Na)^+$, 580 $(M+Na+CH_3CN)^+$. RMN ^1H (300 MHz, CD_3OD): δ 0.66 (t, *J* = 6.9, 3H), 0.91 (d, *J* = 6.3, 3H), 1.26-1.35 (m, 2H), 1.40 (t, *J* = 7.5, 3H), 1.75-1.77 (m, 6H), 2.75 (s, 3H), 3.28-3.34 (m, 1H), 3.80-3.83 (m, 1H), 4.09-4.15 (m, 1H), 4.31 (c, *J* = 7.2, 2H), 7.29-7.43 (m, 5H).

Datos analíticos para el compuesto I-131: EM (ES): *m/z* 517 $(M+H)^+$, 539 $(M+Na)^+$, 580 $(M+Na+CH_3CN)^+$. RMN ^1H (300 MHz, CD_3OD): δ 0.66 (t, *J* = 6.9, 3H), 0.91 (d, *J* = 6.3, 3H), 1.26-1.35 (m, 2H), 1.40 (t, *J* = 7.5, 3H), 1.75-1.77 (m, 6H), 2.75 (s, 3H), 3.28-3.34 (m, 1H), 3.80-3.83 (m, 1H), 4.09-4.15 (m, 1H), 4.31 (c, *J* = 7.2, 2H), 7.29-7.43 (m, 5H).

Ejemplo 116: Síntesis del intermediario 116.1.

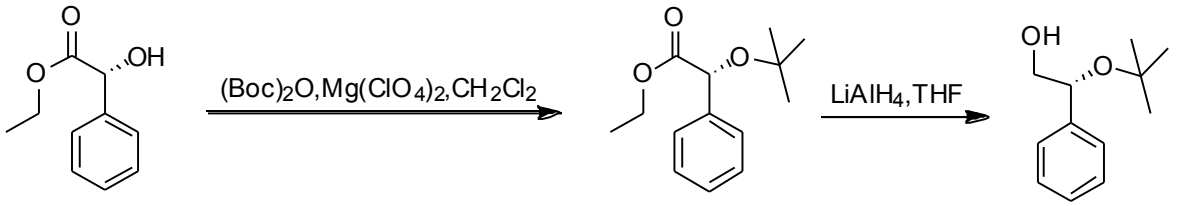


110.3 **116.1**

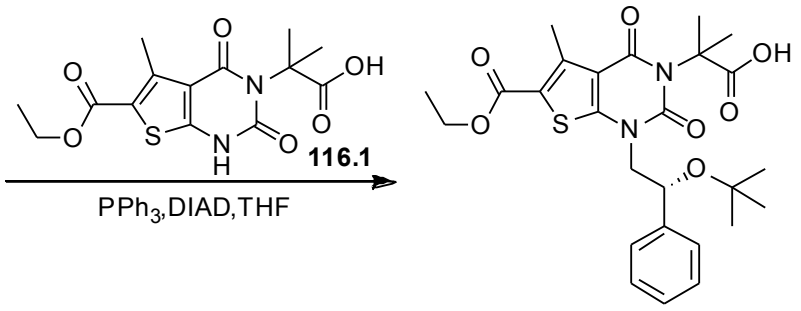
En un matraz de fondo redondo de 25 ml se coloca 110.3 (500 mg, 1.26 mmol, 1.00 equivalentes), 10 ml de diclorometano y 3 ml de CF_3COOH. La solución resultante se

agita durante 3 h a temperatura ambiente y después se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:20). La purificación proporciona 0.409 g (95%) del intermediario 116.1 como un sólido blanco.

Ejemplo 117: Síntesis del ácido 2-[1-[(2R)-2-(ter-butoxi)-2-feniletil]-6-(etoxicarbonil)-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-127).



117.1 117.2 117.3



I-127

Síntesis del compuesto 117.2. En un matraz de fondo redondo de 3 cuellos de 100 ml se coloca (2R)-2-hidroxi-2-fenilacetato de etilo (117.1, 5 g, 27.75 mmol, 1.00 equivalentes), 50 ml de diclorometano, $Mg(ClO_4)_2$ (0.619 g, 0.10 equivalentes) y $(BoC)_2O$ (13.912 g, 63.74 mmol, 2.30

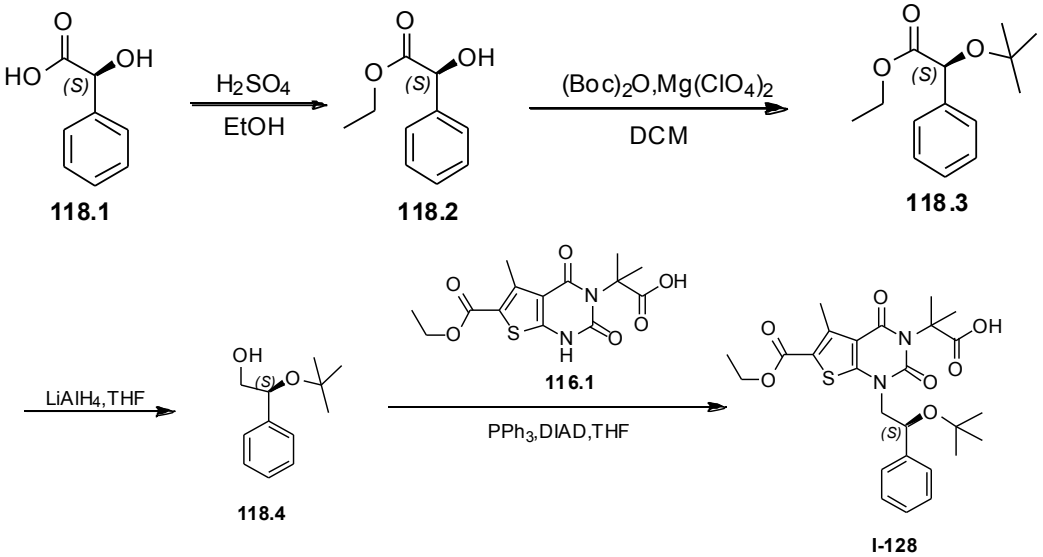
equivalentes). La solución resultante se agita durante la noche a 40°C. La reacción después se suspende por adición de agua. La solución resultante se extrae con acetato de etilo y las capas orgánicas se combinan, se secan y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con EA/PE (1:25). La purificación proporciona 2.5 g (38%) de (2R)-2-(ter-butoxi)-2-fenilacetato de etilo (117.2) como un líquido amarillo claro.

Síntesis del compuesto 117.3. En un matraz de fondo redondo de 50 ml se colocan 10 ml de tetrahidrofurano, 117.2 (500 mg, 2.12 mmol, 1.00 equivalentes) y $LiAlH_4$ (81 mg, 2.13 mmol, 1.01 equivalentes). La solución resultante se agita durante 2 h a 0°C en un baño de agua/hielo. La reacción después se suspende por la adición de 20 ml de acetato de etilo. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:5). La purificación proporciona 0.38 g (92%) de (2R)-2-(ter-butoxi)-2-feniletan-1-ol (117.3) como un sólido blanco.

Síntesis de compuesto I-127. En un matraz de fondo redondo de 3 cuellos de 100 ml purgado y mantenido con una atmósfera inerte de nitrógeno se coloca 116.1 (200 mg, 0.59 mmol, 1.00 equivalentes), 30 ml de tetrahidrofurano, DIAD (238 mg, 1.18 mmol, 2.00 equivalentes), PPh_3 (309 mg, 1.18 mmol, 2.00 equivalentes) y 117.3 (114 mg, 0.59 mmol, 1.00

equivalentes). La solución resultante se agita durante la noche a temperatura ambiente y después se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/hexan0 (1:25). El producto obtenido de esta manera (100 mg) se purifica por *HPLC* preparativa bajo las siguientes condiciones (Waters): Columna: Xbridge Prep Phenil 5 µm, 19*150 mm; fase móvil: agua (NH_4HCO_3 0.05%) y CH_3CN (CH_3CN 6.0% hasta 50.0% en 10 min); detector: 220/254 nm. Se obtienen 24.9 mg (8%) del compuesto I-127 como un sólido blanco. EM (ES): *m/z* 517 $(M+H)^+$; 443 $(M-C_4H_9O)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 0.94 (s, 9H), 1.22-1.27 (t, 3H), 1.58-1.61 (d, 6H), 2.61 (s, 3H), 3.80-3.86 (c, 2H), 4.19-4.24 (m, 2H), 4.66-4.70 (m, 1H), 7.09-7.46 (m, 5H), 12.38-12.51 (s, 1H).

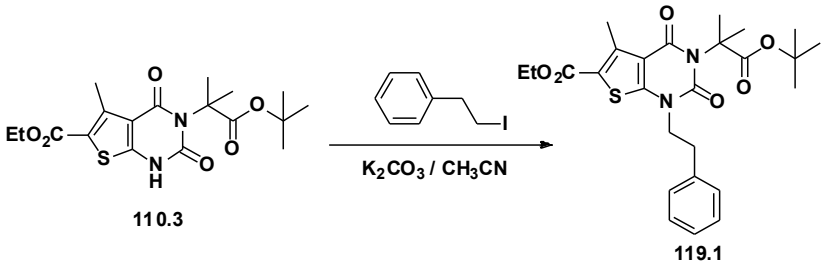
Ejemplo 118: Síntesis del ácido 2-[1-[(2S)-2-(ter-butoxi)-2-feniletil]-6-(etoxicarbonil)-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-128).



Síntesis del compuesto 118.4. El compuesto 118.4 se prepara a partir de 118.1 de una manera análoga al compuesto 117.3. Se aíslan 220 mg de un sólido blanco con un rendimiento general de 16%.

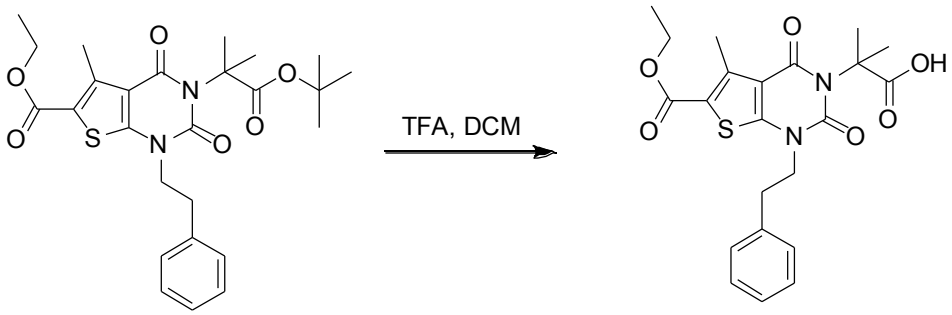
Síntesis de compuesto I-128. El compuesto I-128 se prepara a partir de 118.4 y 116.1 de una manera análoga al Ejemplo 117. EM (ES): *m/z* 517 $(M+H)^+$, 443 $(M-C_4H_9O)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 0.94 (s, 9H), 1.22-1.27 (t, 3H), 1.59-1.61 (d, 6H), 2.61 (s, 3H), 3.79-3.82 (c, 2H), 4.19-4.26 (c, 2H), 4.66-4.70 (m, 1H), 7.09-7.43 (m, 5H), 12.382 (s, 1H).

Ejemplo 119: Síntesis de Intermediario 119.1.



Síntesis del compuesto 119.1. En un matraz de fondo redondo de 3 cuellos de 100 ml se coloca 110.3 (1 g, 2.52 mmol, 1.00 equivalentes), 50 ml de CH_3CN, carbonato de potasio (1.045 g, 7.56 mmol, 3.00 equivalentes) y (2-yodoetil)benceno (1.172 g, 5.05 mmol, 2.00 equivalentes). La solución resultante se agita durante 4 h a 80°C. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con EA/PE (1:100-1:15). La purificación proporciona 1.24 g (98%) de 119.1 como un sólido blanco.

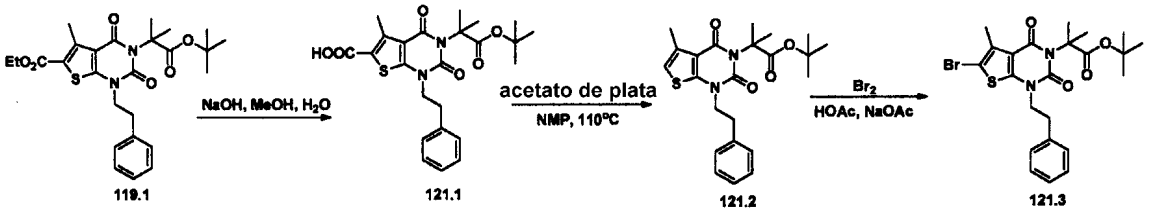
Ejemplo 120: Síntesis del ácido 2-[6-(etoxicarbonil)-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-70).



119.1 I-70

El compuesto I-70 se sintetiza siguiendo el procedimiento del intermediario 116.1. Se aíslan 50 mg de un sólido blanco con un rendimiento de 38%. EM (ES): *m/z* 445 $(M+H)^+$. RMN ^1H (DMSO-d_6, 300 MHz): δ 1.29 (t, *J* = 9.6 Hz, 3H), 1.63 (s, 6H), 2.70 (s, 3H), 2.98 (t, *J* = 9.6 Hz, 2H), 4.07 (t, *J* = 9.6 Hz, 2H), 4.27 (c, *J* = 9.6 Hz, 2H), 7.19-7.31 (m, 5H), 12.40 (s, 1H).

Ejemplo 121: Síntesis del intermediario 121.3.



119.1 121.1 121.2 121.3

Síntesis del compuesto 121.1. En un matraz de fondo

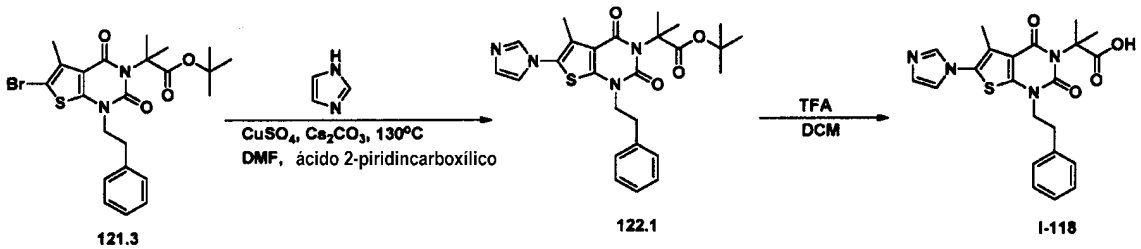
redondo de 3 cuellos de 100 ml se coloca 119.1 (1.017 g, 2.03 mmol, 1.00 equivalentes) y 40 ml de metanol. Después se agrega a gotas una solución de hidróxido de sodio (162 mg, 4.05 mmol, 2.00 equivalentes) en 5 ml de agua. La solución resultante se agita durante la noche a temperatura ambiente. La reacción después se suspende por la adición de HCl acuoso. La solución resultante se extrae con acetato de etilo y las capas orgánicas se combinan y se concentran bajo vacío. El producto crudo se purifica por recristalización a partir de EA/PE en la relación de 1:4. Se obtienen 0.578 g (60%) de 121.1 como un sólido blanco.

Síntesis del compuesto 121.2. En un matraz de fondo redondo de 3 cuellos de 100 ml se coloca 121.1 (578 mg, 1.22 mmol, 1.00 equivalentes), 40 ml de NMP, carbonato de potasio (169 mg, 1.22 mmol, 1.00 equivalentes) y 0.204 g de AgOAc. La solución resultante se agita durante 2 h a 110°C. La reacción después se suspende por la adición de agua. La solución resultante se extrae con acetato de etilo y las capas orgánicas se combinan y concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con EA/PE (1:25). La purificación proporciona 0.445 g (85%) de 121.2 como un sólido blanco

Síntesis del compuesto 121.3. En un matraz de fondo redondo de 50 ml se coloca 121.2 (445 mg, 1.04 mmol, 1.00 equivalentes), 5 ml de ácido acético y 0.170 g CH_3COONa.

Después se agregan a gotas Br_2 (167 mg, 1.04 mmol, 1.01 equivalentes). La solución resultante se agita durante 15 min a temperatura ambiente y después se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con EA/PE (1:25). La purificación proporciona 0.502 g (95%) del intermediario 121.3 como un sólido blanco.

Ejemplo 122: Síntesis del ácido 2-[6-(1H-imidazol-1-il)-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-118).



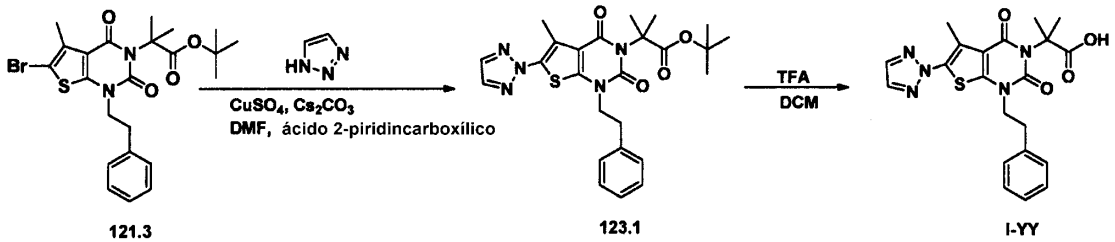
121.3 122.1 I-118

Síntesis del compuesto 122.1. En un tubo sellado de 10 ml, purgado y mantenido con una atmósfera de nitrógeno, se coloca una solución de 121.3 (200 mg, 0.39 mmol, 1.00 equivalentes) en 5 ml de N,N-dimetilformamida, 1H-imidazol (200 mg, 2.94 mmol, 7.45 equivalentes), ácido piridin-2-carboxílico (50 mg, 0.41 mmol, 1.03 equivalentes), $CuSO_4$ (100 mg, 0.63 mmol, 1.60 equivalentes) y Cs_2CO_3 (400 mg, 1.23 mmol, 3.11 equivalentes). La solución resultante se agita durante la noche a 140°C. La reacción después se suspende por la adición de 5 ml de NH_4Cl acuoso. La solución resultante se extrae con 3 x 5 ml de acetato de etilo y las capas orgánicas se combinan

y concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:2). La purificación proporciona 166 mg (85%) de 122.1 como un aceite café.

Síntesis del compuesto I-118. En un matraz de fondo redondo de 100 ml se coloca 122.1 (166 mg, 0.34 mmol, 1.00 equivalentes), 10 ml de diclorometano y 2 ml de ácido trifluoroacético. La solución resultante se agita durante 4 h a temperatura ambiente y después se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con diclorometano/metanol (50:1). La purificación proporciona 121.7 mg (83%) de I-118 como un sólido amarillo. EM (ES): *m/z* 439 $(M+H)^+$. RMN ^1H (DMSO-d_6, 300 MHz): δ 1.61 (s, 6 H), 2.13 (s, 3 H), 2.95 (t, *J* = 7.2 Hz, 2H), 4.00 (t, *J* = 7.2 Hz, 2 H), 7.47-7.16 (m, 5 H), 7.47 (s, 1 H), 8.09 (s, 1 H), 12.38 (s amplio, 1 H).

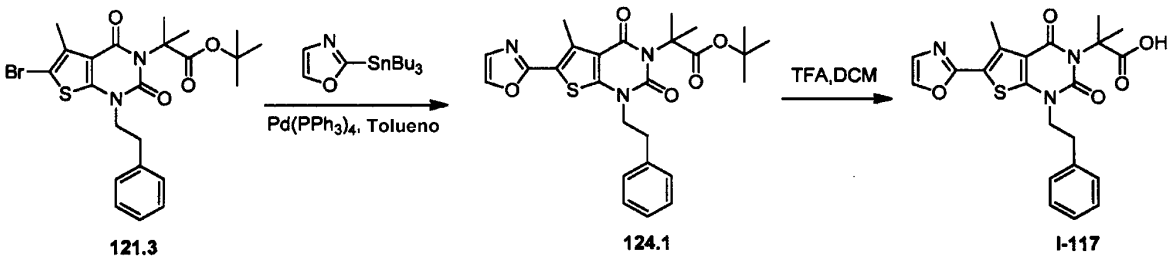
Ejemplo 123: Síntesis del ácido 2-metil-2-[5-metil-2,4-dioxo-1-(2-feniletil)-6-(2H-1,2,3-triazol-2-il)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-122).



El compuesto I-122 se prepara a partir de 1H-

1,2,3-triazol y el intermediario 121.3 siguiendo el procedimiento del ejemplo 122. Se aíslan 20.6 mg de un sólido blanco con un rendimiento de 5% a partir de 123.1. EM (ES): *m/z* 440 $(M+H)^+$. RMN ^1H (CD_3OD, 300 MHz): δ 1.75 (s, 6H), 2.51 (s, 3H), 3.05 (t, *J* = 7.2 Hz, 2H), 4.08 (t, *J* = 7.2 Hz, 2H), 7.26-7.12 (m, 5H), 7.91 (s, 1H).

Ejemplo 124: Síntesis del ácido 2-metil-2-[5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-117).

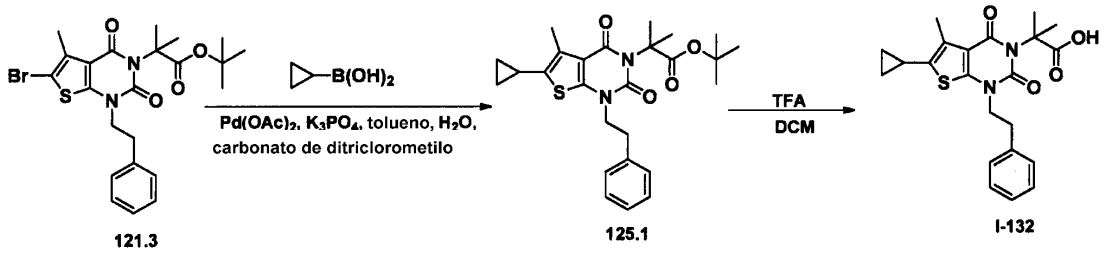


121.3 124.1 I-117

Se prepara el compuesto I-117 a partir de 121.3 de una manera análoga al procedimiento del ejemplo 7. EM (ES): *m/z* 440 $(M+H)^+$. RMN ^1H (400 MHz, CD_3OD): δ 1.79 (s, 6 H), 2.78 (s, 3 H), 3.11 (t, *J* = 7.2 Hz, 2 H), 4.15 (t, *J* = 7.2 Hz , 2 H), 7.19-7.23 (m, 1 H), 7.25-7.31 (m, 5 H) , 7.96 (s, 1 H).

Ejemplo 125: Síntesis del ácido 2-[6-ciclopropil-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-

metilpropanoico (I-132).

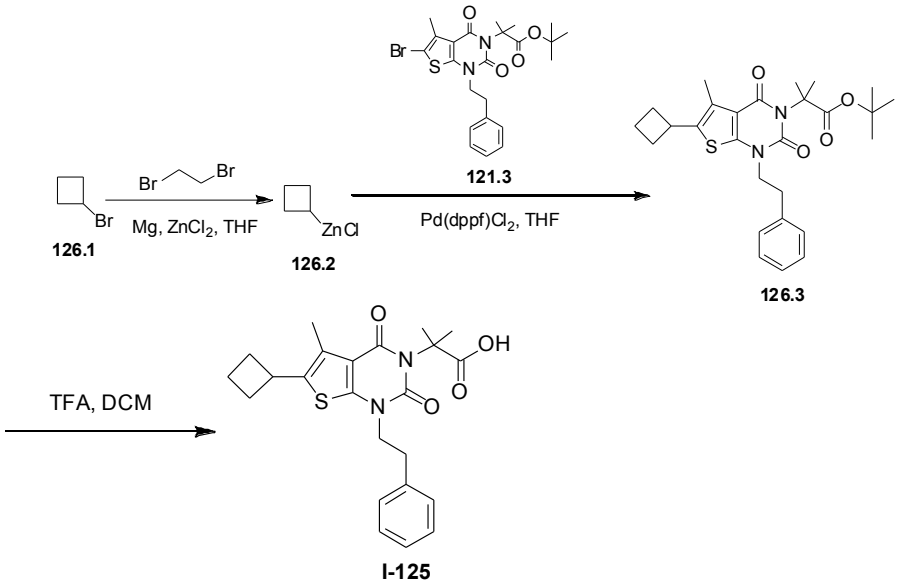


Síntesis del compuesto 125.1. En un matraz de fondo redondo de 3 cuellos de 100 ml, purgado y mantenido con una atmósfera inerte de nitrógeno se coloca 121.3 (200 mg, 0.39 mmol, 1.00 equivalentes), ácido ciclopropilborónico (200 mg, 2.33 mmol, 5.91 equivalentes), carbonato de ditriclorometilo (20 mg, 0.07 mmol, 0.17 equivalentes), K_3PO_4 (300 mg, 1.41 mmol, 3.59 equivalentes), $Pd(OAc)_2$ (10 mg, 0.04 mmol, 0.11 equivalentes), 0.5 ml de agua y 20 ml de tolueno. La solución resultante se calienta a reflujo durante 2 h y después se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:10). La purificación proporciona 170 mg de un sólido blanco.

Síntesis del compuesto I-132. En un matraz de fondo redondo de 50 ml se coloca 125.1 (170 mg, 0.36 mmol, 1.00 equivalentes), 1 ml de ácido trifluoroacético y 5 ml de diclorometano. La solución resultante se agita durante la noche a temperatura ambiente y después se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con diclorometano/metanol (20:1). La purificación proporciona

22 mg (15%) de I-132 como un sólido blanco. EM (ES): *m/z* 413 $(M+H)^+$. RMN ^1H (CD_3OD, 400 MHz): δ 0.67 (t, *J* = 5.2 Hz, 2H), 0.97 (t, *J* = 8 Hz, 2H), 1.80 (s, 6H), 1.90-2.00 (m, 1H), 2.41 (s, 3H), 3.03 (t, *J* = 6.8 Hz, 2H), 4.08 (t, *J* = 6.8 Hz, 2H), 7.29-7.18 (m, 5H).

Ejemplo 126: Síntesis del ácido 2-[6-ciclobutil-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-125).



Síntesis del compuesto 126.2. En matraz de fondo redondo de 3 cuellos de 100 ml se coloca una suspensión de 0.46 g de Mg en 10 ml de tetrahidrofurano, seguido por una porción de aproximadamente 10% de un lote de 2 g de bromociclobutano (14.81 mmol, 1.00 equivalentes). Después se agregan varias gotas de 1,2-dibromoetano para iniciar la reacción. Esto es seguido por la adición de una solución de bromociclobutano remanente (2 g, 14.81 mmol, 1.00

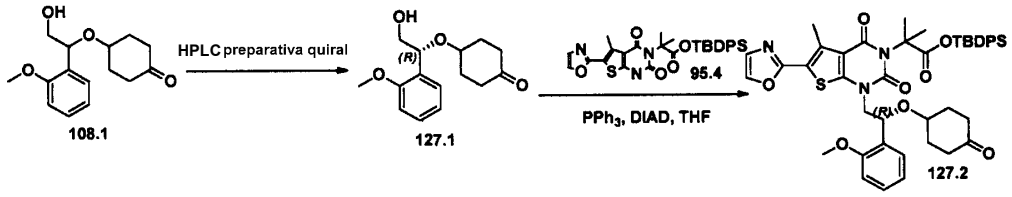
equivalentes) en TF a gotas. La solución resultante se agita 2 h a temperatura ambiente. Después de enfriar a 0°C, se agrega en porciones $ZnCl_2$ (2.22 g, 16.29 mmol, 1.10 equivalentes). La solución resultante se agita durante 2 h a temperatura ambiente y se utilizan directamente para la siguiente etapa.

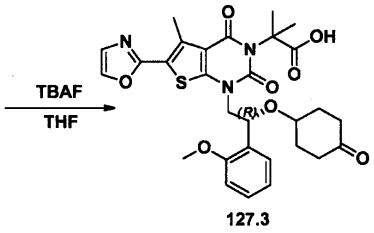
Síntesis del compuesto 126.3. Una solución de $Pd(dppf)Cl_2$ (72 mg, 0.10 mmol, 0.10 equivalentes) y 121.3 (500 mg, 0.99 mmol, 1.00 equivalentes) en 5 ml de tetrahidrofurano se agrega a un matraz de cloro(ciclobutil)zinc (126.2, solución cruda). La solución resultante se agita durante la noche a temperatura ambiente. La reacción después se suspende por la adición de 50 ml de NH_4Cl acuoso. La solución resultante se extrae con 3 x 100 ml de acetato de etilo y las capas orgánicas se combinan y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:40). La purificación proporciona 240 mg (50%) de 126.3 como un aceite incoloro.

Síntesis del compuesto I-125. En un matraz de fondo redondo de 50 ml se colocan 5 ml de diclorometano, 126.3 (240 mg, 0.50 mmol, 1.00 equivalentes) y 2 ml de ácido trifluoroacético. La solución resultante se agita durante 2 h a temperatura ambiente y después se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con diclorometano/metanol (50:1). La purificación proporciona 43.5 mg (21%) del compuesto I-125 como un sólido blanco. EM (ES):

m/z 426 $(M+H)^+$, 449 $(M+Na)^+$, 490 $(M+Na+CH_3CN)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 1.59 (s, 6H), 1.77-1.81 (m, 1H), 1.90-2.00 (m, 3H), 2.18 (s, 3H), 2.31-2.34 (m, 2H), 2.93 (t, *J* = 7.5, 2H), 3.71-3.77 (m, 1H), 3.99 (t, *J* = 7.5, 2H), 7.15-7.28 (m, 5H).

Ejemplo 127: Síntesis del intermediario 127.3

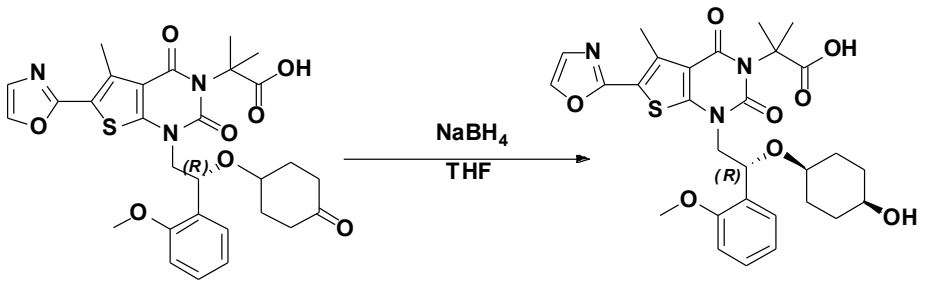




Síntesis del compuesto 127.1. Los enantiómeros de la forma racémica de 108.1 (400 mg) se separan por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): columna: Venusil Chiral OD-H, 21.1*25 cm, 5 µm; fase móvil: hexanos e IPA (que se mantiene en 5% IPA durante 36 min); detector: UV 254/220 nm. Se obtienen 180 mg de 127.1

Síntesis del compuesto 127.3. El compuesto 127.3 se prepara a partir de 95.4 y 127.1 de una manera análoga al procedimiento del ejemplo 96. Se aísla un sólido blanco con un rendimiento de 53% a partir de 95.4.

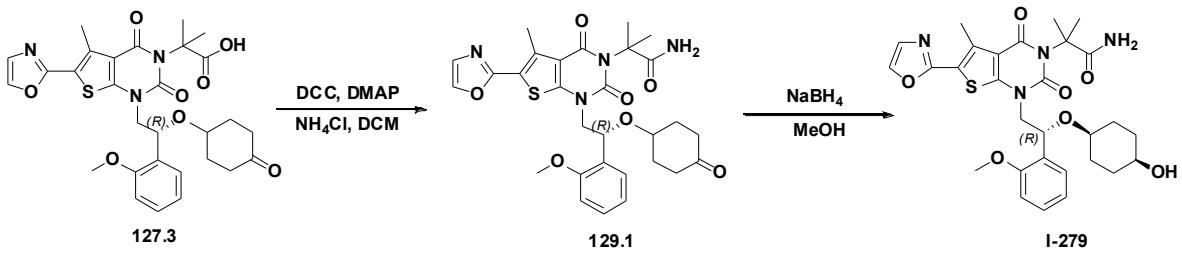
Ejemplo 128: Síntesis del ácido 2-[1-[(2R)-2-[(4-hidroxiciclohexil)oxi]-2-(2-metoxifenil)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-278).



127.3 I-278

En un matraz de fondo redondo de 25 ml se coloca 127.3 (600 mg, 1.03 mmol, 1.00 equivalentes) y 5 ml de metanol. Después se agrega borohidruro de sodio (40 mg, 1.09 mmol, 1.00 equivalentes) a 0°C. La solución resultante se agita durante la noche a temperatura ambiente y después se concentra bajo vacío. Se purifican 400 mg del producto crudo por *HPLC* preparativa bajo las siguientes condiciones (Waters): columna: Xbridge Prep Fenil 5 µm, 19*150 mm; fase móvil: agua (NH_4HCO_3 50 mM) y CH_3CN (CH_3CN 40.0% hasta 60.0% en 20 min); detector: UV 254/220 nm. Se obtienen 93.5 mg (16%) del compuesto I-278 como un sólido blanco. EM (ES): *m/z* 584 $(M+H)^+$, 606 $(M+Na)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 1.21-1.40 (m, 6H), 1.56 (m, 2H), 1.68 (d, 6H), 2.74 (s, 3H), 3.17 (m, 2H), 3.78 (s, 3H), 3.89-4.03 (m, 2H), 5.24 (t, 1H), 6.99 (m, 2H) , 7.26 (m,1H), 7.38 (s, 1H), 7.47 (m,1H), 8.21 (s, 1H).

Ejemplo 129: Síntesis de 2-[1-[(2R)-2-[(4-hidroxiciclohexil)oxi]-2-(2-metoxifenil)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanamida (I-279).

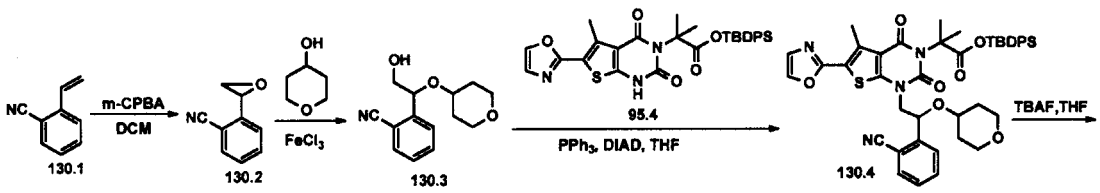


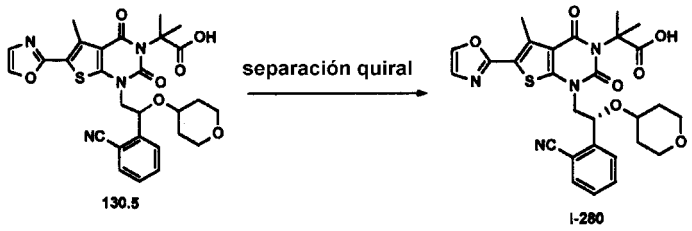
Síntesis del compuesto 129.1. El compuesto 129.1 se prepara a partir de 127.3 y cloruro de amonio siguiente el procedimiento del ejemplo 4. Se aíslan 530 mg de un sólido blanco con rendimiento cuantitativo.

Síntesis del compuesto I-279. En un matraz de fondo redondo se coloca 129.1 (530 mg, 0.91 mmol, 1.00 equivalentes), 10 ml de metanol y borohidruro de sodio (35 mg, 0.95 mmol, 1.04 equivalentes). La solución resultante se agita durante la noche a temperatura ambiente y se concentra bajo vacío. Se purifican 150 mg del producto crudo por *HPLC* preparativa bajo las siguientes condiciones (Waters): columna: HPrepC-012(T) Xbridge Prep Fenil 5 µm, 19*150 mm; fase móvil: agua (NH_4HCO_3 50 mM) y CH_3CN (CH_3CN 30.0% hasta 70.0% en 15 min); detector: 254/220 nm. La purificación proporciona 39.1 mg (7%) del compuesto I-279 (tR = 8.21 min) como un sólido blanco. EM (ES): *m/z* 605

$(M+Na)^+$. RMN ^1H (300 MHz, DEMO-d_6): δ 1.17-1.30 (m, 6H), 1.53 (m, 2H), 1.66 (d, 6H), 2.74 (s, 3H), 3.17 (m, 1H), 3.31 (m, 1H), 3.78 (s, 3H), 3.99 (m, 2H), 4.29 (s, 1H), 5.28 (t, 1H), 6.79-7.28 (m, 4H), 7.30 (m, 1H), 7.37 (s, 1H), 7.47 (m, 1H), 8.21 (s, 1H).

Example 130: Síntesis del ácido 2-[1-[(2R)-2-(2-cianofenil)-2-(oxan-4-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-280).





Síntesis del compuesto 130.2. En un matraz de fondo redondo de 100 ml se coloca 2-etenilbenzonitrilo (2.73 g, 21.14 mmol, 1.00 equivalentes), bicarbonato de sodio (1.77 g, 21.07 mmol, 4.61 equivalentes), 20 ml de diclorometano y 20 ml de agua. Después se agregan m-CPBA (10.9 g, 63.16 mmol, 2.25 equivalentes) a 0°C en varios

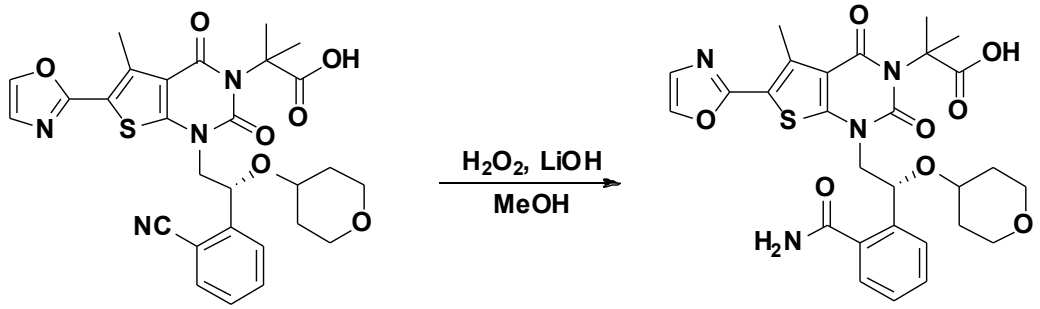
lotes. La solución resultante se agita durante la noche a temperatura ambiente y después se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con PE/EA (50:1). La purificación proporciona 400 mg (13%) de 2-(oxiran-2-il)benzonitrilo como un aceite amarillo.

Síntesis del compuesto 130.3. El compuesto 130.3 se prepara a partir de 130.2 de una manera análoga a la síntesis de 57.3. Se aísla un aceite amarillo con un rendimiento de 59%.

Síntesis del compuesto I-280. El compuesto I-280 se prepara a partir de 95.4 y 130.3 de acuerdo con el procedimiento del ejemplo 97. Purificación: los enantiómeros de 130.5 se separan por *HPLC* preparativa quiral bajo las siguientes condiciones:: Gilson Gx 281; columna: Chiralpak IA, 2*25 cm, 5 µm; fase móvil: hexanos e IPA (que se mantiene en IPA 20.0% durante 4 min); detector: UV 254/220 nm. EM (ES): *m/z* 565 $(M+H)^+$, 587 $(M+Na)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.41-1.45 (m, 2H), 1.61-1.72 (m, 8H), 2.70 (s, 3H), 3.20-3.33 (m, 3H), 3.43-3.59 (m, 1H), 3.60-3.62 (m, 2H), 4.08-4.19 (m, 2H), 5.19-5.24 (m, 1H), 7.17-7.17 (s, 1H), 7.42-7.45 (m, 1H), 7.63-7.68 (m, 3H), 7.87 (s, 1H).

Ejemplo 131: Síntesis del ácido 2-[1-[(2R)-2-(2-carbamoilfenil)-2-(oxan-4-iloxi)etil]-5-metil-6-(1,3-oxazol-2-

il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-281).

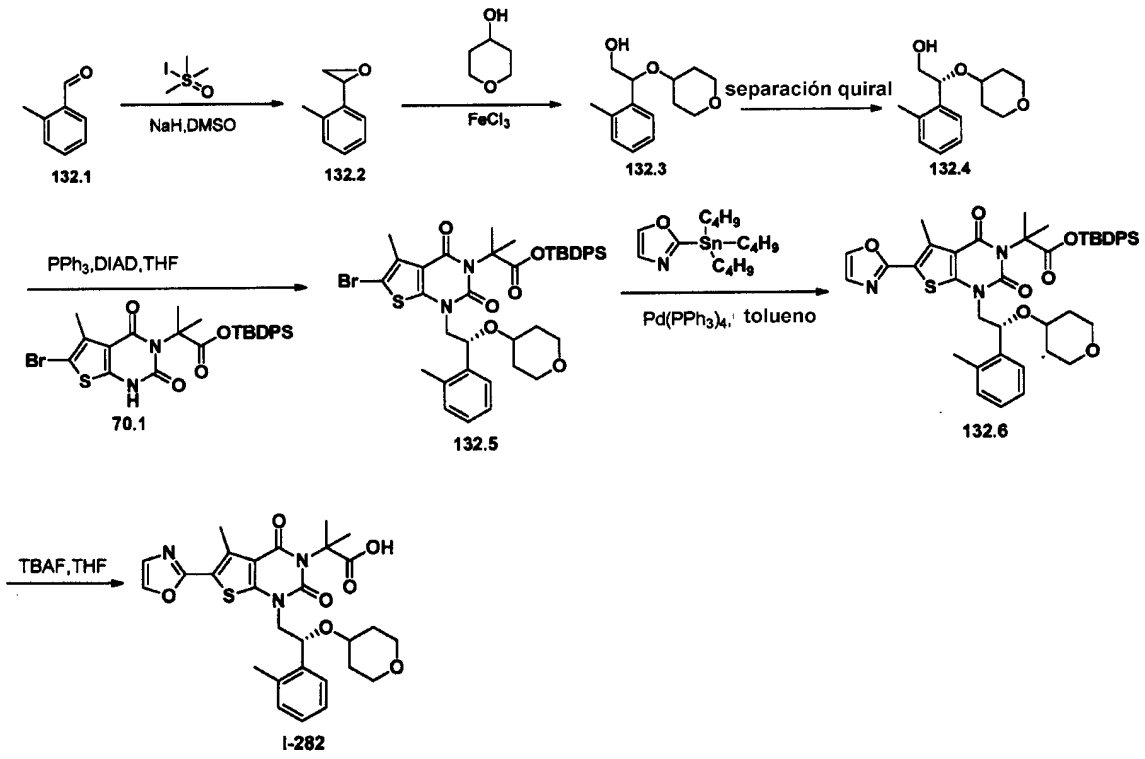


I-YY I-281

En un matraz de fondo redondo de 50 ml se coloca I-280 (30 mg, 0.05 mmol, 1.00 equivalentes), $LiOH \cdot H_2O$ (7 mg, 0.17 mmol, 5.50 equivalentes), H_2O_2 (8 mg, 30%) y 10 ml de metanol. La solución resultante se agita durante la noche a 35°C. La mezcla resultante se concentra bajo vacío. El residuo se purifica por cromatografía en capa delgada revelado con diclorometano/metanol (30:1). Se obtienen 2.8 mg (9%) del compuesto I-281 como un sólido blanco. EM (ES): *m/z* 583 $(M+H)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.24-1.25 (m, 2H), 1.57-1.67 (m, 8H), 2.76 (s, 3H), 3.22-3.34 (m, 3H), 3.44-3.48 (m, 2H), 4.09-4.25 (m, 2H), 5.36-5.37 (m, 1H), 7.38-7.42 (m, 3H), 7.54 (s, 2H), 7.65-7.66 (m, 1H), 7.92 (s, 1H), 8.24 (s, 1H).

Ejemplo 132: Síntesis del ácido 2-metil-2-[5-metil-1-[(2R)-2-(2-metilfenil)-2-(oxan-4-iloxi)etil]-6-(1,3-oxazol-

2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-282).

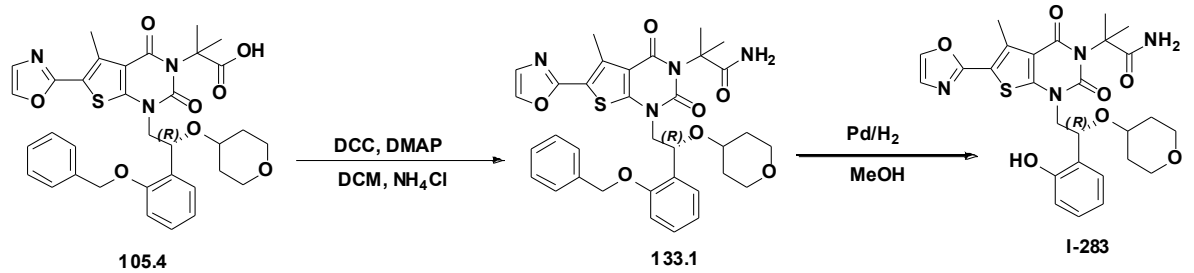


Síntesis del compuesto 132.4. El compuesto 132.4 se sintetiza a partir de 2-metilbenzaldehído de una manera análoga a la síntesis del compuesto 57.5. Se aíslan 680 mg de un aceite amarillo con un rendimiento de 5% a partir de 132.1.

Síntesis del compuesto I-282. El compuesto I-282 se prepara a partir de 70.1 y 132.4 de una manera análoga al procedimiento para el ejemplo 57. Se aíslan 173 mg de un sólido blanco con un rendimiento de 14% a partir de 70.1. EM (ES): *m/z* 554 $(M+H)^+$, 576 $(M+Na)^+$. RMN ^1H (400 MHz, CD_3OD): δ 1.30-1.33 (m, 2H), 1.62-1.72 (m, 8H), 2.44-2.51 (s, 3H), 2.77

(s, 3H), 3.20-3.24 (m, 2H), 3.33-3.39 (m, 2H), 3.41-3.64 (m, 2H), 4.21-4.24 (m, 1H), 5.10-5.13 (m, 1H), 7.21-7.32 (m, 3H), 7.41 (s, 1H), 7.54-7.56 (m, 1H), 8.25 (s, 1H), 12.49 (s, 1H).

Ejemplo 133: Síntesis de 2-[1-[(2R)-2-(2-hidroxifenil)-2-(oxan-4-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanamida (I-283).

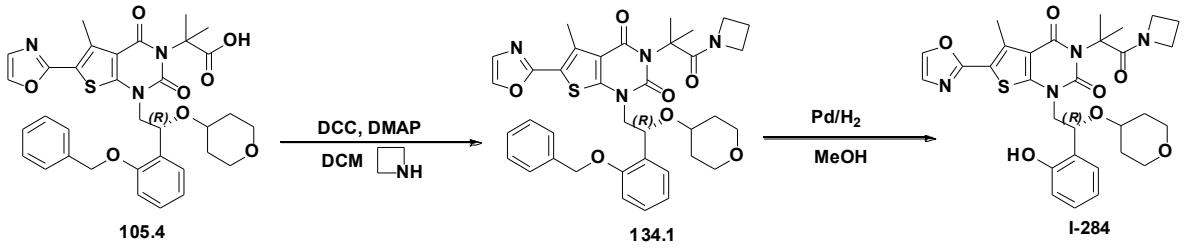


Síntesis del compuesto 133.1. El compuesto 133.1 se prepara a partir de 105.4 de acuerdo con el procedimiento del ejemplo 4. Se aísla un sólido blanco con rendimiento de 70%.

Síntesis del compuesto I-283. En un matraz de fondo redondo de 100 ml se coloca 133.1 (290 mg, 0.45 mmol, 1.00 equivalentes) y 30 ml de metanol. Esto es seguido por la adición de 50 mg de paladio en carbono. El matraz se evacua y se purga tres veces con nitrógeno, seguido por purgado con hidrógeno. La mezcla se agita durante la noche a temperatura ambiente bajo una atmósfera de hidrógeno. Los sólidos se preparan por filtración. El filtrado se

concentra bajo vacío. El residuo se purifica por cromatografía en capa delgada revelado con diclorometano/MeOH/HOAc (30:1:0.15). Se obtienen 91.6 mg (37%) del compuesto I-283 como un sólido blanco. EM (ES): *m/z* 577 $(M+Na)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 1.23 (m, 2H), 1.65-1.68 (m, 8H), 2.75 (s, 3H), 3.21 (m, 2H), 3.50 (m, 2H), 3.90 (m, 1H), 4.13 (m, 1H), 5.29 (t, 1H), 6.79-6.89 (m, 3H), 7.10 (m, 2H), 7.38 (m, 2H), 8.23 (s, 1H), 9.72 (s, 1H).

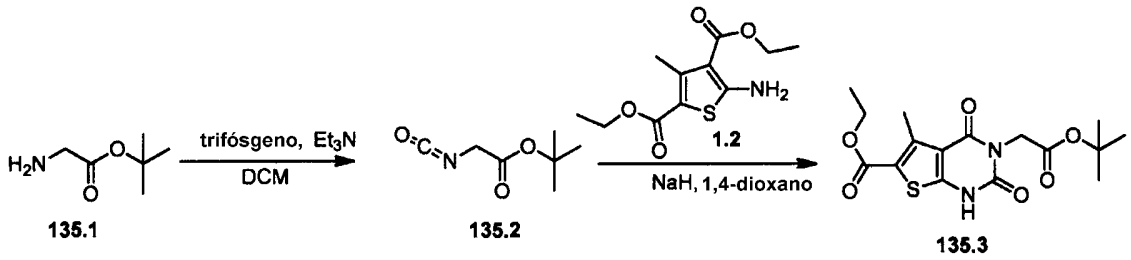
Example 134: Síntesis de 3-[1-(azetidin-1-il)-2-metil-1-oxopropan-2-il]-1-[(2R)-2-(2-hidroxifenil)-2-(oxan-4-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-2,4-diona (I-284)



Se prepara el compuesto I-284 de acuerdo con el procedimiento para el ejemplo 133, sustituyendo azetidina por cloruro de amonio en la primera etapa. EM (ES): *m/z* 595 $(M+H)^+$, 617 $(M+Na)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 1.18-1.32 (m, 2H), 1.63-1.70 (m, 8H), 2.08-2.16 (m, 2H), 2.77 (s, 3H), 3.20 (m, 2H), 3.50 (m, 1H), 3.50-3.60 (m, 2H), 3.76-4.13 (m, amplio, 6H), 5.29 (t, 1H) , 6.79-6.89 (m, 2H) , 7.10 (m, 1H),

7.37 (m, 2H), 8.23 (s, 1H) , 9.74 (s, 1H).

Ejemplo 135: Síntesis del intermediario 135.3.

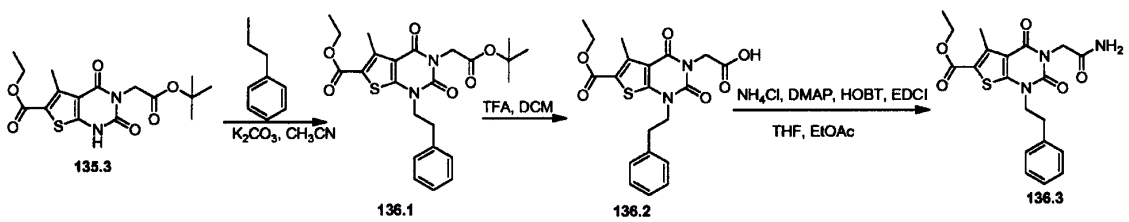


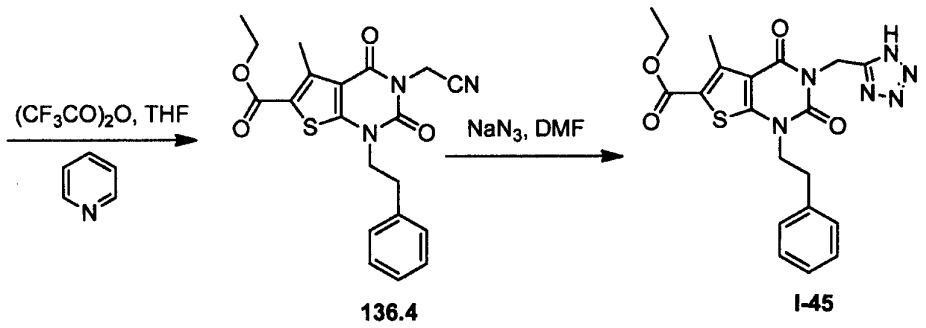
Síntesis del compuesto 135.2. En un matraz de fondo redondo de 3 cuellos de 500 ml se coloca 2-aminoacetato de terbutilo (135.1, 5.9 g, 44.98 mmol, 1.00 equivalentes). Después se agregan 180 ml de diclorometano y carbonato de ditriclorometilo (4.43 g, 14.93 mmol, 0.33 equivalentes) a 0°C. Después de 30 min se agrega trietilamina (13.65 g, 134.89 mmol, 3.00 equivalentes) a la mezcla anterior. La solución resultante se agita durante 4 h a 5-10°C en un baño de agua/hielo. Los sólidos se separan por filtración. El filtrado se concentra bajo vacío. La solución resultante se diluye con 50 ml de etiléter. Los sólidos se separan por filtración. La mezcla resultante se concentra bajo vacío. La purificación proporciona 7.1 g (crudo) de 2-isocianatoacetato de terbutilo (135.2) como un aceite amarillo.

Síntesis del intermediario 135.3. En un matraz de fondo redondo de 3 cuellos de 250 ml se coloca 1.2 (7.9 g, 30.70 mmol, 1.00 equivalentes) y 80 ml de 1,4-dioxano. Después se agregan a 0°C hidruro de sodio (1.32 g, 33.0 mmol, 1.07

equivalentes, 60%). La mezcla se agita durante 15 min a temperatura ambiente. Después se agrega a gotas una solución de 2-isocianatoacetato de terbutilo (7.1 g, 45.17 mmol, 1.47 equivalentes) en 20 ml de 1,4-dioxano, a gotas, con agitación, a 0°C en 15 min. La solución resultante se agita durante 30 min a 10-15°C en un baño de agua/hielo. La solución resultante se permite que reaccione, con agitación durante la noche mientras la temperatura se mantiene a 100°C en un baño de aceite. La mezcla de reacción se enfría a 20°C con un baño maría. La reacción después se suspende por la adición de 80 ml de NH_4Cl acuoso. La solución resultante se extrae con 3 x 200 ml de acetato de etilo, las capas orgánicas se combinan y se secan sobre sulfato de magnesio anhidro y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:7). La purificación proporciona 5.1 g (45%) del intermediario 135.3 como un sólido blanco.

Ejemplo 136: Síntesis de 5-metil-2,4-dioxo-1-(2-feniletil)-3-(1H-1,2,3,4-tetrazol-5-ilmetil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxilato de etilo (I-45).





Síntesis del compuesto 136.1. El compuesto 136.1 se prepara a partir de 135.3 y (2-yodoetil)benceno de una manera análoga a la síntesis del compuesto 9.1. Se aíslan 1.7 g (66%) de 136.1 como un sólido blanco.

Síntesis del compuesto 136.2 (I-13). En un matraz de fondo redondo de 50 ml se coloca una solución de 136.1 (2.4 g, 5.08 mmol, 1.00 equivalentes) en 20 ml de diclorometano. Después se agregan a gotas 3 ml de CF_3COOH. La solución resultante se agita durante 30 min a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con diclorometano/metanol (10:1). La purificación proporciona 1.7 g (80%) de 136.2 (I-13) como un sólido blanco. EM (ES): *m/z*: (M+H)+ calculado para $C_{20}H_{21}N_2O_6S$ 417, encontrado 417; RMN ^1H (300MHz, DMSO-d_6) δ13.08 (1H, s amplio), 7.22-7.34 (5H, m), 4.57 (2H, s), 4.27-4.34 (2H, q), 4.13-4.18 (2H, t), 3.00-3.05 (2H, t), 2.77 (3H, s),1.27-1.34 (3H,t).

Síntesis del compuesto 136.3. En un matraz de fondo redondo de 3 cuellos de 250 ml se coloca HOBt (220 mg,

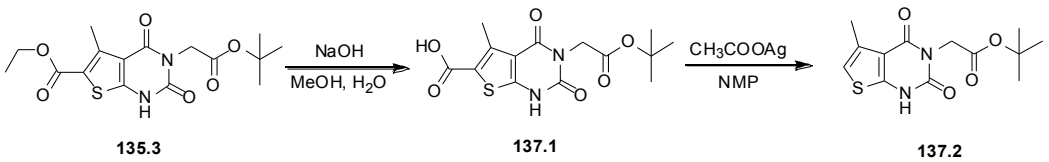
163 mmol, 1.13 equivalentes), 136.2 (600 mg, 1.44 mmol, 1.00 equivalentes), NH_4Cl (1.5 g, 28.04 mmol, 19.46 equivalentes), EDCI (310 mg, 1.62 mmol, 1.12 equivalentes), 20 ml de CH_3CN, 20 ml de acetato de etilo y 4-dimetilaminopiridina (200 mg, 1.64 mmol, 1.14 equivalentes). La solución resultante se agita durante la noche a temperatura ambiente. La reacción después se suspende por la adición de 20 ml de agua. La solución resultante se extrae con 3 x 50 ml de acetato de etilo y las capas orgánicas se combinan y se secan sobre sulfato de magnesio anhidro y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con diclorometano/metanol (50:1). La purificación proporciona 0.3 g (50%) de 136.3 como un sólido blancuzco.

Síntesis del compuesto 136.4. En un matraz de fondo redondo de 3 cuellos de 100 ml se coloca 136.3 (300 mg, 0.72 mmol, 1.00 equivalentes), piridina (280 mg, 3.54 mmol, 4.90 equivalentes) y 10 ml de tetrahidrofurano. Esto es seguido por la adición de $(CF_3CO)_2$ (0.38 g, 1.75 mmol, 2.50 equivalentes) a gotas, con agitación a 0-10°C. La solución resultante se agita durante 3 h a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:5). La purificación proporciona 250 mg (87%) de 136.4 como un sólido blanco.

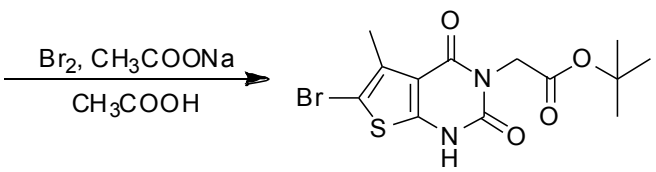
Síntesis del compuesto I-45. En un tubo sellado de

8 ml se coloca 136.4 (50 mg, 0.3 mmol, 1.00 equivalentes), NaN_3 (13 mg, 0.20 mmol, 1.57 equivalentes) y 3 ml de N,N-dimetilformamida. La solución resultante se agita durante la noche a 120°C en un baño de aceite. La reacción después se suspende por la adición de 5 ml de agua. La solución resultante se extrae con 3 x 20 ml de acetato de etilo las capas orgánicas se combinan, se secan sobre sulfato de magnesio anhidro y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:2). La purificación proporciona 2.5 mg (5%) del compuesto I-45 como un sólido blanco. EM (ES): *m/z* 441 $(M+H)^+$. ^1H NMR (400 MHz, CD_3OD): δ 1.43 (t, *J* = 7.2 Hz, 3H), 2.83 (s, 3H), 3.12 (t, *J* = 8.0 Hz, 2H), 4.19 (t, *J* = 8.0 Hz, 2H), 4.35 (q, *J* = 4.8 Hz, 2H), 5.43 (s, 2H), 7.23-7.33 (m, 5H).

Ejemplo 137: Síntesis del intermediario 137.3.



135.3 137.1 137.2



137.3

Síntesis del compuesto 137.1. En un matraz de fondo redondo de 3 cuellos de 250 ml se coloca 135.3 (5 g,

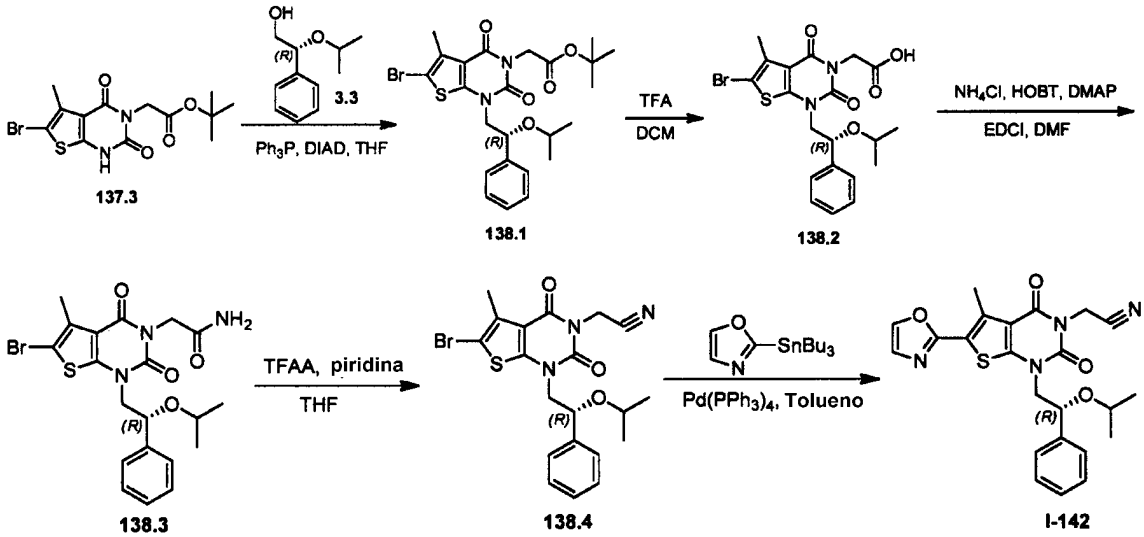
13.57 mmol, 1.00 equivalentes), 50 ml de agua, hidróxido de sodio (1.63 g, 40.75 mmol, 3.00 equivalentes) y 50 ml de metanol. La solución resultante se agita durante 5 h a 50°C. El valor de pH de la solución se ajusta a 4 con cloruro de hidrógeno (10%). La mezcla resultante se concentra bajo vacío. El residuo se extrae con 3 x 50 ml de acetato de etilo y las capas orgánicas se combinan, se lavan con 100 ml de salmuera y se secan sobre sulfato de magnesio anhidro y se concentran bajo vacío. Se obtienen 4.6 g (crudo) de 137.1 como un sólido blanco.

Síntesis del compuesto 137.2. En un matraz de fondo redondo de 30 ml se coloca 137.2 (4.6 g, 13.52 mmol, 1.00 equivalentes), CH_3COOAg (2.48 g, 14.85 mmol, 1.10 equivalentes) y 30 ml de NMP. La solución resultante se agita durante 2 h a 110°C. La reacción después se suspende por la adición de 50 ml de agua. La solución resultante se extrae con 3 x 100 ml de acetato de etilo y las capas orgánicas se combinan, se lavan con 150 ml de agua y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:5). La purificación proporciona 1.3 g (32%) de 137.2 como un sólido blanco.

Síntesis del intermediario 137.3. En un matraz de fondo redondo de 50 ml se coloca CH_3COONa (720 mg, 8.78 mmol, 2.00 equivalentes), 137.2 (1.3 g, 4.39 mmol, 1.00 equivalentes) y 20 ml de ácido acético. Esto es seguido

por la adición de Br_2 (780 mg, 4.88 mmol, 1.11 equivalentes) a gotas, con agitación. La solución resultante se agita durante 30 min a temperatura ambiente y después se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:5). La purificación proporciona 1.6 (97%) de 137.3 como un sólido blanco.

Ejemplo 138: Síntesis de 2-(1-((R)-isopropoxi-2-feniletil)-5-metil-6-(oxazol-2-il)-2,4-dioxo-1,2-dihidrotieno[2,3-d]pirimidin-3(4H)-il)-acetonitrilo (I-142).



Síntesis del compuesto 138.2. El compuesto 138.2 se prepara a partir de 137.3 y 3.3 de una manera análoga a la síntesis del compuesto 2.5. Se aíslan 400 mg de un aceite amarillo con un rendimiento de 78% a partir de 137.3.

Síntesis del compuesto 138.3. En un matraz de fondo redondo de 50 ml se coloca 138.2 (400 mg, 0.83 mmol,

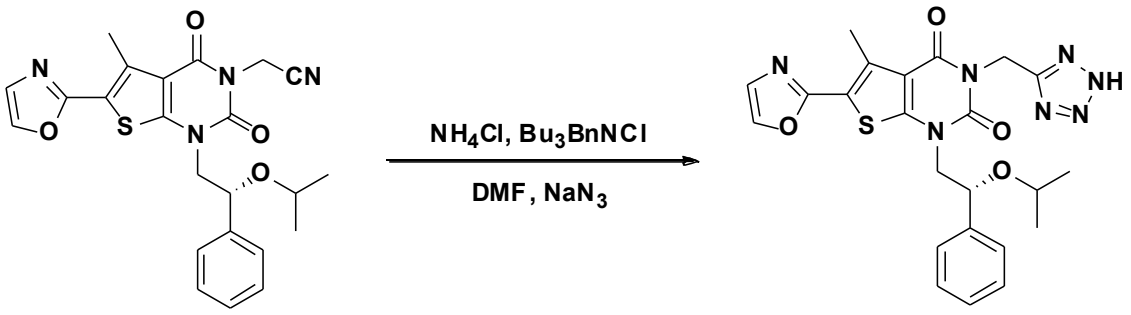
1.00 equivalentes), NH_4Cl (90 mg, 1.68 mmol, 2.02 equivalentes), HOBt (169 mg, 1.25 mmol, 1.51 equivalentes), 4-dimetil-aminopiridina (152 mg, 1.24 mmol, 1.50 equivalentes), EDCI (240 mg, 1.25 mmol, 1.51 equivalentes) y 10 ml de N,N-dimetilformamida. La solución resultante se agita durante 3 h a temperatura ambiente. La reacción después se suspende por la adición de 30 ml de agua. La solución resultante se extrae con 3 x 50 ml de acetato de etilo y las capas orgánicas se combinan y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con diclorometano/metanol (100:1). La purificación proporciona 390 mg (98%) de 138.3 como un sólido blanco.

Síntesis del compuesto 138.4. En un matraz de fondo redondo de 50 ml se coloca una solución de 138.3 (390 mg, 0.81 mmol, 1.00 equivalentes) en 10 ml de tetrahidrofurano y piridina (321 mg, 4.06 mmol, 5.00 equivalentes). Esto es seguido por la adición de TFAA (426 mg, 2.03 mmol, 2.50 equivalentes) a gotas, con agitación, a 0°C. La solución resultante se agita durante 2 h a temperatura ambiente y después se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:5). La purificación proporciona 360 mg (96%) de 138.4 como un sólido amarillo.

Síntesis del compuesto I-142. En un matraz de fondo redondo de 50 ml, que se mantiene en una atmósfera inerte de

nitrógeno, se coloca 138.4 (360 mg, 0.78 mmol, 1.00 equivalentes), $Pd(PPh_3)_4$ (90 mg, 0.08 mmol, 0.10 equivalentes), 2-(tributilestanil)-1,3-oxazol (560 mg, 1.56 mmol, 2.00 equivalentes) y 10 ml de tolueno. La solución resultante se agita durante la noche a 110°C y después se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:5). La purificación proporciona 60 mg (17%) del compuesto I-142 como un sólido amarillo. EM (ES): *m/z* 451 $(M+H)^+$, 473 $(M+Na)^+$, 492 $(M+H+CH_3CN)^+$. RMN ^1H (400 MHz, CD_3CN): δ 0.93-1.00 (m, 6H), 2.85 (s, 3H), 3.47-3.53 (m, 1H), 3.93-3.99 (m, 1H), 4.16-4.20 (m, 1H), 4.91 (s, 2H), 4.92-4.94 (m, 1H), 7.28 (s, 1H), 7.35-7.51 (m, 5H), 7.92 (s, 1H).

Ejemplo 139: Síntesis de 5-metil-6-(1,3-oxazol-2-il)-1-[(2R)-2-fenil-2-(propan-2-iloxi)etil]-3-(1H-1,2,3,4-tetrazol-5-ilmetil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-2,4-diona (I-153).

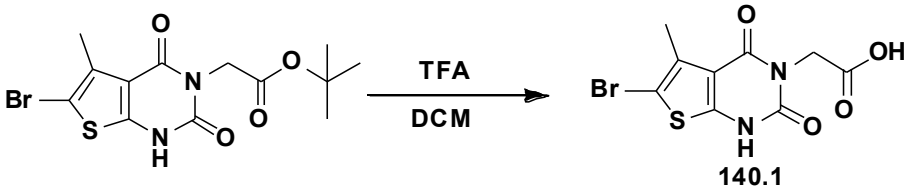


I-142 I-153

En un matraz de fondo redondo de 50 ml se coloca I-

142 (Ejemplo 138) (60 mg, 0.13 mmol, 1.00 equivalentes), NH_4Cl (29 mg, 0.54 mmol, 4.07 equivalentes), 5 ml de N,N-dimetilformamida, 42 mg de Bu_3BnNCl y NaN_3 (35 mg, 0.54 mmol, 4.04 equivalentes). La solución resultante se agita durante la noche a 135°C. Los sólidos se separan por filtración. Se purifican 50 mg del producto crudo por *HPLC* preparativa instantánea bajo las siguientes condiciones (IntelFlash-1): Columna: gel de sílice C18; fase móvil (acetonitrilo:agua = 0:100 que aumenta a acetonitrilo:agua = 100:0 en los siguientes 29 min; detector: UV 220 nm. Se obtienen 16 mg (24%) del compuesto I-153 como un sólido blancuzco. EM (ES): *m/z* 494 $(M+H)^+$, 535 $(M+H+CH_3CN)^+$. RMN ^1H (400 MHz, CD_3CN): δ 0.90-0.91 (d, *J* = 6.0, 3H), 0.97-0.99 (d, *J* = 6.4, 3H), 2.85 (s, 3H), 3.45-3.51 (m, 1H), 3.92-3.98 (m, 1H), 4.14-4.19 (m, 1H), 4.89-4.92 (d, 1H), 5.47 (s, 2H), 7.28 (s, 1H), 7.33-7.49 (m, 5H), 7.91 (s, 1H).

Ejemplo 140: Síntesis del intermediario 140.1.

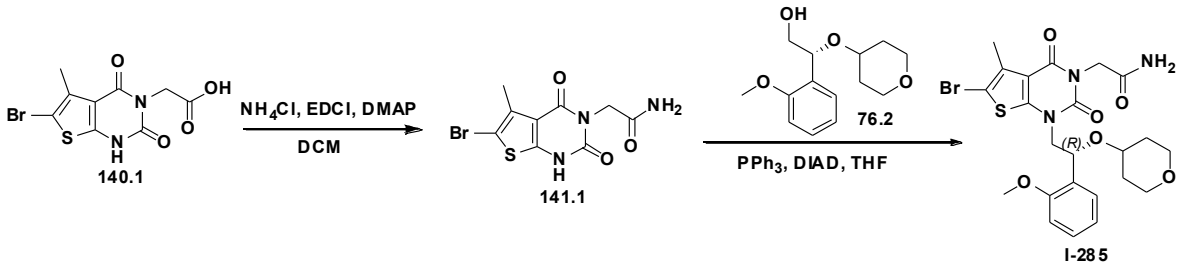


137.3 140.1

Síntesis del compuesto 140.1. En un matraz de fondo redondo de 250 ml se coloca 137.3 (2.3 g, 6.13 mmol, 1.00 equivalentes), 100 ml de diclorometano, 20 ml de ácido

trifluoroacético. La solución resultante se agita durante 6 h a temperatura ambiente y después se concentra bajo vacío. El producto crudo se recristaliza a partir de acetato de etilo/hexano en la relación de 1:10 para proporcionar 1.9 g (97%) de 140.1 como un sólido blanco.

Ejemplo 141: Síntesis de 2-[6-bromo-1-[(2R)-2-(2-metoxifenil)-2-oxan-4-iloxi)etil]-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acetamida (I-285).



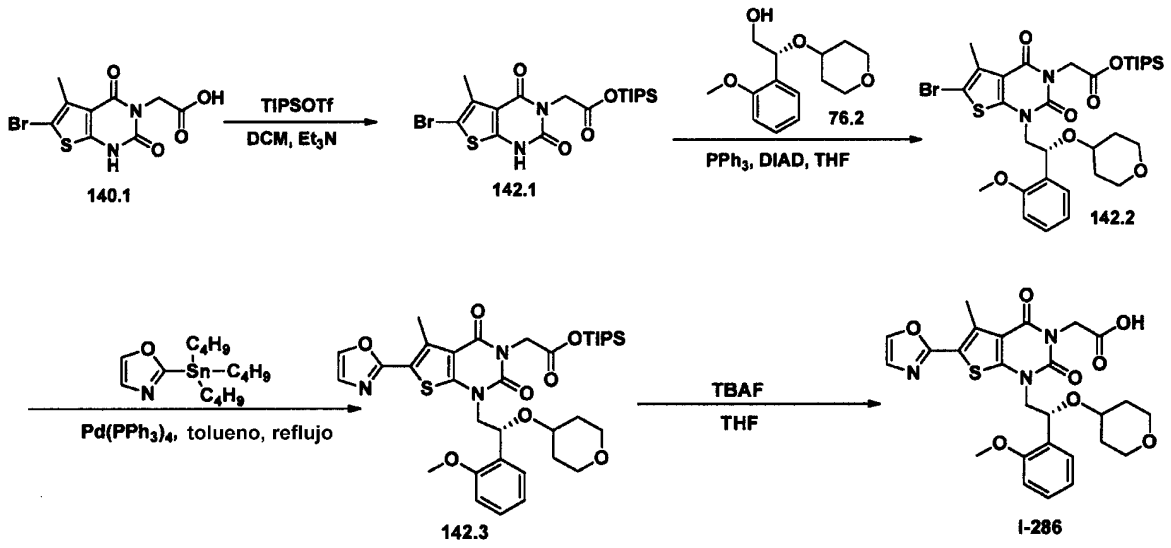
Síntesis del compuesto 141.1. En un matraz de fondo redondo de 100 ml se coloca 140.1 (1 g, 3.13 mmol, 1.00 equivalentes), NH_4Cl (500 mg, 9.35 mmol, 2.98 equivalentes), 4-dimetilaminopiridina (575 mg, 4.71 mmol, 1.50 equivalentes), EDCI (900 mg, 4.69 mmol, 1.50 equivalentes) y 25 ml de diclorometano. La solución resultante se agita durante la noche a temperatura ambiente. La reacción después se suspende por la adición de 10 ml de agua. La solución resultante se extrae con 2 x 100 ml de acetato de etilo y las capas orgánicas se combinan, se secan sobre sulfato de sodio anhidro y se concentran bajo vacío. El residuo se

aplica sobre una columna de gel de sílice con diclorometano/metanol (20/1/0.1). La purificación proporciona 320 mg (32%) de 141.1 como un sólido blanco.

Síntesis del compuesto I-285. En un matraz de fondo redondo de 50 ml, purgado y mantenido con una atmósfera inerte de nitrógeno se coloca 141.1 (300 mg, 0.94 mmol, 1.00 equivalentes), 76.2 (303 mg, 1.20 mmol, 1.27 equivalentes), 15 ml de tetrahidrofurano, DIAD (379 mg, 1.87 mmol, 1.99 equivalentes) y PPh_3 (490 mg, 1.87 mmol, 1.98 equivalentes). La solución resultante se agita durante 8 h a temperatura ambiente y después se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:1). La purificación proporciona 106 mg (20%) del compuesto I-285 como un sólido blanco. . EM (ES): *m/z* 554, 552 ($M+H^+$). RMN ^1H (DMSO-d_6, 300 MHz): δ 7.69 (1H, s), 7.46-7.44 (1H, d, J = 6.9 Hz), 7.32-7.23 (2H, m) 7.04-7.00 (2H, m), 5.18-5.13 (1H, m), 4.61-4.46 (2H, m), 4.42-4.38 (1H, m), 4.27-4.25 (1H, m), 3.81 (3H, s), 3.80-3.78 (1H, m), 3.48-3.41 (1H, m), 3.27-3.22 (1H, m), 2.38 (3H, s), 1.89-1.85 (1H, m), 1.70-1.64 (1H, m), 1.49-1.35 (2H, m).

Ejemplo 142: Síntesis del ácido 2-[1-[(2R)-2-(2-metoxifenil)-2-oxan-4-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-

2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acético (I-286).

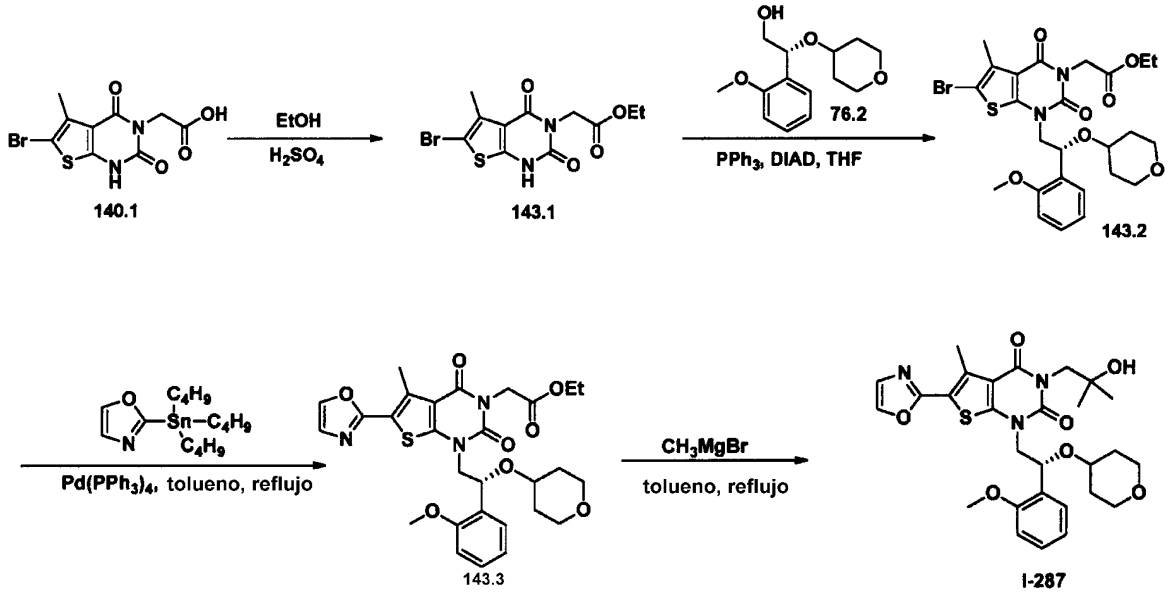


Síntesis de 142.1. En un matraz de fondo redondo de 3 cuellos de 100 ml se coloca 140.1 (450 mg, 1.41 mmol, 1.00 equivalentes) y 10 ml de diclorometano. Esto es seguido por la adición de TIPSOTf (475 mg, 1.55 mmol, 1.10 equivalentes) a gotas, con agitación, durante 2 min. A esto se agrega TEA (171 mg, 1.69 mmol, 1.20 equivalentes) a gotas con agitación durante 2 min. La solución resultante se agita durante 2 h a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:5). La purificación proporciona 235 mg (35%) de 142.1 como un sólido blanco.

Síntesis del compuesto 1-286. El compuesto I-286 se prepara a partir de 142.1 y 76.2 de una manera análoga al

Ejemplo 57. Se aíslan 3.6 mg (1.4% a partir de 142.1) de I-286 como un sólido blanco. EM (ES): *m/z* 542 $(M+H)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.18-1.42 (m, 2H), 1.59-1.62 (m, 2H), 2.741 (s, 3H), 3.16-3.63 (m, 4H), 3.75 (s, 3H), 3.92-4.13 (m, 2H), 4.45-4.76 (m, 1H), 5.32-5.35 (m, 1H), 6.85-6.95 (m, 2H), 7.17-7.23 (m, 2H), 7.44-7.47 (m, 1H), 7.85 (s, 1H).

Ejemplo 143: Síntesis de 3-(2-hidroxi-2-metilpropil)-1-[(2R)-2-(2-metoxifenil)-2-(oxan-4-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-2,4-diona (I-287)



Síntesis del compuesto 143.1. En un matraz de fondo redondo de 100 ml se coloca 140.1 (420 mg, 1.32 mmol, 1.00 equivalentes), 30 ml de etanol y 100 mg de ácido sulfúrico concentrado. La solución resultante se agita durante la noche a 80°C en un baño de aceite. La reacción después se

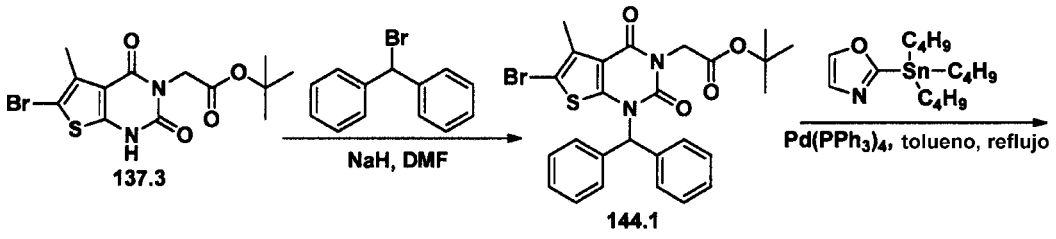
suspende por la adición de 5 ml de bicarbonato de sodio saturado. La solución resultante se extrae con 2 x 150 ml de acetato de etilo y las capas orgánicas se combinan, se secan sobre sulfato de sodio anhidro y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:5). La purificación proporciona 230 mg (50%) de 143.1 como un sólido blanco.

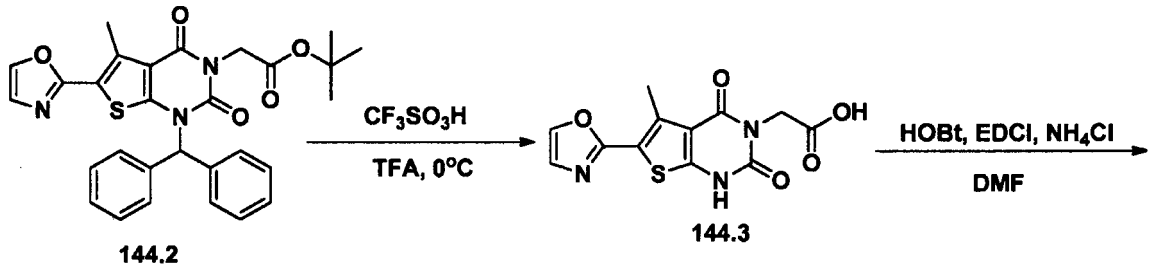
Síntesis del compuesto 143.3. El compuesto 143.3 se prepara a partir de 143.1 de una manera análoga al compuesto 13.5. Se aísla un sólido blanco con un rendimiento de 8%.

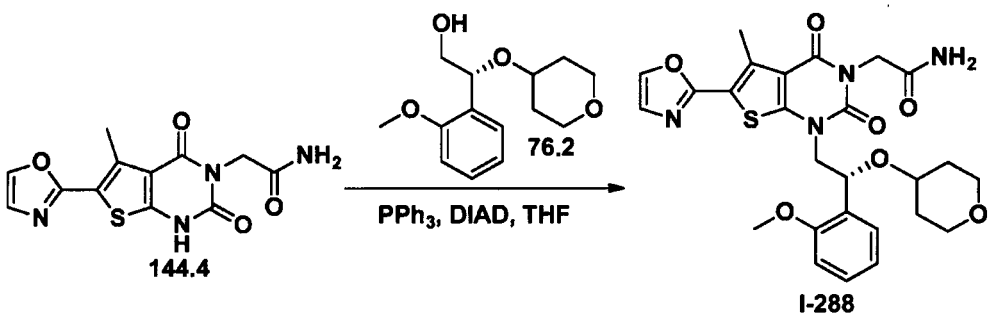
Síntesis del compuesto I-287. En un tubo sellado de 10 ml purgado y mantenido con una atmósfera inerte de nitrógeno se coloca en una solución de 143.3 (57 mg, 0.10 mmol, 1.00 equivalentes) en 1 ml de tolueno. Esto es seguido por la adición de bromo (metil)magnesio (1 M en THF, 3 ml) a gotas con agitación a temperatura ambiente. La solución resultante se calienta a reflujo durante la noche. La reacción después se suspende por la adición de 1 ml de NH_4Cl acuoso saturado. La solución resultante se extrae con 3 x 2 ml de acetato de etilo y las capas orgánicas se combinan y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con metanol/DCM/HOAc (7:200:1). La purificación proporciona 2.2 mg (4%) de I-287 como un sólido blanco. EM (ES): *m/z* 556 $(M+H)^+$. RMN ^1H (CD_3OD, 300 MHz): δ 7.92 (1H, s), 7.54-7.50 (1H, d), 7.30-7.24 (2H, m), 7.02-6.92 (2H,

m), 5.45-5.40 (1H, m), 4.20-4.10 (4H, m), 3.80 (3H, s), 3.70-3.51 (2H, m), 3.43-3.33 (1H, m), 2.83 (3H, s), 1.73-1.67 (2H, m), 1.48-1.33 (2H, m), 1.21-1.20 (6H, d).

Ejemplo 144: Síntesis de 2-[5-metil-1-[(2R)-2-(oxan-4-iloxi)-2-feniletil]-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acetamida (I-288).







Síntesis del compuesto 144.1. En un matraz de fondo redondo de 3 cuellos de 100 ml, purgado y mantenido durante bajo una atmósfera inerte de nitrógeno se colocan 137.3 (2.651 g, 7.06 mmol, 1.00 equivalentes) y 50 ml de N,N-dimetilformamida. Esto es seguido por la adición de hidruro de

sodio (368 mg, 9.20 mmol, 1.30 equivalentes, 60%) en porciones, a 0°C durante 10 min. La solución resultante se agita durante 30 min a temperatura ambiente. A esto se agrega [bromo(fenil)metil]benceno (2.3 g, 9.31 mmol, 1.32 equivalentes) en porciones a 0°C en 10 min. La solución resultante se agita durante la noche a temperatura ambiente. La reacción después se suspende por la adición de 50 ml de NH_4Cl acuoso. La solución resultante se extrae con 3 x 100 ml de acetato de etilo y las capas orgánicas se combinan y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:5). La purificación proporciona 2.26 g (59%) de 144.1 como un sólido blanco.

Síntesis del compuesto 144.2. A un matraz de fondo redondo de 3 cuellos de 100 ml, purgado y mantenido bajo una atmósfera inerte de nitrógeno, se agrega 144.1 (2.26 g, 4.17 mmol, 1.00 equivalentes), 50 ml de tolueno, 2-(tributilestanil)-1,3-oxazol (3 g, 8.38 mmol, 2.01 equivalentes) y $Pd(PPh_3)_4$ (728 mg, 0.63 mmol, 0.15 equivalentes). La solución resultante se agita durante la noche a 110°C y después se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:2). La purificación proporciona 1.9 g (crudo) de 144.2 como un sólido amarillo.

Síntesis del compuesto 144.3. En un matraz de fondo

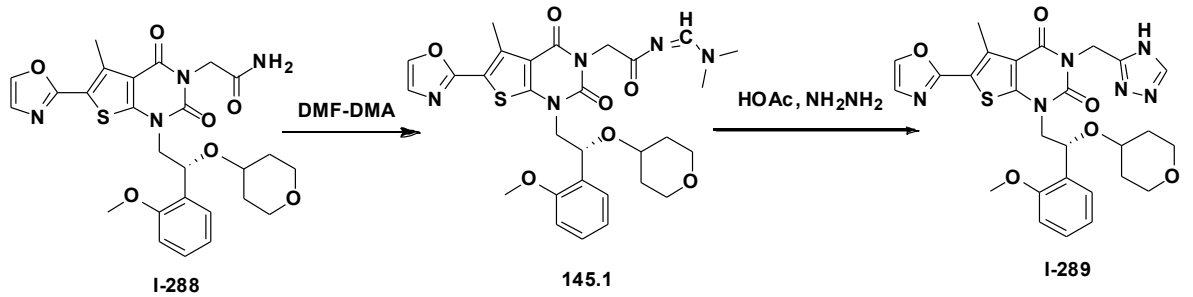
redondo de 50 ml se coloca 144.2 (950 mg, 1.79 mmol, 1.00 equivalentes) y 10 ml de CF_3COOH. Esto es seguido por la adición de 540 mg de CF_3SO_3H a gotas, con agitación, a 0°C durante 2 min. La solución resultante se agita durante 20 min a temperatura ambiente. La reacción después se suspende por la adición de 50 ml de agua. Los sólidos se lavan con 100 ml de EA y después se recolectan por filtración para proporcionar 490 mg (89%) de 144.3 como un sólido blanco.

Síntesis del compuesto 144.4. En un matraz de fondo redondo de 3 cuellos de 50 ml, purgado y mantenido con una atmósfera inerte de nitrógeno se colocan 144.3 (490 mg, 1.59 mmol, 1.00 equivalentes), HOBt (432 mg, 3.20 mmol, 2.00 equivalentes), 10 ml de N,N-dimetilformamida, 4-dimetilaminopiridina (390 mg, 3.19 mmol, 2.00 equivalentes) y EDCI (614 mg, 3.20 mmol, 2.01 equivalentes). La solución resultante se agita durante 2 horas a temperatura ambiente. Después se agrega NH_4Cl (346 mg, 6.47 mmol, 4.06 equivalentes). La solución resultante se agita durante la noche a temperatura ambiente. La reacción después se suspende por la adición de 50 ml de agua. Los sólidos se recolectan por filtración y se lavan con EA. La purificación proporciona 90 mg (18%) de 144.4 como un sólido blanco.

Síntesis del compuseto I-288. En un matraz de fondo redondo de 3 cuellos de 50 ml, purgado y mantenido con una atmósfera inerte de nitrógeno se coloca 144.4 (90 mg,

0.29 mmol, 1.00 equivalentes), 76.2 (89 mg, 0.35 mmol, 1.20 equivalentes), DIAD (119 mg, 0.59 mmol, 2.00 equivalentes), 5 ml de tetrahidrofurano y PPh_3 (154 mg, 0.59 mmol, 2.00 equivalentes). La solución resultante se agita durante la noche a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con diclorometano/metanol (20:1). La purificación proporciona 11.1 mg (7%) del compuesto I-288 como un sólido rosa. EM (ES): *m/z* 541 $(M+H)^+$. RMN ^1H (300 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.7 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.36-7.26 (m, 1H), 7.23 (s, 1H), 7.06-7.01 (m, 1H), 6.88 (d, *J* = 8.1 Hz, 1H), 5.81-5.47 (m, 2H), 5.41 (d, *J* = 8.7 Hz, 1H), 4.80-4.69 (m, 2H), 4.27 (d, *J* = 14.7 Hz, 1H), 4.01-3.93 (m, 2H), 3.88 (s, 2H), 3.75-3.63 (m, 2H), 3.42-3.28(m, 3H), 2.90 (s, 3H), 1.68-1.37 (m, 4 H).

Ejemplo 145: 1-[(2R)-2-(2-metoxifenil)-2-(oxan-4-iloxi)etil]-5-metil-6-[1,3-oxazol-2-il)-3-(4H-1,2,4-triazol-3-ilmetil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-2,4-diona (I-289).



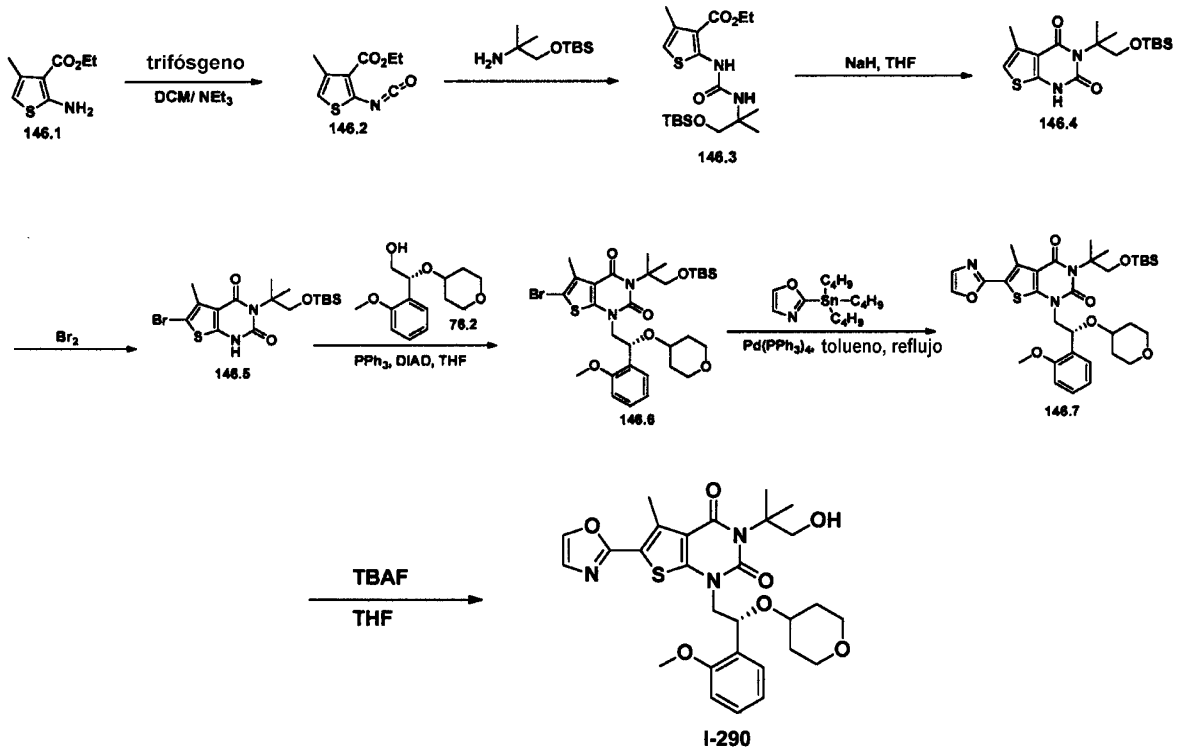
I-288 145.1 I-289

Síntesis del compuesto 145.1. En un matraz de fondo

redondo de 25 ml, purgado y mantenido con una atmósfera inerte de nitrógeno se coloca el compuesto I-288 (Ejemplo 144) (20 mg, 0.03 mmol, 1.00 equivalentes, 90%) y 0.5 ml de (dimetoximetil)dimetilamina. La solución resultante se agita durante 2 h a 120°C. La mezcla resultante se concentra bajo vacío para proporcionar 20 mg (crudo) de 145.1 como un líquido amarillo.

Síntesis del compuesto I-289. En un matraz de fondo redondo de 25 ml, purgado y mantenido en una atmósfera inerte de nitrógeno se colocan 145.1 (20 mg, 0.03 mmol, 1.00 equivalentes), 1 ml de AcOH y NH_2NH_2 (4 mg, 0.06 mmol, 1.91 equivalentes, 98%). La solución resultante se agita durante 2 h a 90°C. La mezcla resultante se concentra bajo vacío. Se purifican 500 mg del producto crudo por *HPLC* preparativa bajo las siguientes condiciones (Waters): Columna: SunFire Prep C18, 19*150 mm 5 µm; fase móvil: agua (NH_4HCO_3 0.5% y CH_3CN (CH_3CN 10.0% hasta 42.0% durante 11 min, hasta 100.0% durante 2 min, disminuye a 10.0% durante 1 min); detector: UV 220, 254 nm. La purificación proporciona 4.5 mg (24%) del compuesto I-289 como un sólido blanco. EM (ES): *m/z* 565 $(M+H)^+$. RMN ^1H (300 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.72 (s, 1H), 7.56 (d, *J* = 7.2 Hz, 1H), 7.33-7.22 (m, 2H), 7.03 (t, *J* = 6.0 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 5.43 (s, 3 H), 4.29-4.09 (m, 2H), 3.85 (s, 3H), 3.75-3.62 (m, 2H), 3.40-3.21 (m, 3H), 2.91 (s, 3H), 1.77-1.25 (m, 4H).

Ejemplo 146: Síntesis de 3-(1-hidroxi-2-metilpropan-2-il)-1-[(2R)-2-(2-metoxifenil)-2-(oxan-4-iloxi)-5-metil-(1,3-oxazol-2-il)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-2,4-diona (I-290).



Síntesis del compuesto 146.2. En un matraz de fondo redondo de 3 cuellos de 250 ml, purgado y mantenido bajo una atmósfera inerte de nitrógeno se coloca 2-amino-4-metiltiofen-3-carboxilato de etilo (146.1, 7.4 g, 39.95 mmol, 1.00 equivalentes) y 150 ml de diclorometano. Esto es seguido por la adición de carbonato de ditriclorometilo (4 g, 13.48 mmol, 0.34 equivalentes) en porciones, a 0°C. La mezcla se agita durante 0.5 h a 0°C. A esto se agregan a gotas, con agitación a 0°C 16.2 g de Et_3N. La solución resultante se

agita durante 5 h a temperatura ambiente. La mezcla se utiliza en la siguiente etapa directamente.

Síntesis del compuesto 146.3. En un matraz de fondo redondo de 3 cuellos de 250 ml, purgado y mantenido con una atmósfera inerte de nitrógeno se coloca la solución cruda de 146.2 (150 ml, de la etapa previa). Esto es seguido por la adición de (2-amino-2-metilpropoxi)(terbutil)dimetilsilano (9.2 g, 45.23 mmol, 1.00 equivalentes) en porciones a 10°C durante 20 min. La solución resultante se agita durante la noche a temperatura ambiente. La reacción después se suspende por la adición de 200 ml de agua. La solución resultante se extrae con 2 x 300 ml de acetato de etilo y las capas orgánicas se combinan, se secan sobre sulfato de sodio y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:20). La purificación proporciona 11 g (61%) de 146.3 como un sólido amarillo.

Síntesis del compuesto 146.4. En un matraz de fondo redondo de 3 cuellos de 250 ml, purgado y mantenido con una atmósfera inerte de nitrógeno, se coloca una solución de 146.3 (2.07 g, 4.99 mmol, 1.00 equivalentes) en 100 ml de tetrahidrofurano. Esto es seguido por la adición de hidruro de sodio (600 mg, 15.00 mmol, 3.00 equivalentes) en porciones a 0-10°C. La solución resultante se agita durante 1 h a 0-10°C y se calienta a 60°C durante la noche. La reacción después se

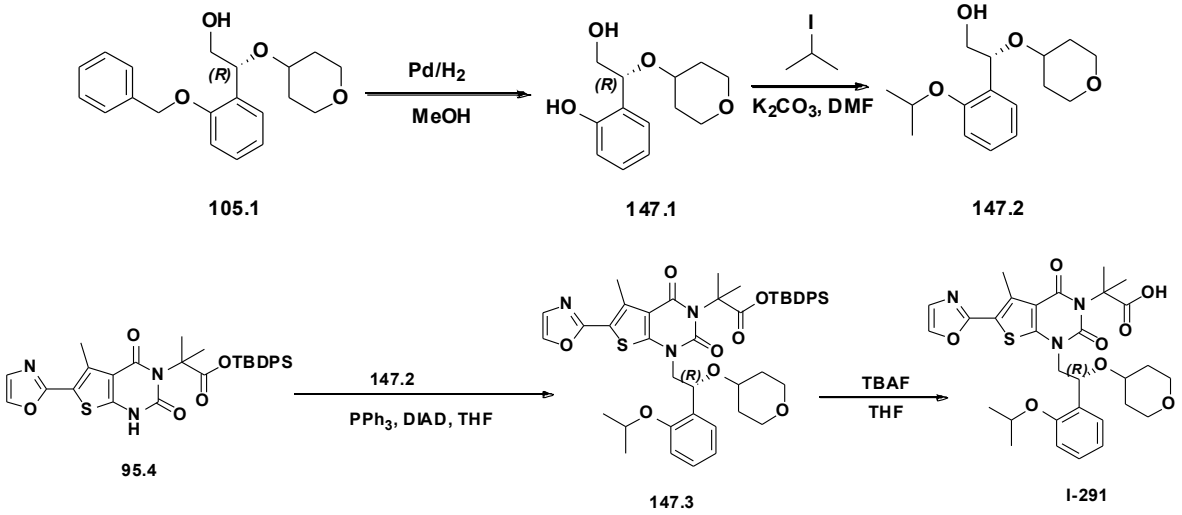
suspende por la adición de 100 ml de NH_4Cl acuoso saturado. La solución resultante se extrae con 3 x 100 ml de acetato de etilo y las capas orgánicas se combinan y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:20). La purificación proporciona 510 mg (28%) de 146.4 como un sólido blanco.

Síntesis del compuesto 146.5. En un matraz de fondo redondo de 50 ml se coloca 146.4 (510 mg, 1.38 mmol, 1.00 equivalentes), 10 ml de ácido acético y 227 mg de NaOAc. La solución resultante se agita durante 30 min a temperatura ambiente. Esto es seguido por la adición a gotas de Br_2 (222 mg, 1.39 mmol, 1.00 equivalentes), con agitación y a temperatura ambiente. La solución resultante se agita durante 30 min a temperatura ambiente. La reacción después se suspende por la adición de 10 ml de Na_2SO_3 acuoso. La solución resultante se diluye con 50 ml de H_2O. La solución resultante se extrae con 2 x 50 ml de acetato de etilo, las capas orgánicas se combinan y concentran bajo vacío. El residuo se purifica por CCD preparativa (acetato de etilo/éter de petróleo = 1:5). La purificación proporciona 334 mg (54%) de 146.5 como un sólido blanco.

Síntesis del compuesto I-290. El compuesto I-290 se prepara a partir de 146.5 y 76.2 de manera análoga al Ejemplo 57. Se aíslan 57.8 mg de un sólido blanco con un rendimiento de 14% a partir de 146.5. EM (ES): *m/z* 556 $(M+H)^+$. RMN ^1H (300

MHz, DMSO-d_6): δ 1.23-1.35 (m, 2H), 1.57-1.65 (m, 8H), 2.74 (s, 3H), 3.20-3.27 (m, 2H), 3.39-3.59 (m, 2H), 3.79-3.96 (m, 7H), 4.72-4.76 (m, 1H), 5.25-5.29 (m, 1H), 7.00-7.05 (m, 2H), 7.27-7.37 (m, 2H) , 7.46-7.49 (d, 1H), 8.20 (s, 1H).

Ejemplo 147: Síntesis del ácido 2-metil-2-[5-metil-1-[(2R)-2-(oxan-4-iloxi)-2-[2-(propan-2-iloxi)fenil]etil]-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-291).



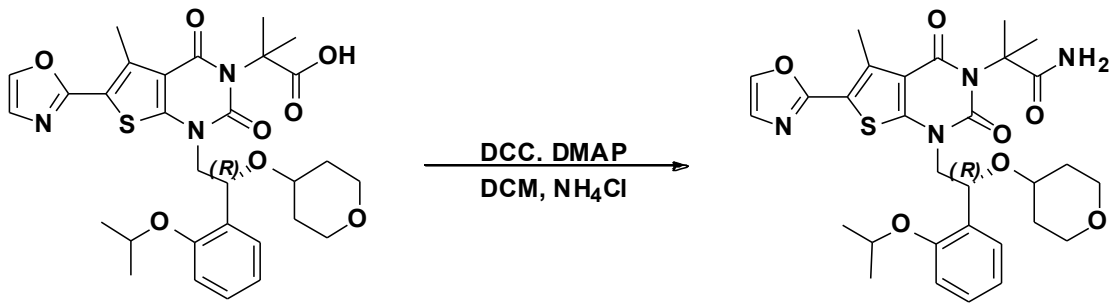
Síntesis del compuesto 147.1. En un matraz de fondo redondo de 100 ml se coloca 105.1 (500 mg, 1.52 mmol, 1.00 equivalentes) y 10 ml de metanol. Esto es seguido por la adición de 50 mg de paladio en carbono. Se agrega al sistema hidrógeno. La solución resultante se agita durante la noche a temperatura ambiente. Los sólidos se separan por filtración. La mezcla resultante se concentra bajo vacío para proporcionar

320 mg (88%) de 147.1 como un aceite.

Síntesis del compuesto 147.2. En un matraz de fondo redondo de 25 ml se coloca 147.1 (280 mg, 1.18 mmol, 1.00 equivalentes), carbonato de potasio (487 mg, 3.52 mmol, 3.00 equivalentes), 5 ml de N,N-dimetilformamida y 2-yodopropano (400 mg, 2.35 mmol, 2.00 equivalentes). La solución resultante se agita durante la noche a temperatura ambiente. La reacción después se suspende por la adición de 10 ml de agua. La solución resultante se extrae con 10 ml de acetato de etilo y las capas orgánicas se combinan y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:50). Esto resulta en 260 mg (79%) de 147.2 como un aceite incoloro.

Síntesis del compuesto I-291. El compuesto I-291 se sintetiza a partir de 147.2 y el intermediario 95.4 de una manera análoga al Ejemplo 96. Se aísla un sólido blanco con un rendimiento de 15% a partir de 95.1. EM (ES): *m/z* 598 $(M+H)^+$, 620 $(M+Na)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 1.19-1.32 (m, 8H), 1.60-1.67 (m, 8H), 2.76 (s, 3H), 3.18-3.35 (m, 2H), 3.45-3.58 (m, 2H), 3.85-4.20 (m,2H), 4.67 (m, 1H), 5.27 (t, 1H), 7.03 (m, 2H), 7.33-7.50 (m, 3H), 8.23 (s, 1H).

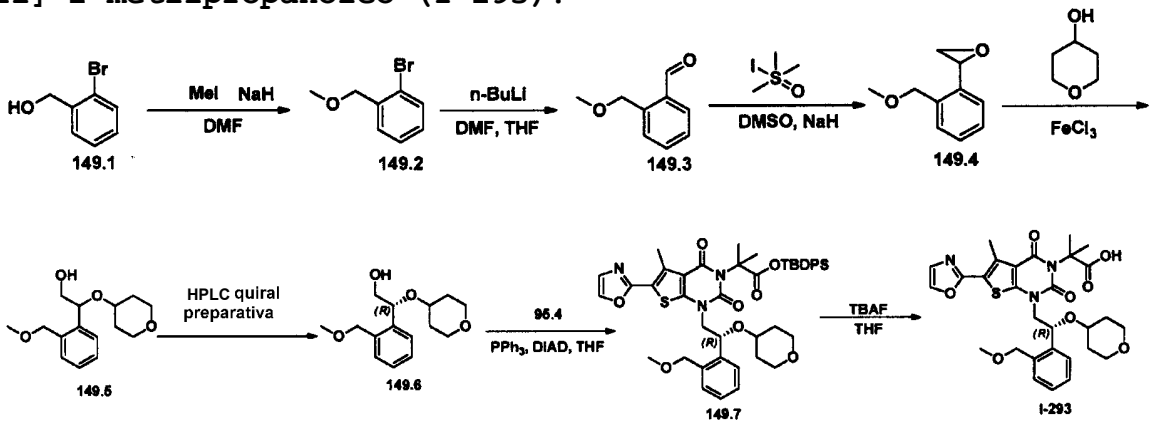
Ejemplo 148: Síntesis de 2-metil-2-[5-metil-1-[(2R)-2-(oxan-4-iloxi)-2-[2-(propan-2-iloxi)fenil]etil]-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanamida (I-292).



I-291 I-292

Síntesis del compuesto I-292. El compuesto I-292 se sintetiza a partir de I-291 de una manera análoga al Ejemplo 4. Se aíslan 284.1 mg de un sólido blanco con un rendimiento de 81%. EM (ES): *m/z* 619 $(M+Na)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 1.18-1.32 (m, 8H), 1.60-1.66 (m, 8H), 2.75 (s, 3H), 3.18-3.33 (m, 2H), 3.47-3.58 (m, 2H), 3.85-4.20 (m, 2H), 4.66 (m, 1H), 5.27 (t, 1H), 6.80 (s amplio, 1H), 7.01 (m, 3H), 7.30 (m,1H), 7.39 (s,1H) , 7.45 (d,1H), 8.22 (s, 1H).

Ejemplo 149: Síntesis del ácido 2-[1-[(2R)-2-[2-(metoximetil)fenil]-2-(oxan-4-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-293).



149.1 149.2 149.3 149.4 149.5 149.6 149.7 I-293

Síntesis del compuesto 149.2. En un matraz de fondo

redondo de 3 cuellos de 250 ml se colocan (2-bromofenil)metanol (20 g, 106.93 mmol, 1.00 equivalentes), 50 ml de N,N-dimetilformamida e hidruro de sodio (5.136 g, 128.40 mmol, 1.20 equivalentes). La solución resultante se agita durante 0.5 h a temperatura ambiente. Esto es seguido por la adición de MeI (45.582 g, 323.28 mmol, 3.02 equivalentes) a gotas, con agitación, a 0°C. Se permite que la solución resultante reaccione, con agitación, durante la noche a temperatura ambiente. La reacción después se suspende por la adición de 100 ml de NH_4Cl acuoso. La solución resultante se extrae con 2 x 200 ml de acetato de etilo y las capas orgánicas se combinan y concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:200). La purificación proporciona 6 g (28%) de 149.2 como un aceite café.

Síntesis del compuesto 149.3. En un matraz de fondo redondo de 3 cuellos de 500 ml, purgado y mantenido con una atmósfera inerte de nitrógeno, se coloca una solución de 149.2 (12 g, 59.68 mmol, 1.00 equivalentes) en 200 ml de tetrahidrofurano. Esto es seguido por la adición de n-butil-litio (26.3 ml, 2.5 M) a gotas, con agitación, a −78°C. La solución resultante se agita durante 1 h a −78°C. A esto se le agrega N,N-dimetilformamida (8.7 g, 119.03 mmol, 1.99 equivalentes) a gotas, con agitación, a −78°C. Se permite que la solución resultante reaccione, con agitación, durante

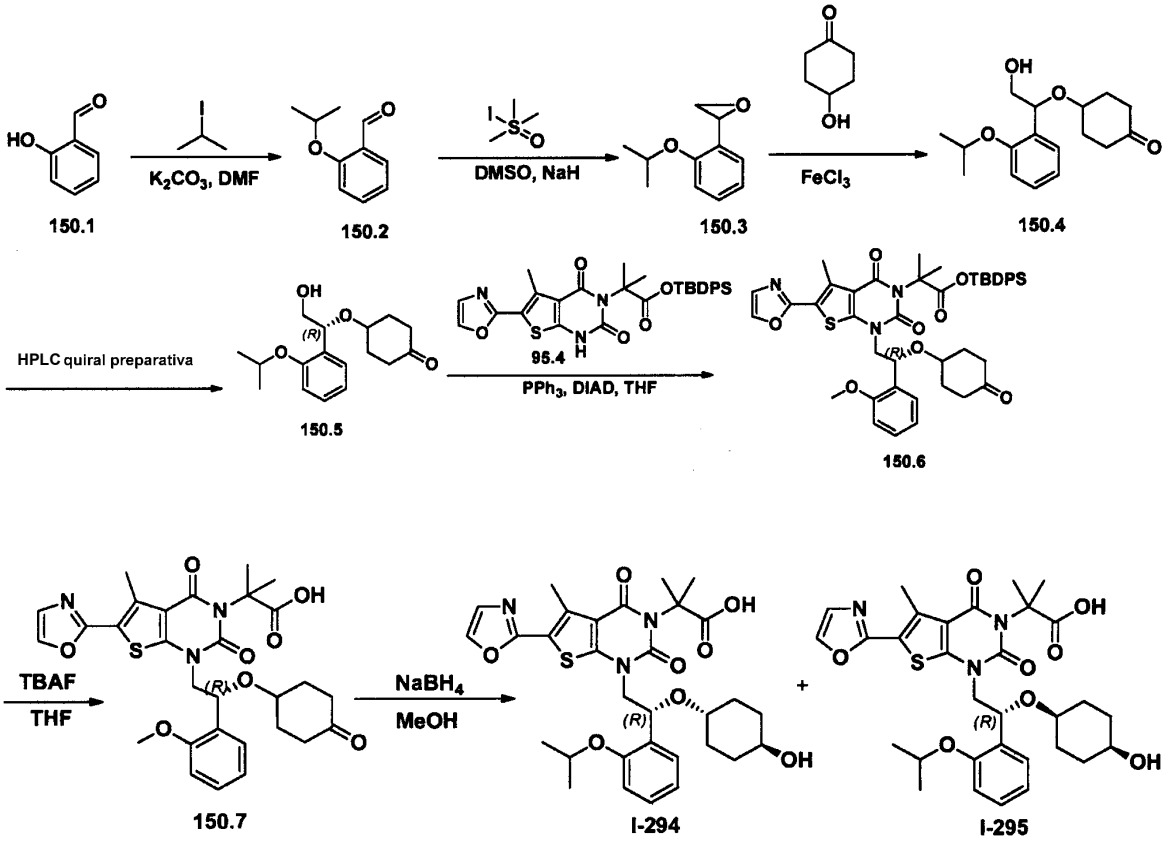
1 h adicional desde –78°C hasta la temperatura ambiente. La reacción después se suspende por la adición de 100 ml de NH_4Cl acuoso. La solución resultante se extrae con 3 x 100 ml de acetato de etilo y las capas orgánicas se combinan y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:50). Esto resulta en 7.7 g (86%) de 149.3 como un aceite incoloro.

Síntesis del compuesto 149.6. El compuesto 149.6 se prepara a partir de 149.3 de una manera consistente con la síntesis del compuesto 57.5. Se aíslan 390 mg de un aceite incoloro con un rendimiento total de 3%.

Síntesis del compuesto I-293. El compuesto I-293 se prepara a partir de 149.6 y 95.4 de una manera análoga al Ejemplo 96. Se aíslan 68.3 mg (23%) de I-293 como un sólido blanco. EM (ES): *m/z* 606 $(M+Na)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 1.23 (m, 2H), 1.56-1.70 (m, 8H), 2.77 (s, 3H), 3.18-3.39 (m, 6H), 3.54 (m, 2H), 3.81(m, 1H), 4.22 (d, 1H), 4.44 (d, 1H), 4.70 (d, 1H), 5.22 (dd, 1H), 7.33-7.47 (m, 4H), 7.64 (m, 1H), 8.24 (s, 1H).

Ejemplo 150: Síntesis del ácido 2-(1-((R)-2-(((1r,4R)-4-hidroxiciclohexil)oxi)-2-(2-isopropoxifenil)etil)-5-metil-6-(oxazol-2-il)-2,4-dioxo-1,2-dihidrotieno[2,3-d]pirimidin-3(4H)-il)-2-metilpropanoico (I-294) y Ejemplo 151: Síntesis del ácido 2-(1-((R)-2-(((1s,4S)-4-hidroxiciclohexil)oxi)-2-(2-isoporoxifenil)etil)-5-metil-6-

(oxazol-2-il)-2,4-dioxo-1,2-dihidrotieno[2,3-d]pirimidin-3(4H)-il)-2-metilpropanoico (I-295).



Síntesis del compuesto 150.2. En un matraz de fondo redondo de 3 cuellos de 1000 ml se coloca 2-hidroxibenzaldehído (36 g, 294.79 mmol, 1.00 equivalentes), 2-yodopropano (100 g, 588.26 mmol, 2.00 equivalentes), carbonato de potasio (122 g, 882.71 mmol, 2.99 equivalentes) y N,N-dimetilformamida (500 g, 6.84 mmol, 23.21 equivalentes). La solución resultante se agita durante la noche a temperatura ambiente. La reacción después se suspende por adición de 1000 ml de agua. La solución resultante se extrae con 3 x 500 ml de acetato de etilo y las capas orgánicas se combinan, se secan

sobre sulfato de sodio anhidro y se concentran bajo vacío para proporcionar 50 g (crudo) de 2-(propan-2-iloxi)benzaldehído como un aceite amarillo.

Síntesis del compuesto 150.5. El compuesto 150.5 se prepara a partir de 150.2 de una manera análoga al compuesto 57.5. Se aíslan 4.7 g de un aceite incoloro con un rendimiento total de 3%.

Síntesis del compuesto 150.7. El compuesto 150.7 se prepara a partir de 150.5 y 95.4 de una manera análoga al Ejemplo 96. Se aíslan 1.2 g de un sólido blanco con un rendimiento total de 25%.

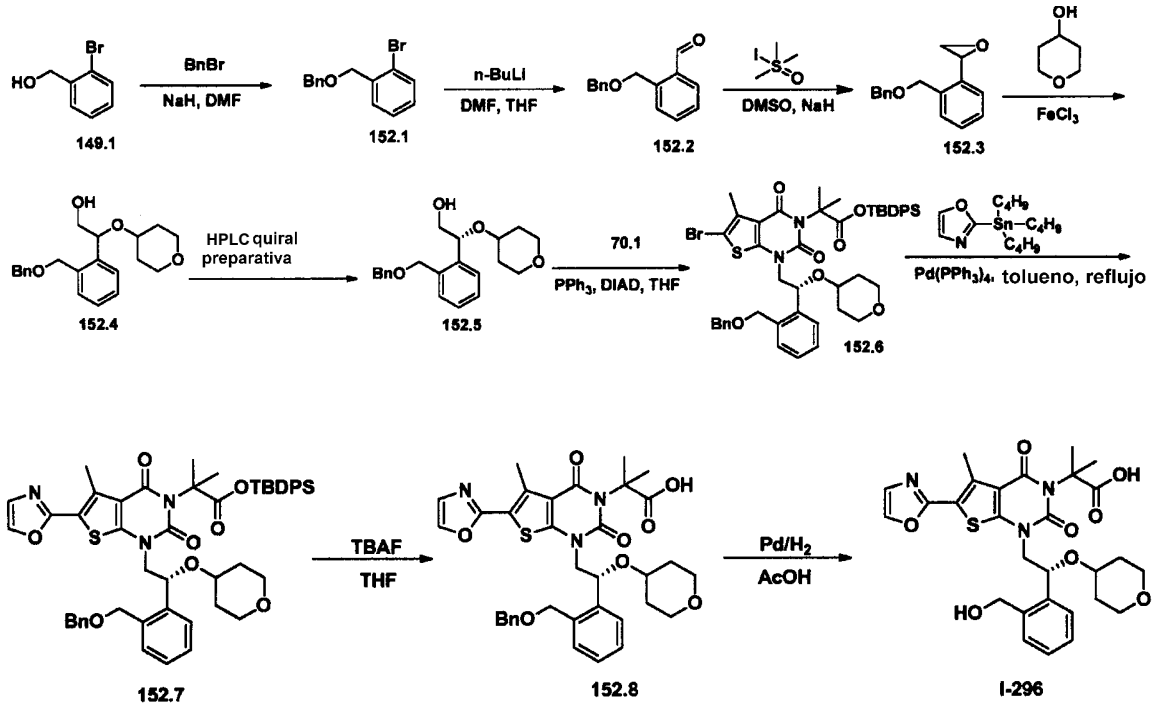
Síntesis de los compuestos I-294 y I-295. En un matraz de fondo redondo de 3 cuellos de 50 ml se coloca 150.7 (1.1 g, 1.89 mmol, 1.00 equivalentes), 20 ml de metanol y $NaBH_4$ (143 mg, 3.78 mmol, 2.00 equivalentes). La solución resultante se agita durante la noche a temperatura ambiente y después se concentra bajo vacío. El residuo se purifica por cromatografía en capa delgada revelado con diclorometano/MeOH/HOAc (30:1:0.15) para proporcionar 122.4 mg (9%) del compuesto I-294 y 256.3 mg (22%) del compuesto I-295.

Datos analíticos para el compuesto I-294: EM (ES): *m/z* 612 $(M+H)^+$, 634 $(M+Na)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 0.96-1.32 (m, 10H), 1.50-1.65 (m, 10H), 2.74 (s, 3H), 3.17 (m, 1H), 3.89-4.03 (m,2H), 4.35 (m, 1H), 4.70 (m, 1H), 5.22 (t, 1H), 6.99 (m, 2H), 7.29 (m,1H), 7.38 (s, 1H), 7.45 (m,1H), 8.21 (s,

1H).

Datos analíticos para el compuesto I-295: EM (ES): *m/z* 612 $(M+H)^+$, 634 $(M+Na)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ1.29-1.30 (m, 12H), 1.50-1.68 (m, 8H), 2.75 (s, 3H), 3.14 (m, 1H), 3.91-3.99 (m, 1H), 4.11 (m, 1H), 4.24 (m, 1H), 4.68 (m, 1H), 5.25 (t, 1H), 6.97 (m, 2H), 7.29(m, 1H), 7.39 (s, 1H), 7.46 (m, 1H), 8.22 (s, 1H), 12.30 (s amplio, 1H).

Ejemplo 152: Síntesis del ácido 2-[1-[(2R)-2-[2-(hidroximetil)fenil]-2-(oxan-4-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3]pirimidin-3-il]-2-metilpropanoico (I-296).



Síntesis del compuesto 152.5. El compuesto 152.5 se prepara a partir de 149.1 de una manera análoga a la

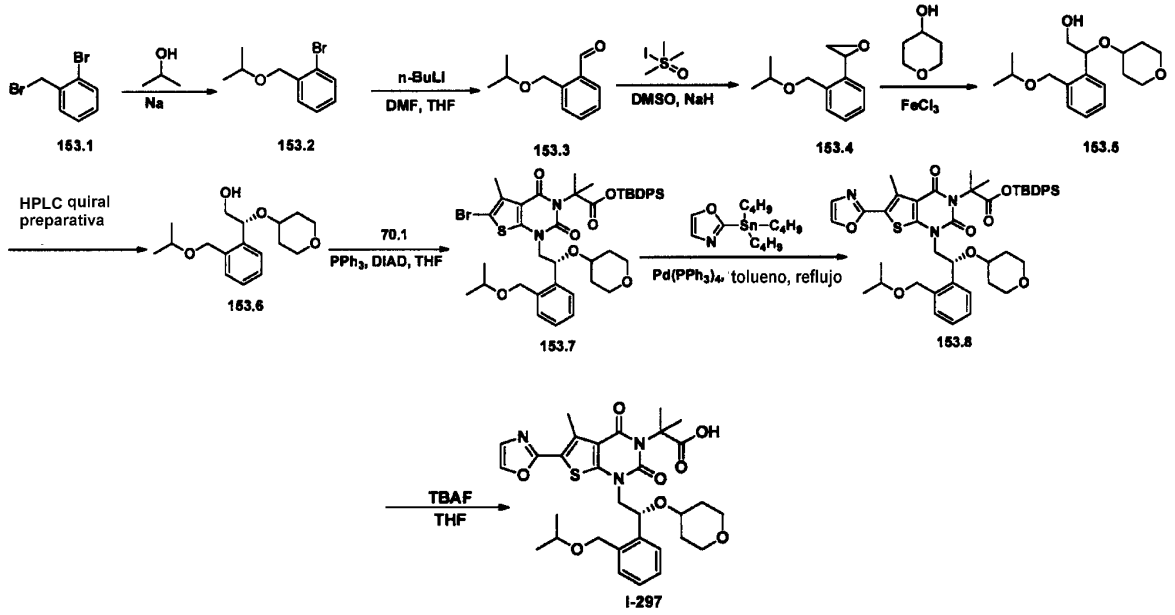
preparación del compuesto 149.6 al sustituir bromuro de bencilo por yoduro de metilo en la primera etapa. Se aíslan 0.814 g de un aceite incoloro con un rendimiento total de 2%.

Síntesis del compuesto 152.8 (I-299). El compuesto 152.8 se prepara a partir de 70.1 y 152.5 de una manera análoga al Ejemplo 57. Se aíslan 50 mg de un sólido blanco con un rendimiento total de 70.1.

Síntesis del compuesto I-296. En un matraz de fondo redondo de 50 ml se coloca 152.8 (100 mg, 0.15 mmol, 1.00 equivalentes), 5 ml de AcOH y 50 mg de 10% de paladio en carbono. La solución resultante se agita durante la noche a temperatura ambiente bajo una atmósfera de hidrógeno. Los sólidos se separan por filtración. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con diclorometano/metanol (20:1). La purificación proporciona 9.9 mg (11%) del compuesto I-296 como un sólido blanco. EM (ES): 570 $(M+H)^+$, 592 $(M+Na)^+$. RMN ^1H (400 MHz, DMSO-d_6): δ 8.25 (s, 1 H), 7.59 (d, 1H), 7.46 (d, 1H), 7.41-7.33 (m, 3H), 5.26-5.21 (m, 2H), 4.77 (d, 1H), 4.63 (d, 1H), 4.25-4.17 (m, 1H), 3.72 (s, 1H), 3.49 (m, 1 H), 3.21 (t, 3H), 2.78 (s, 3H), 1.71 (s, 3H), 1.70 (s, 3H), 1.62-1.58 (m, 2H), 1.28-1.24 (m, 2H).

Ejemplo 153: Síntesis del ácido 2-metil-2-[5-metil-1-[(2R)-2-(oxan-4-iloxi)-2-[2-[(propan-2-iloxi)metil]fenil]etil]-6-(1,3-oxazol-2-il)-2,4-dioxo-

1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-297).

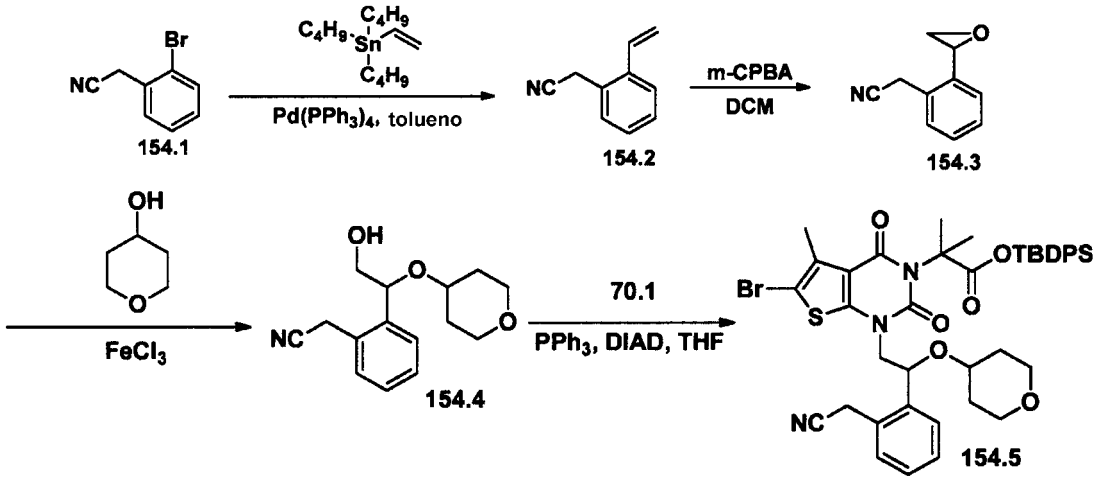


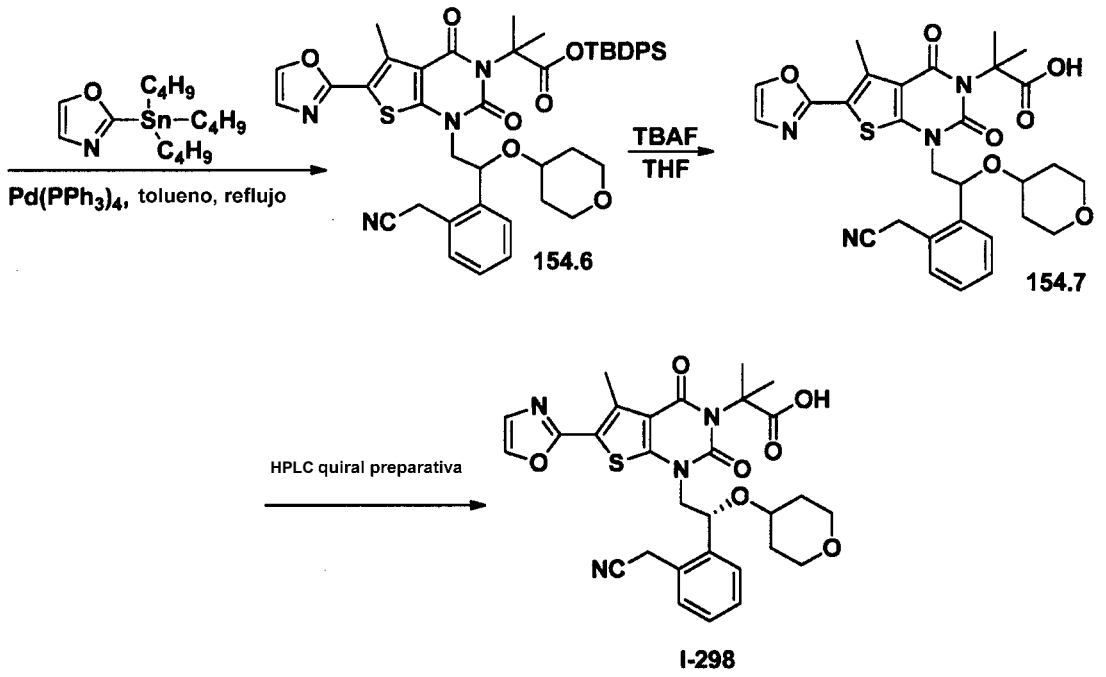
Síntesis del compuesto 153.2. En un matraz de fondo redondo de 3 cuellos de 250 ml se coloca propan-2-ol (48 g, 798.74 mmol, 9.98 equivalentes). Esto es seguido por la adición de 3.68 g de Na a 80°C. Cuando los sólidos han desaparecido, se agrega a gotas, con agitación 1-bromo-2-(bromometil)benceno (20 g, 80.02 mmol, 1.00 equivalentes). La solución resultante se agita durante la noche a 80°C en un baño de aceite. La reacción después se suspende por la adición de 200 ml de agua. La solución resultante se extrae con 200 ml de acetato de etilo y las capas orgánicas se combinan y concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:100). Esto resulta en 16 g (87%) de 153.2 como un aceite amarillo claro.

Síntesis del compuesto 153.6. El compuesto 153.6 se prepara a partir de 153.2 de una manera análoga a la síntesis del compuesto 149.6 a partir de 149.2. Se aíslan 0.8 g de un aceite incoloro con un rendimiento de 13% a partir de 153.2.

Síntesis del compuesto I-297. El compuesto I-297 se prepara a partir de 70.1 y 153.6 de una manera análoga al Ejemplo 57. Se aíslan 7.4 mg de un sólido blanco con un rendimiento total de 2%. EM (ES): *m/z* 634 $(M+Na)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 1.15-1.31 (m, 8H), 1.59-1.71 (m, 8H), 2.73 (s, 3H), 3.20-3.24 (m, 2H), 3.33-3.42 (m, 2H), 3.64-3.81 (m, 2H), 4.24-4.29 (d, 1H), 4.42-4.46 (d, 1H), 4.72-4.76 (d, 1H), 5.27-5.29 (d, 1H), 7.30-7.45 (m, 4H), 7.61-7.64 (d, 1H), 8.24 (s, 1H).

Ejemplo 154: Síntesis del ácido 2-[1-[(2R)-2-[2-(cianometil)fenil]-2-(oxan-4-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-298).





Síntesis del compuesto 154.2. En un matraz de fondo redondo de 3 cuellos de 500 ml, purgado y mantenido con una atmósfera inerte de nitrógeno se coloca 2-(2-bromofenil)acetonitrilo (10 g, 51.01 mmol, 1.00 equivalentes), 200 ml de tolueno, $Pd(PPh_3)_4$ (5.9 g, 5.11 mmol, 0.10 equivalentes) y tributil(etenil)estanano (25.6 g, 80.73 mmol, 1.58 equivalentes). La solución resultante se agita durante la noche a 110°C. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:100). Esto resulta en 5.5 g (75%) de 154.2 como un aceite incoloro.

Síntesis del compuesto 154.3. En un matraz de fondo redondo de 250 ml se coloca 154.2 (5.5 g, 38.41 mmol, 1.00 equivalentes), 100 ml de diclorometano y m-CPBA (20.4 g,

82.75 mmol, 2.15 equivalentes, 70%). La solución resultante se agita durante 5 h a temperatura ambiente. Los sólidos se separan por filtración. La solución resultante se extrae con 2 x 100 ml de Na_2SO_3 acuoso y las capas orgánicas se combinan. La solución resultante se extrae con 100 ml de bicarbonato de sodio acuoso y las capas orgánicas se combinan y concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo 1:2. La purificación proporciona 5.4 g (88%) de 154.3 como un aceite incoloro.

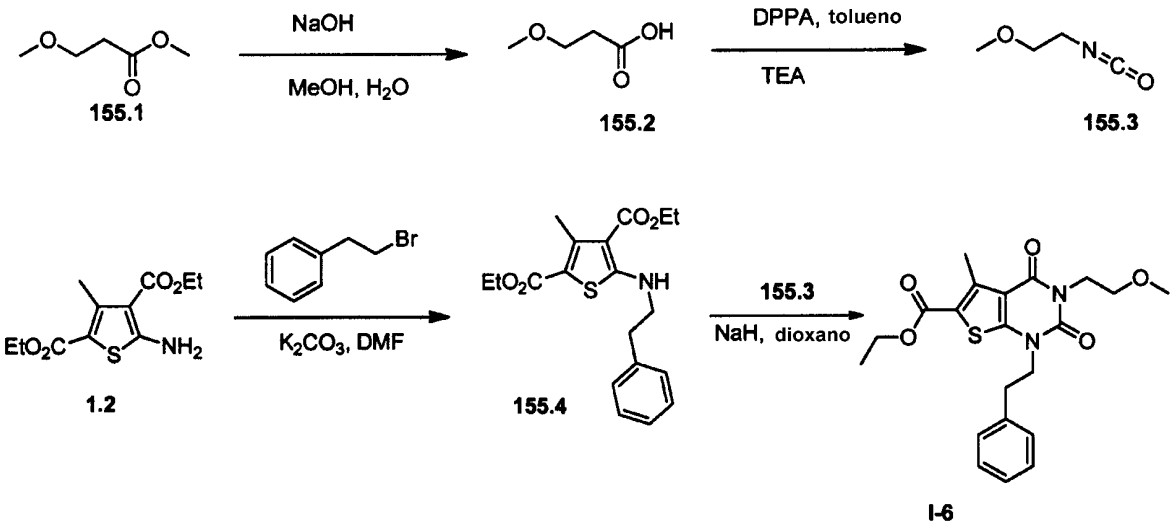
Síntesis del compuesto 154.4. El compuesto 154.4 se prepara a partir de 154.3 de una manera análoga a la síntesis de 57.3. Se aíslan 3.0 g (34%) de 154.4 como un aceite incoloro.

Síntesis del compuesto 154.7. El compuesto 154.7 se sintetiza a partir de 154.4 y 70.1 de una manera análoga al ejemplo 57. Se aíslan 120 mg de 154.7 como un sólido blanco con un rendimiento total de 6% a partir de 70:1.

Purificación del compuesto I-298. Los enantiómeros de 154.7 (120 mg, 0.21 mmol, 1.00 equivalentes) se separan por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): Columna: Chiralpak IC, 2*25cm, 5 µM; fase móvil: hexanos (AcOH 0.1%) e IPA que se mantiene a IPEA 30.0% durante 30 min); detector: UV 220/254 nm. Esto resulta en 11.4 mg de I-298 (tR = 23.375 min; 10%) como un sólido blanco.

Datos analíticos para I-298: EM (ES): *m/z* 579 $(M+H)^+$, 601 $(M+Na)^+$. (400 MHz, DMSO-d_6): δ 12.41 (s amplio, 1 H) , 8.26 (s, 1 H) , 7.63 (d, 1 H), 7.49-7.42 (m, 4H), 5.12 (d, 1H), 4.31-4.16 (m, 3H), 3.70 (s, 1H), 3.53 (d, 1H), 3.43-3.32 (m, 2H), 3.25-3.20 (m, 2H), 2.78 (s, 3H), 1.72-1.62 (m, 8H), 1.33-1.21 (m, 2H).

Ejemplo 155: Síntesis de 3-(2-metoxietil)-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxilato de etilo (I-6).



Síntesis del compuesto 155.2. Una mezcla de 3-metoxipropanoato de metilo (3 g, 25.40 mmol, 1.00 equivalentes), 60 ml de metanol, 12 ml de agua y sodiumol (3.2 g, 80 mmol, 3.15 equivalentes) se agita durante 2 h a 50°C en un baño de aceite. El valor de pH de la solución se ajusta a 2-3 con ácido clorhídrico (2 moles/l). La solución resultante se extrae con 3 x 50 ml de diclorometano y las capas orgánicas se combinan. La

mezcla resultante se lava con 50 ml de salmuera. La solución resultante se seca sobre sulfato de sodio anhidro y se concentra bajo vacío para proporcionar 2.0 g (76%) de 155.2 como un aceite incoloro.

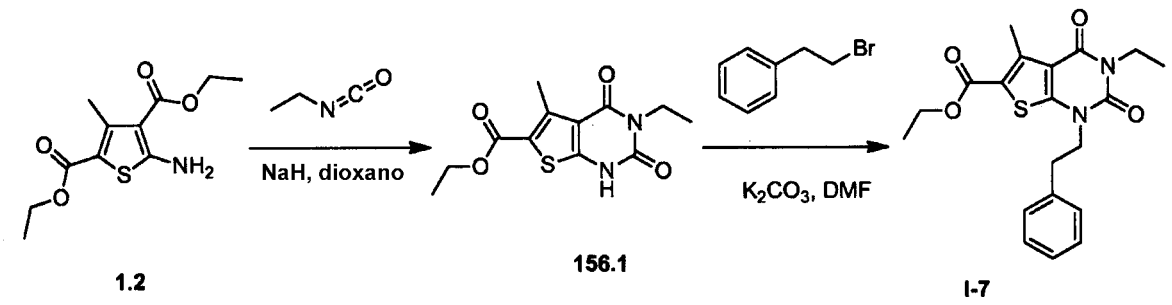
Síntesis del compuesto 155.3. Una mezcla de ácido 3-metoxipropanoico (3.0 g, 28.82 mmol, 1.00 equivalentes), DPPA (8.0 g, 29.07 mmol, 1.01 equivalentes) y trietilamina (2.92 g, 28.86 mmol, 1.00 equivalentes) en 80 ml de tolueno seco se calienta a reflujo durante 2 h bajo una atmósfera de nitrógeno. La mezcla de reacción se enfría a temperatura ambiente y después se suspende por la adición de 50 ml de agua/hielo. La solución resultante se extrae con 100 ml de acetato de etilo y la capa orgánica se seca sobre sulfato de sodio anhidro y se concentra bajo vacío para proporcionar 1.5 g (51%) de 155.3 como un aceite incoloro.

Síntesis del compuesto 155.4. Una mezcla de 5-amino-3-metiltiofen-2,4-dicarboxilato de 2,4-dietilo (5.0 g, 19.43 mmol, 1.00 equivalentes) y carbonato de potasio (5.4 g, 39.07 mmol, 2.01 equivalentes) en 70 ml de N,N-dimetilformamida se agita durante 15 min a 25°C. A esto se le agrega (2-bromoetil)benceno (7.2 g, 38.91 mmol, 2.00 equivalentes). La solución resultante se agita durante la noche a 50°C en un baño de aceite. La reacción después se suspende por la adición de 100 ml y una mezcla

de agua y hielo. La solución resultante se extrae con 2 x 100 ml de acetato de etilo y las capas orgánicas se combinan. La solución resultante se seca sobre sulfato de sodio anhidro y se concentra bajo vacío. El residuo se aplica a una columna de gel de sílice con acetato de etilo: éter de petróleo (1:10) para proporcionar 4.0 g (57%) de 155.4 como un sólido café. Los 500 mg de material crudo se recristalizan con EtOH para obtener 208.9 mg del compuesto puro.

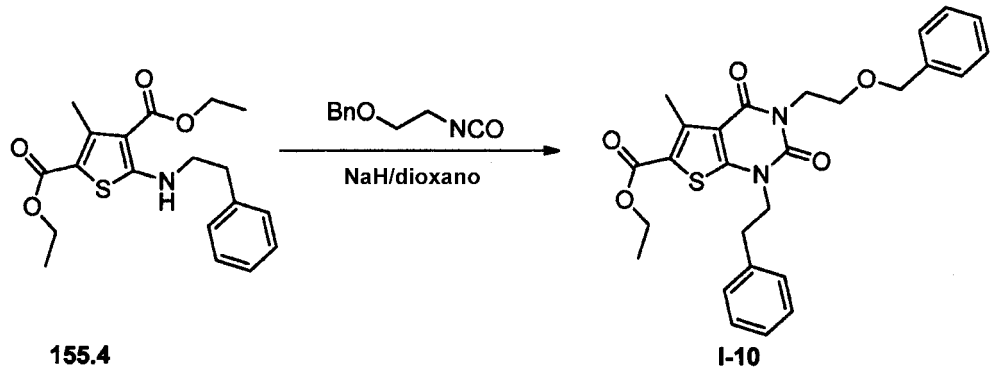
Síntesis del compuesto I-6. Se agrega hidruro de sodio (60%) (100 mg, 2.5 mmol, 1.81 equivalentes) a una solución de 155.4 (500 mg, 1.38 mmol, 1.00 equivalentes) en 15 ml de dioxano por lotes bajo una atmósfera de nitrógeno. A los 30 minutos después se agregan 155.3 (300 mg, 2.97 mmol, 2.15 equivalentes). La solución resultante se calienta a reflujo durante 8 h en un baño de aceite. La mezcla de reacción se enfría a temperatura ambiente y se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1/10) para proporcionar 0.25 g (43%) de I-6 como un sólido blanco. EM (ES): *m/z* $(M+H)^+$ calculado para $C_{21}H_{25}N_2O_5S$ 417, encontrado 417. RMN ^1H (400 MHz, $CDCl_3$) δ 7.28-7.35 (5h, m), 4.36-4.41 (2H, c), 4.26-4.28 (2H, t), 4.14-4.18 (2H, t), 3.64-3.67 (2H, t), 3.39 (3H, s), 3.07-3.11 (2H, t), 2.90 (3H, s), 1.40-1.44 (3H, t).

Ejemplo 156: Síntesis de 3-etil-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxilato de etilo (I-7).



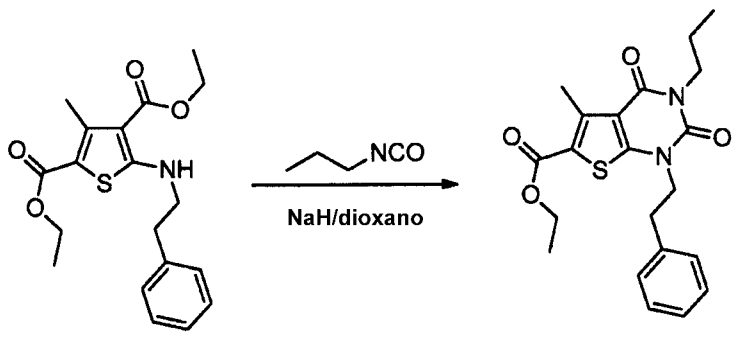
Síntesis del compuesto I-7. El compuesto I-7 se prepara a partir de isocianatoetano y 1.2 de una manera análoga a la síntesis del compuesto 136.1. Se aísla un sólido blanco con un rendimiento de 45%. EM (ES): *m/z* $(M+H)^+$ calculado para $C_{20}H_{23}N_2O_4S$ 387, encontrado 387. RMN ^1H (400 MHz, $CDCl_3$) δ 7.29-7.39 (5H, m), 4.36-4.43 (2H, c), 4.115-4.20 (2H, t), 4.05-4.10 (2H, c), 3.08-3.13 (2H, t), 2.92 (3H, s), 1.41-1.45 (3H, t), 1.25-1.29 (3H, t).

Ejemplo 157: Síntesis de 3-[2-(benciloxi)etil]-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxilato de etilo (I-10).



Se prepara el compuesto I-10 a partir de 155.4 y [(2-isocianatoetoxi)metil]benceno de una manera análoga al compuesto I-6 (Ejemplo 155). Se aísla un sólido blanco con un rendimiento de 51%. EM (ES): *m/z:* 493 $(M+H)^+$. RMN ^1H (400 MHz, $CDCl_3$) δ 7.21-7.35 (10H, m), 4.55 (2H, s), 4.33-4.40 (2H, c), 4.27-4.31 (2H, t), 4.07-4.13 (2H, t), 3.73-3.77 (2H, t), 3.01-3.06 (2H, t), 2.87 (3H, s), 1.38-1.42 (3H, t).

Ejemplo 157: Síntesis de 5-metil-2,4-dioxo-1-(2-feniletil)-3-propil-1H,2H,3H-4H-tieno[2,3-d]pirimidin-6-carboxilato de etilo (I-9).

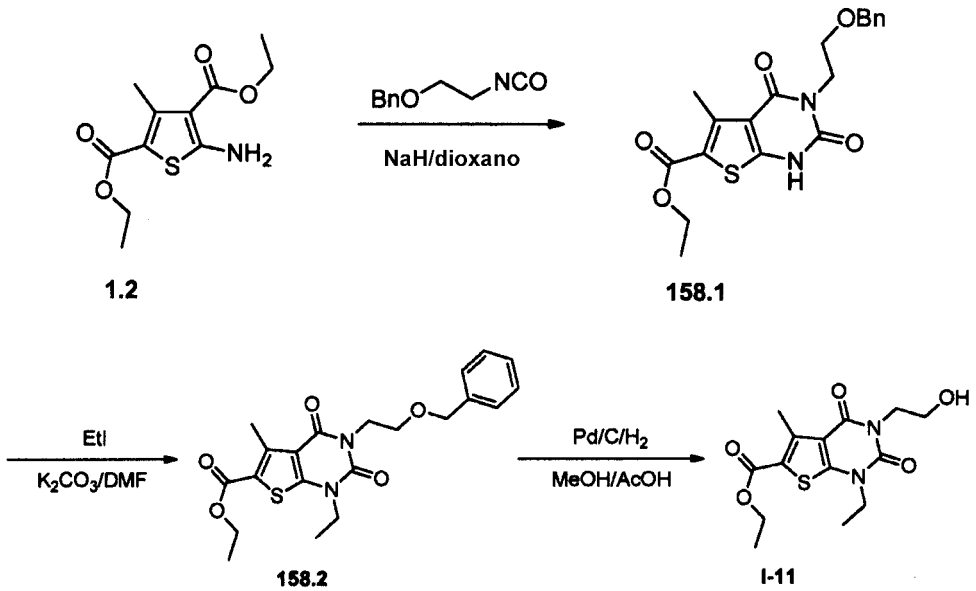


155.4 I-9

Se prepara el compuesto I-9 a partir de 155.4 y 1-isocianatopropano de una manera análoga al compuesto I-6 (Ejemplo 155). Se aísla un sólido blanco con un rendimiento de 3%. EM (ES): *m/z*: 401 $(M+H)^+$. RMN ^1H (400 MHz, $CDCl_3$) δ 7.28-7.35 (5H, m), 4.35-4.42 (2H, c), 4.14-4.16 (2H, t), 3.95-4.00 (2H, t), 3.07-3.12 (2H, t), 2.90 (3H, s), 1.67-1.72 (2H, c), 1.40-1.45 (3H, t), 0.96-1.01 (3H, t).

Ejemplo 158: Síntesis de 1-etil-3-(2-hidroxietil)-5-

metil-2,4-dioxo-1H,2H,3H,4H-tien[2,3-d]pirimidin-6-carboxilato (I-11).



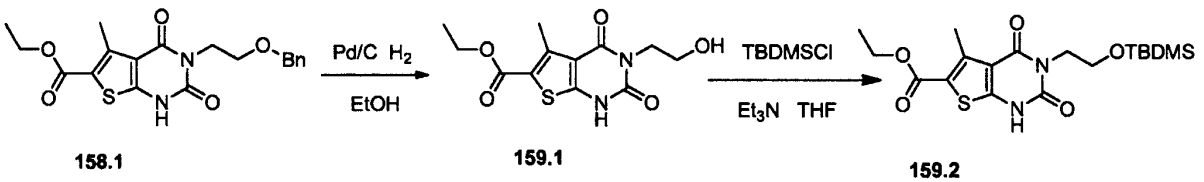
Síntesis del compuesto 158.1. Se prepara el compuesto 158.1 a partir de 1.2 y [(2-isocianatoetoxi)metil]benceno de una manera análoga a la síntesis del compuesto 135.3. Se aíslan 38.9 mg de un sólido blanco con un rendimiento de 10%. EM (ES): *m/z:* 389$(M+H)^+$. RMN ^1H (400 MHz, $CDCl_3$) δ 9.68 (1H, s), 7.21-7.34 (5H, m), 4.60 (2H, s), 4.28-4.40 (4H, m), 3.81-3.85 (2H, t), 2.86 (3H, s), 3.38-1.42 (3H, t).

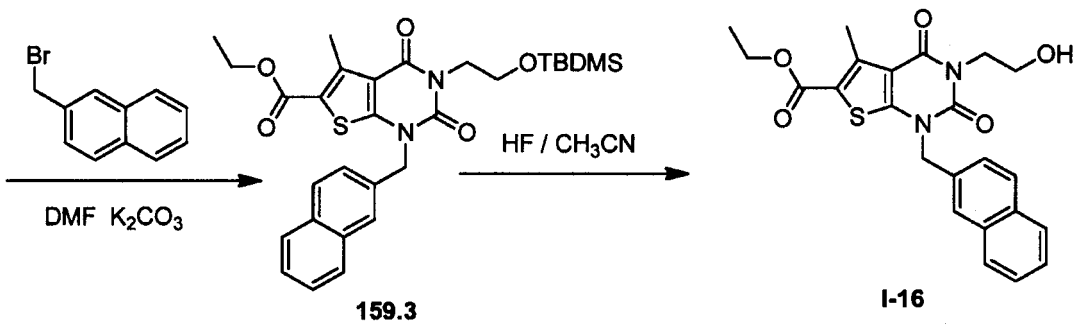
Síntesis del compuesto 158.2. Una mezcla de 158.1 (200 mg, 0.51 mmol, 1.00 equivalentes), carbonato de potasio (140 mg, 1.01 mmol, 1.95 equivalentes) y yodoetano (321 mg, 2.06 mmol, 4.00 equivalentes) en 10 ml de N,N-dimetilformamida se agita durante 4 h a 35°C. La reacción después se suspende por la adición de 15 ml de una mezcla de agua y hielo. La

solución resultante se extrae con 2 x 15 ml de acetato de etilo y las capas orgánicas se combinan. La mezcla resultante se lava con 2 x 20 ml de salmuera. La mezcla se seca sobre sulfato de sodio anhidro y se concentra bajo vacío para proporcionar 120 mg (56%) de 158.2 como un sólido amarillo.

Síntesis del compuesto I-11. Se introduce hidrógeno gaseoso en exceso en una mezcla de 158.2 (120 mg, 0.29 mmol, 1.00 equivalentes), 5 ml del ácido acético, 100 mg de paladio 10% en carbono en 20 ml de etanol y se mantiene la presión a 4 atm. La solución resultante se agita durante 12 h a temperatura ambiente. Los sólidos se separan por filtración. El filtrado se concentra bajo vacío. El residuo se purifica por recristalización a partir de etanol para proporcionar 12.4 mg (13%) de I-11 como un sólido blanco. EM (ES): *m/z*: 327 $(M+H)^+$. RMN ^1H (400 MHz, $CDCl_3$) δ 4.32-4.39 (2H, c), 4.27-4.30 (2H, t), 4.00-4.07 (2H, c), 3.89-3.92 (2H, t), 2.87 (3H, s), 1.36-1.42 (6H, dt).

Ejemplo 159: Síntesis de 3-(2-hidroxietil)-5-metil-1-(naftalen-2-ilmetil)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-carboxilato de etilo (I-16).





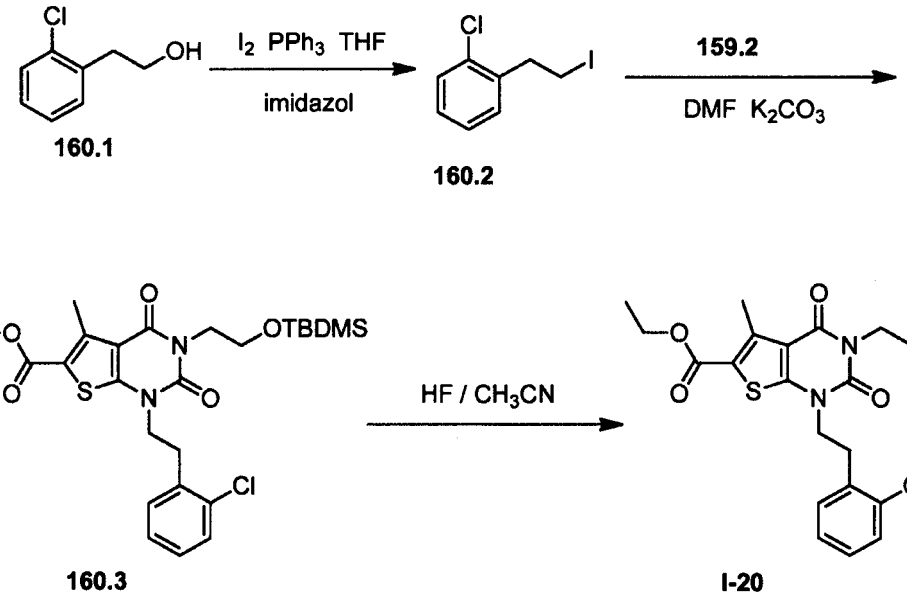
Síntesis del compuesto 159.1. En un matraz de fondo redondo de 100 ml se coloca 158.1 (650 mg, 1.67 mmol, 1.00 equivalentes), 35 ml de etanol, 7 ml del ácido acético y 300 mg de paladio 10% en carbón. Se introduce hidrógeno (4 atm). La solución resultante se agita durante 24 h a temperatura ambiente. Los sólidos se separan por filtración. El filtrado se concentra bajo vacío para proporcionar 400 mg (80%) de 159.1 como un sólido café.

Síntesis del compuesto 159.2. Una mezcla de 159.1 (400 mg, 1.34 mmol, 1.00 equivalentes), terbutil(cloro)dimetilsilano (240 mg, 1.59 mmol, 1.19 equivalentes) y trietilamina (203 mg, 2.01 mmol, 1.50 equivalentes) en 20 ml de oxolano se agita durante 12 h a temperatura ambiente. La reacción después se suspende por la adición de 20 ml de agua. La solución resultante se extrae con 2 x 40 ml de acetato de etilo y las capas orgánicas se combinan y se secan sobre sulfato de sodio anhidro y se concentran bajo vacío para proporcionar 360 mg (65%) de 159.2 como un aceite blanco.

Síntesis del compuesto 159.3. Una mezcla de 159.2 (120 mg, 0.29 mmol, 1.00 equivalentes), carbonato de potasio (60 mg, 0.43 mmol, 1.48 equivalentes) y 2-(bromometil)naftaleno (77 mg, 0.35 mmol, 1.20 equivalentes) en 10 ml de N,N-dimetilformamida se agita durante 12 h a 35°C. La reacción después se suspende por la adición de 10 ml de agua. La solución resultante se extrae con 2 x 15 ml de acetato de etilo y las capas orgánicas se combinan. La mezcla resultante se lava con 1 x 35 ml de salmuera. La mezcla se seca sobre sulfato de sodio anhidro y se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1 / 15 – 1 / 10) para proporcionar 60 mg (37%) de 159.3 como un sólido amarillo.

Síntesis del compuesto I-16. En un matraz de fondo redondo de 50 ml se coloca una solución de 159.3 (20 mg, 0.04 mmol, 1.00 equivalentes, 99%) en 5 ml de CH_3CN. Esto es seguido por la adición de 0.25 ml de HF a gotas con agitación. La solución resultante se agita durante la noche a temperatura ambiente. La solución resultante se diluye con 30 ml de agua. Los sólidos se recolectan por filtración y se secan bajo presión reducida para proporcionar 15 mg (93%) de I-16 como un sólido blanco. EM (ES, *m/z)*: 439 $(M+H)^+$. RMN ^1H (300 MHz, $CDCl_3$): δ 7.84 (d, 4H), 7.52-7.45 (m, 3H), 5.35 (s, 2H), 4.37-4.27 (m, 4H), 3.96 (t 2H), 2.85 (s, 3H), 2.31 (s, 1H), 1.35 (t, 3H).

Ejemplo 160: Síntesis de 1-[2-(2-clorofenil)etil]-3-(2-hidroxietil)-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxilato de etilo (I-20).

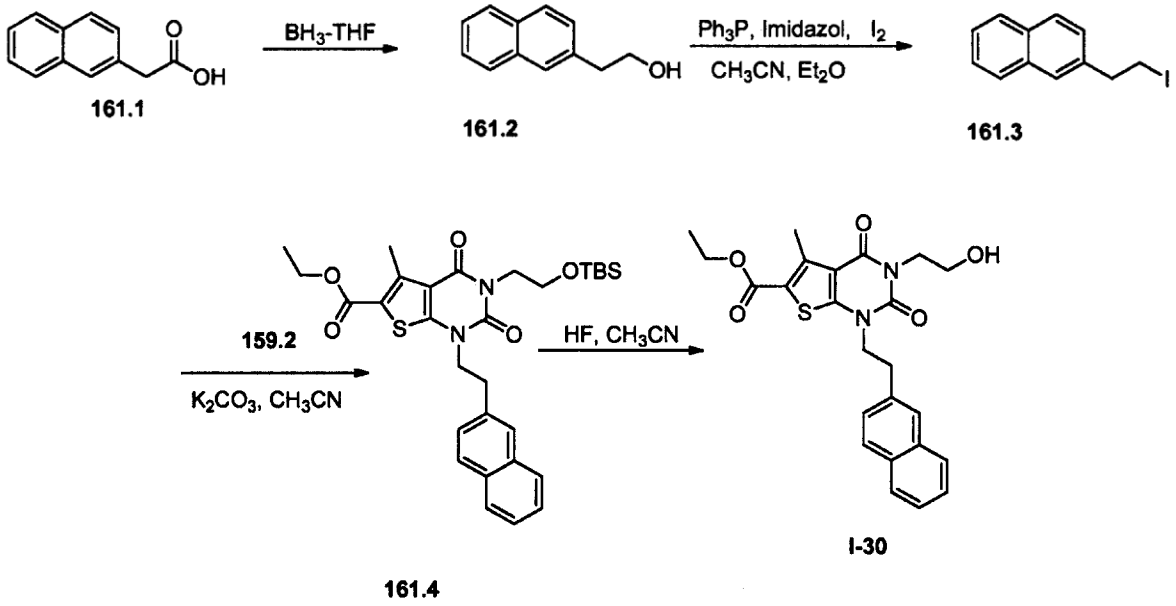


Síntesis del compuesto 160.2. En un matraz de fondo redondo de 3 cuellos de 50 ml se coloca 2-(2-clorofenil)etan-1-ol (1.5 g, 9.58 mmol, 1.00 equivalentes), PPh_3 (2.5 g, 9.53 mmol, 1.00 equivalentes), 30 ml de tetrahidrofurano e imidazol (0.9 g, 13.2 mmol, 1.4 equivalentes). Esto es seguido por la adición de 3.4 g de I_2 en varios lotes. La solución resultante se agita durante 30 min a 0-5°C y después se suspende por la adición de 20 ml de agua/hielo. La solución resultante se extrae con 2 x 50 ml de éter y las capas orgánicas se combinan. La mezcla resultante se lava con 1 x 50 ml de Na_2SO_3 acuoso saturado. La mezcla se seca sobre

sulfato de sodio anhidro y se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1 / 3). Esto resulta en 2.5 g (98%) de 160.2 como un aceite incoloro.

Síntesis del compuesto I-20. Se prepara el compuesto I-20 a partir de 159.2 y 160.2 de una manera análoga a la síntesis del compuesto I-16 (Ejemplo 159). Aislada con un sólido blanco en 54% de rendimiento. EM (ES): *m/z*: 437 $(M+H)^+$. RMN ^1H (300 MHz, $CDCl_3$): δ 7.39-735 (m, 1H), 7.22-7.19 (m, 3H), 4.39-4.32 (m, 2H), 4.28-4.18 (m, 4H), 3.87 (t, 2H), 3.24 (t, 2H), 2.86 (s, 3H), 2.26 (s, 1H), 1.39 (t, 3H).

Ejemplo 161: Síntesis de 3-(2-hidroxietil)-5-metil-1-[2-(naftalen-2-il)etil]-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxilato de etilo (I-30).

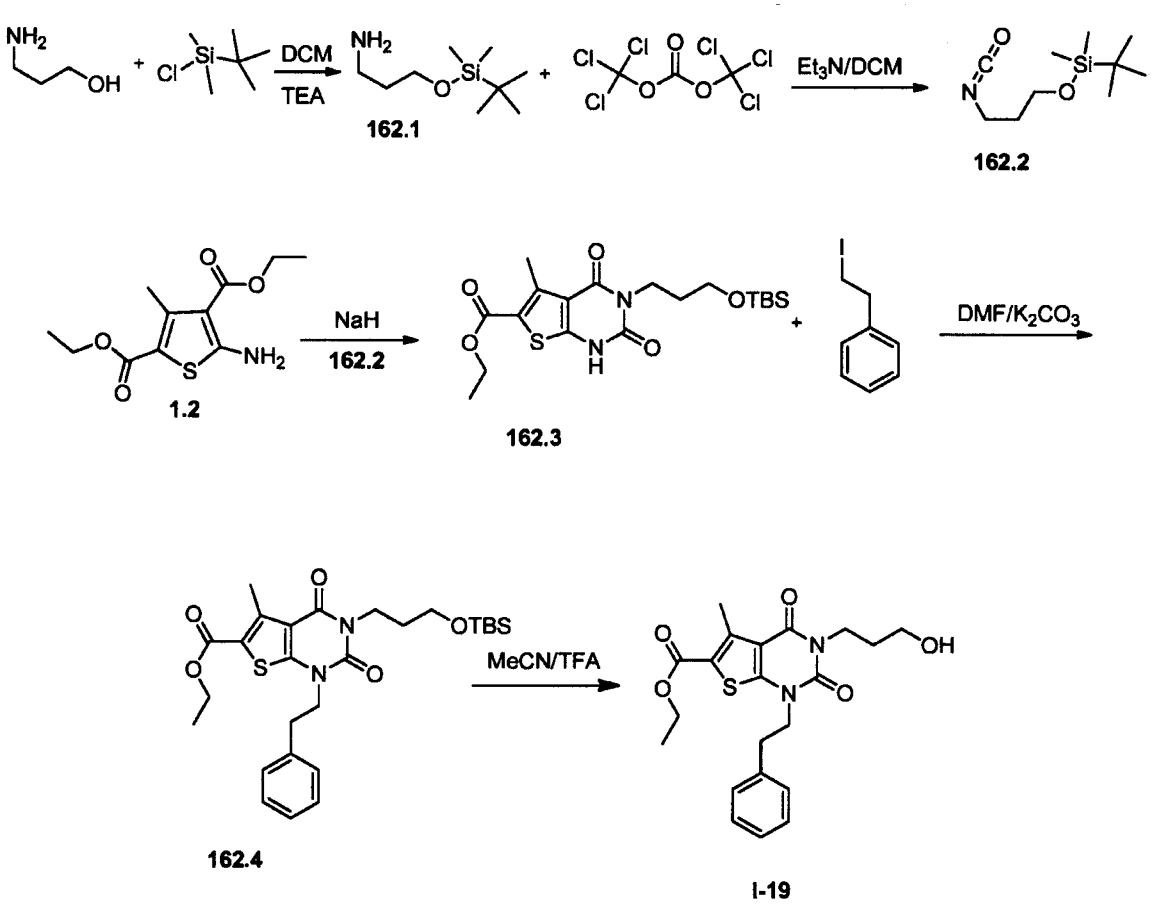


Síntesis del compuesto 161.2. En un matraz de fondo redondo de 250 ml purgado y mantenido con una atmósfera inerte de nitrógeno se coloca 161.1 (7.44 g, 39.96 mmol, 1.00 equivalentes) y 80 ml de tetrahidrofurano. Esto es seguido por la adición de 80 ml de BH_3/THF (1 M) a gotas con agitación a 0°C. La solución resultante se agita durante 2 h a temperatura ambiente. La reacción después se suspende por la adición de 20 ml de agua. La solución resultante se extrae con 2 x 150 ml de acetato de etilo y las capas orgánicas se combinan y se secan sobre sulfato de sodio anhidro y se concentran bajo vacío. Esto resulta en 7.05 g (crudo) de 161.2 como un aceite incoloro.

Síntesis del compueto I-30. Se prepara el compuesto I-30 a partir de 161.2 y 159.2 de una manera análoga a la síntesis del compuesto I-20 (Ejemplo 160). Aislado como un sólido blanco con un rendimiento de 31% a partir de 159.2. EM (ES): *m/z*: $(M+H)^+$ 453, $(M+Na)^+$ 475. RMN ^1H (400 MHz, DMSO-d_6): δ 1.28 (t, J = 7.2, 3H), 2.76 (s, 3H), 3.18 (t, J = 7.6, 2H), 3.49 (t, J = 6.4, 2H), 3.95 (t, J = 6.4, 2H), 4.20-4.30 (m, 4H), 7.42-7.51 (m, 3H), 7.78 (s, 3H), 7.85-7.90 (m, 3H).

Ejemplo 162: Síntesis de 3-(3-hidroxipropil)-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-

d]pirimidin-6-carboxilato de etilo (I-19).



Síntesis del compuesto 162.1. En un matraz de fondo redondo de 3 cuellos de 500 ml se coloca una solución de 3-aminopropan-1-ol (15 g, 195.71 mmol, 1.00 equivalentes, 98%) en 200 ml de diclorometano, terbutil(cloro)dimetilsilano (36 g, 234.07 mmol, 1.20 equivalentes), trietilamina (60.6 g, 588.00 mmol, 3.00 equivalentes, 98%). La solución resultante se agita durante 18 h a 20°C. La reacción después se suspende por la adición de 200 ml de agua. La solución resultante se extrae con 1 x 200 ml de diclorometano y las capas orgánicas

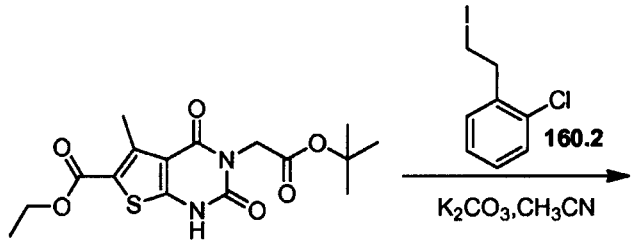
se combinan. La mezcla resultante se lava con 1 x 200 ml de salmuera. La mezcla se seca sobre sulfato de magnesio anhidro y se concentra bajo vacío. Esto resulta en 20 g (51%) de 162.1 como un aceite incoloro.

Síntesis del compuesto 162.2. Se prepara el compuesto 162.2 a partir de 162.1 de una manera análoga a 135.2. Se aíslan 2 g de un aceite amarillo en 74% de rendimiento.

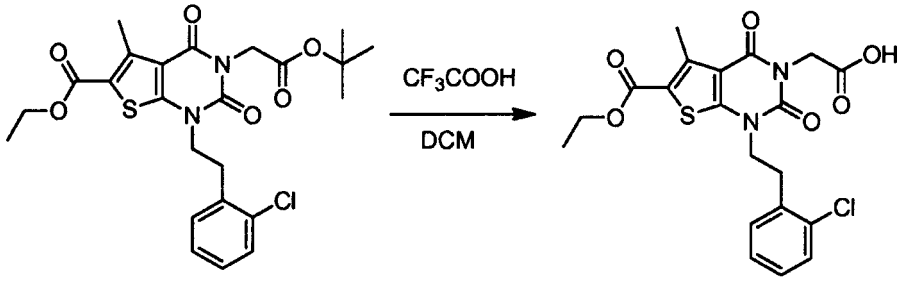
Síntesis del compuesto 162.4. Se prepara el compuesto 162.4 a partir de 162.2 y 1.2 de una manera análoga a la síntesis del compuesto 136.1 (Ejemplos 135 y 136). Se aíslan 110 mg de un sólido blanco con 15% de rendimiento a partir de 1.2.

Síntesis del compuesto I-19. En un matraz de fondo redondo de 50 ml se coloca una solución de 162.4 (110 mg, 0.20 mmol, 1.00 equivalentes, 98%) en 20 ml de CH_3CN y 1 ml de fluoruro de hidrógeno. La solución resultante se agita durante 3 h a 20°C. La reacción después se suspende por la adición de 10 ml de agua. Los sólidos se recolectan por filtración y se secan bajo presión reducida para proporcionar 60 mg (70%) de I-19 como un sólido blanco. EM (ES): *m/z* 417 $(M+H)^+$. RMN ^1H (400 MHz, $CDCl_3$): δ 7.327 (m, 4H), 7.261 (m, 1H), 4.385 (m, 2H), 4.137 (m, 4H), 3.513 (t, 2H), 3.084 (t, 2H), 2.873 (s, 3H), 1.429 (t, 2H), 0.962 (t, 3H).

Ejemplo 163: Síntesis del ácido 2-[1-[2-(2-clorofenil)etil]-6-(etoxicarbonil)-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acético (I-31).



135.3

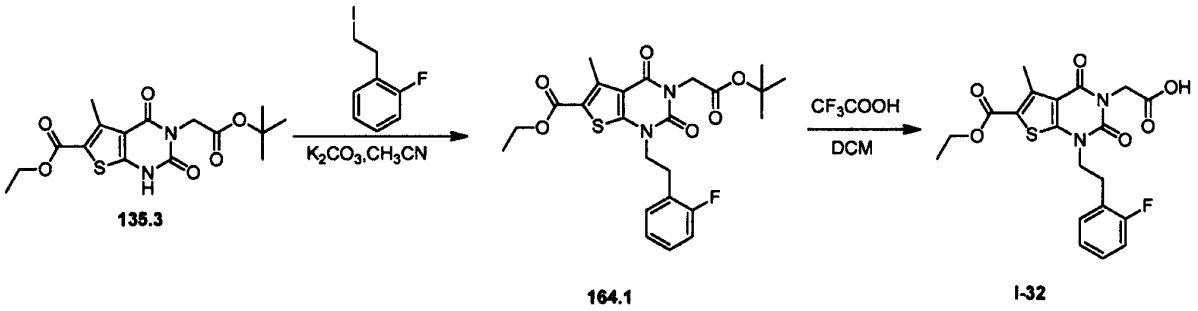


163.1 I-31

Se prepara el compuesto I-31 a partir de 135.3 y 160.2 de una manera análoga a la síntesis de 136.2. Se aíslan 73.1 mg de un sólido blanco con un rendimiento total de 11%. EM (ES): *m/z* $(M+H)^+$ 451. RMN ^1H (400 MHz, CD_3OD): δ 1.35-1.86 (t, 3H), 3.27-3.37 (m, 2H), 4.23-4.27 (t, 2H), 4.30-4.35 (c, 2H), 4.71 (s, 2H), 7.21-7.23 (t, 2H), 7.30-7.36 (m, 1H), 7.36-7.37 (m, 1H).

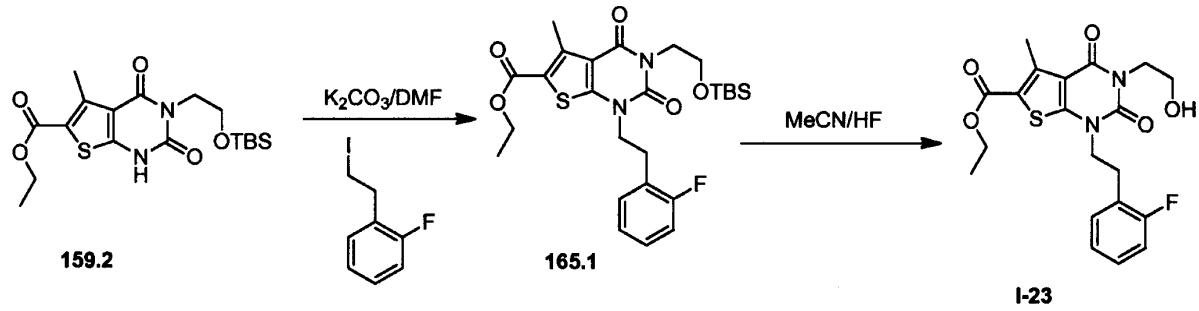
Ejemplo 164: Síntesis del ácido 2-[6-(etoxicarbonil)-1-[2-(2-fluorofenil)etil]-5-metil-2,4-dioxo-

1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acético (I-32).



Se prepara el compuesto I-32 a partir de 135.3 y 1-fluoro-2-(2-yodoetil)benceno de una manera análoga a la síntesis de 136.2. Se aíslan 42.9 mg de un sólido blanco con un rendimiento total de 23%. EM (ES): *m/z* $(M+H)^+$ 435. RMN ^1H (300 MHz, CD_3OD): δ 1.36-1.94 (t, 3H), 2.81 (s, 1H), 3.16-3.20 (t, 2H), 4.21-4.24 (t, 2H), 4.31-4.37 (c, 2H), 4.70 (s, 2H), 7.01-7.11 (m, 2H), 7.26-7.28 (c, 2H). RMN ^{19}F (400 MHz, CD_3OD): δ -120.64(1).

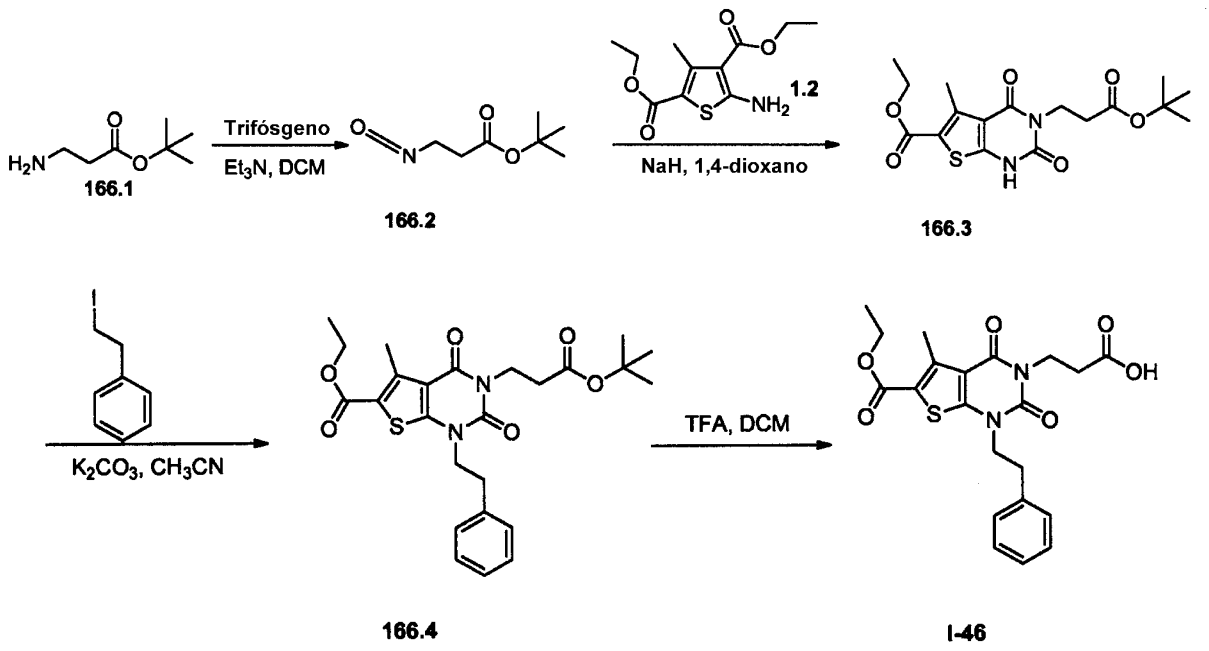
Ejemplo 165: Síntesis de 1-[2-(2-fluorofenil)etil]-3-(2-hidroxietil)-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxilato de etilo (I-23).



Se prepara el compuesto I-23 a partir de 159.2 y 1-fluoro-2-(2-yodoetil)benceno de una manera análoga a la síntesis del compuesto I-16 (Ejemplo 159). Se aíslan 500 mg de

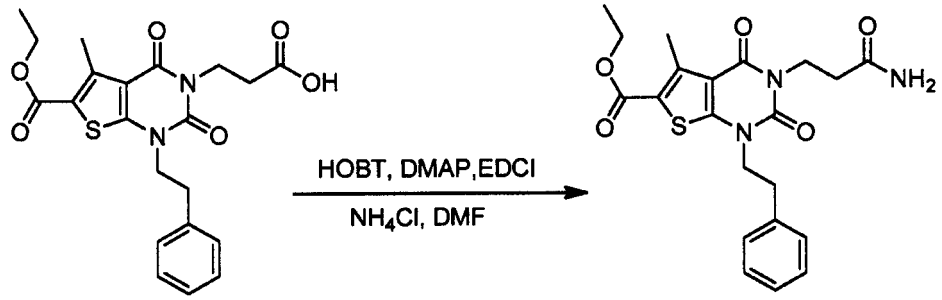
un sólido blanco con un rendimiento total de 59%. EM (ES): *m/z* 421 $(M+H)^+$ RMN ^1H (300 MHz, $CDCl_3$): δ 7.279 (m, 2H), 7.053 (m, 2H), 4.370 (m, 2H), 4.162 (m, 4H), 3.870 (t, 2H), 3.144 (m, 2H), 2.861 (s, 3H), 1.396 (t, 3H).

Ejemplo 166: Síntesis del ácido 3-[6-(etoxicarbonil)-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-46).



Se prepara el compuesto I-46 a partir de 166.1 y 1.2 de una manera análoga a la síntesis del compuesto 136.2 (Ejemplos 135 y 136). Se aíslan 1.8 g de un sólido blanco con un rendimiento total de 25%. EM (ES): *m/z* $(M+H)^+$ 431, $(M+Na)^+$ 453. RMN ^1H (300 MHz, DMSO-d_6): δ 1.29 (t, J = 7.2, 3H), 2.75 (s, 3H), 3.09 (t, J = 6.3, 2H), 4.04-4.13 (m, 4H), 4.28 (c, J = 6.9, 2H), 7.20-7.32 (m, 5H), 12.37 (s, 1H).

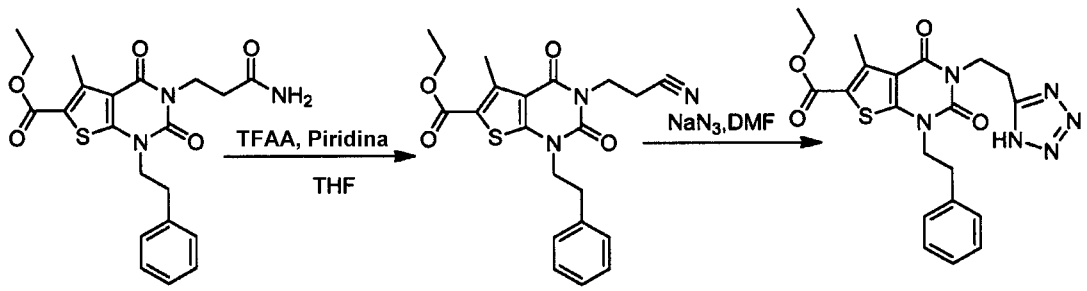
Ejemplo 167: Síntesis de 3-(2-carbamoiletil)-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxilato de etilo (I-55).



I-46 I-55

Se prepara el compuesto I-55 a partir de I-46 de una manera análoga a la síntesis de 136.3. Se aíslan 0.2 g de un sólido blanco con un rendimiento de 56%. EM (ES): *m/z* $(M+H)^+$ 430. RMN ^1H (300 MHz, DMSO-d_6): δ 1.29 (t, J = 7.2, 3H), 2.34 (t, J = 7 .5, 2H), 2.76 (s, 3H), 3.00 (t, J = 7.5, 2H), 4.02-4.13 (m, 4H), 4.28 (c, J = 7.2, 2H), 6.86 (s, 1H), 7.24-7.38 (m, 6H).

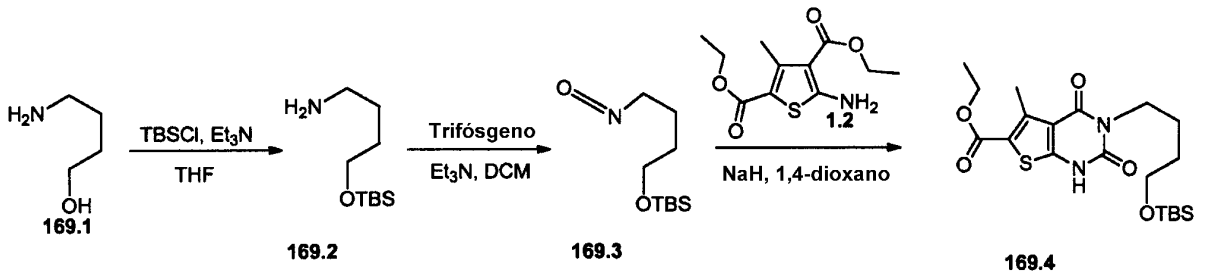
Ejemplo 168: Síntesis de 5-metil-2,4-dioxo-1-(2-feniletil)-3-[2-(1H-1,2,3,4-tetrazol-5-il)etil]-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxilato de etilo (I-61).

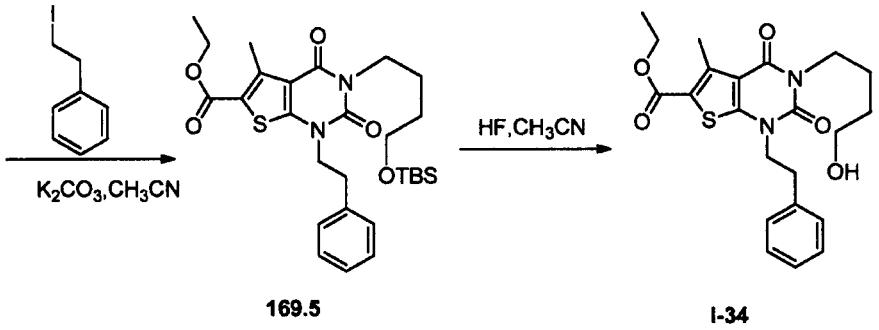


I-55 168.1 I-61

Se prepara el compuesto I-61 a partir de I-55 de una manera análoga a la síntesis del compuesto I-45 a partir de 136.3 (Ejemplo 136). Se aíslan 16.7 mg de un sólido blanco con un rendimiento total de 10%. EM (ES): *m/z* $(M+H)^+$ 455 $(M+H+CH_3CN)^+$ 496. RMN ^1H (400 MHz, CD_3OD): δ 1.38 (t, J = 7.2, 3H), 2.79 (s, 3H), 3.05 (t, J = 7.2, 2H), 3.27 (t, J = 7.2, 2H), 3.27 (t, J = 7.2, 2H), 4.13 (t, J = 7.2, 3H), 4.31-4.39 (m, 4H), 7.23-7.32 (m, 5H).

Ejemplo 169: Síntesis de 3-(4-hidroxibutil)-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxilato de etilo (I-34).

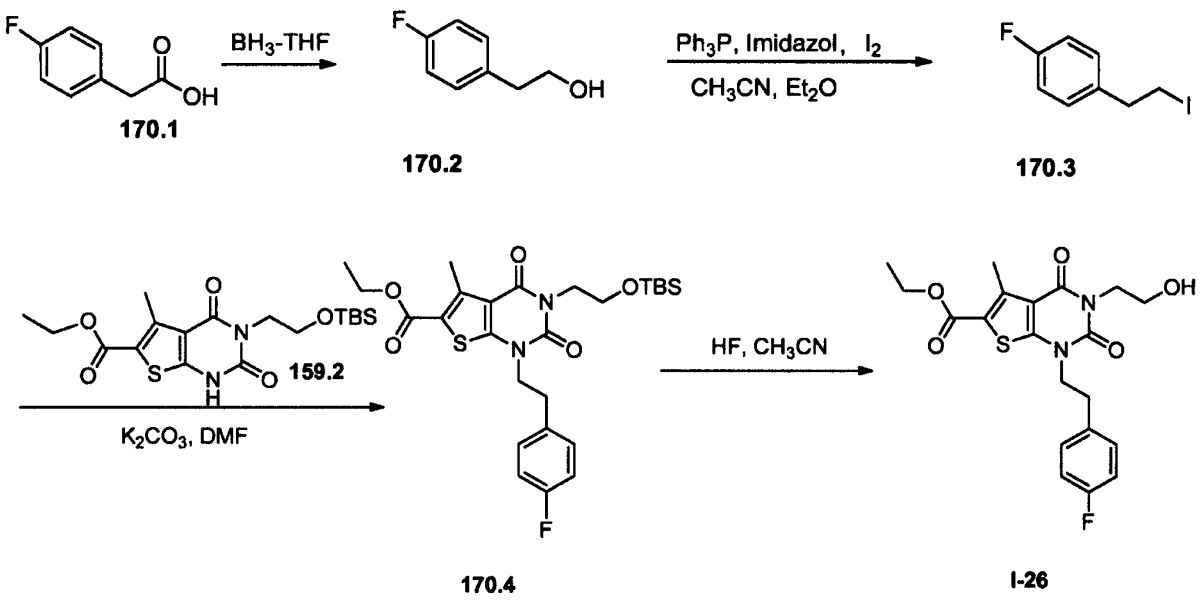




Se prepara el compuesto I-34 a partir de 169.1 y 1.2 de una manera análoga al compuesto I-19 (Ejemplo 162). Se aíslan 26 mg de un aceite incoloro con un rendimiento total de

1.4%. EM (ES): *m/z* $(M+H)^+$ 431. RMN ^1H (400 MHz, CD_3OD): δ 1.38 (t, J = 7.5, 2H), 1.52-1.64 (m, 2H), 1.66-1.78 (m, 2H), 2.82 (s, 3H), 3.10 (t, J = 7.2, 2H), 3.60 (t, J = 6.3, 2H), 3.99 (t, J = 7.2, 2H), 4.19 (t, J = 7.5, 2H), 4.34 (c, J = 7.2, 2H), 7.19-7.31 (m, 2H).

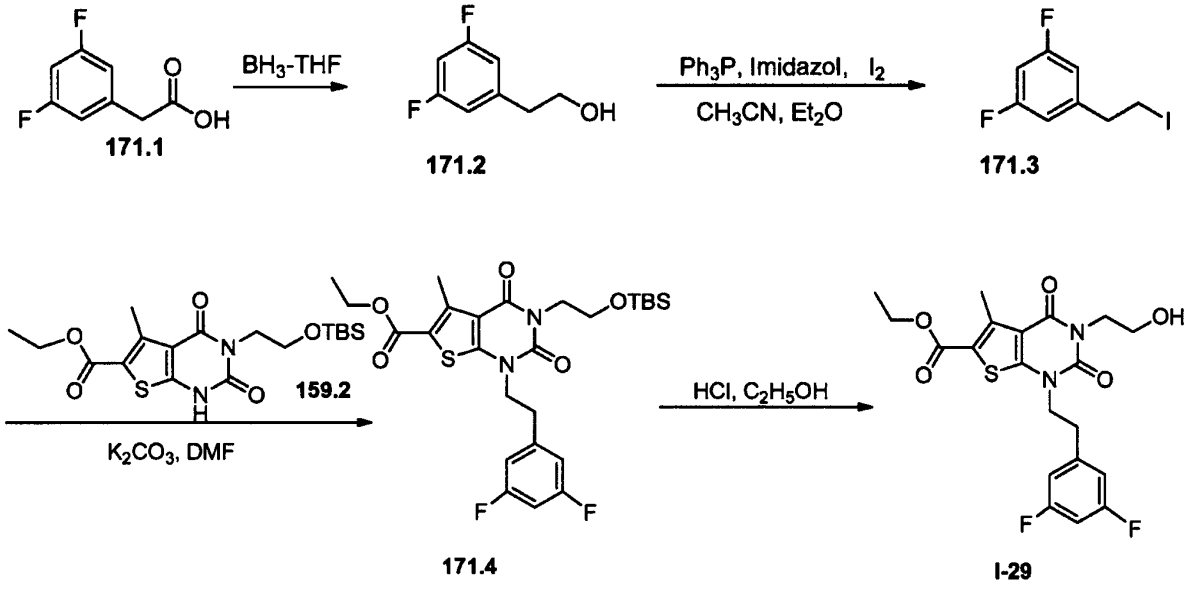
Ejemplo 170: Síntesis de 1-[2-(4-fluorofenil)etil]-3-(2-hidroxietil)-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxilato de etilo (I-26).



Se prepara el compuesto I-26 a partir de 170.1 y 159.2 de una manera análoga a la síntesis del compuesto I-30 (Ejemplo 161). Se aíslan 80 mg de un sólido blanco con un rendimiento total de 60%. EM (ES): *m/z* $(M+H)^+$ 421. RMN ^1H (300 MHz, $CDCl_3$): δ 1.40 (t, J = 7.2, 3H), 2.24 (s, 3H), 2.87 (s, 3H), 3.06 (t, J = 7.5, 2H), 3.89 (s, 2H), 3.89 (s, 2H), 4.12

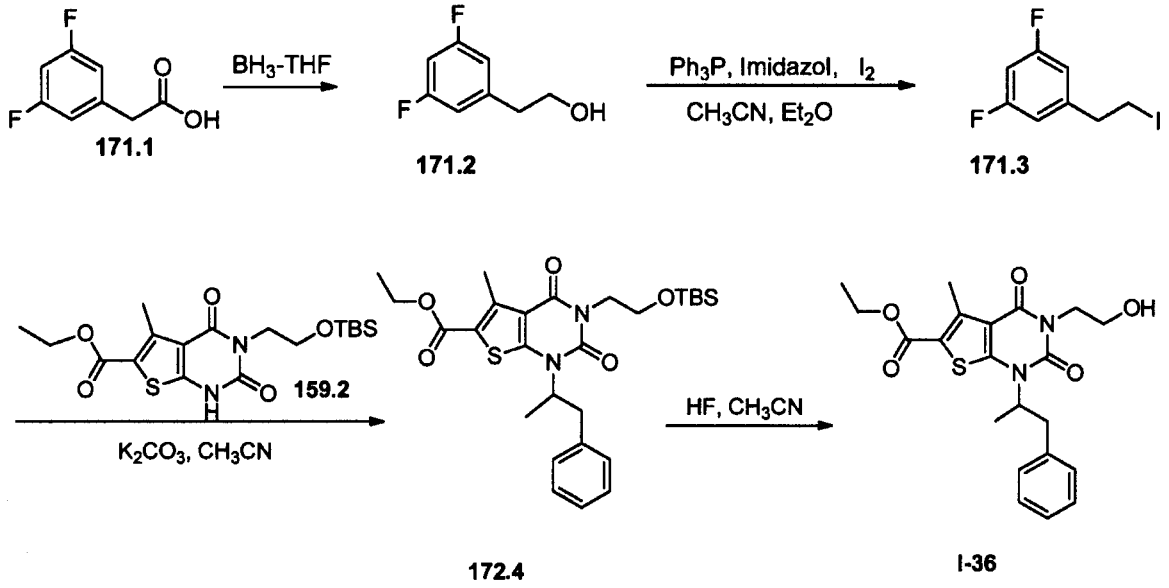
(t, J = 7.8, 2H), 4.27 (t, J = 5.1, 3H), 4.37 (c, J = 7.2, 3H), 6.91-7.26 (m, 4H).

Ejemplo 171: Síntesis de 1-[2-(3,5-difluorofenil)etil]-3-(2-hidroxietil)-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxilato de etilo (I-29).



Se prepara el compuesto I-29 a partir de 171.1 y 159.2 de una manera análoga al Compuesto I-30 (Ejemplo 161), excepto que se utiliza HCl/etanol en la última en vez de HF/acetonitrilo. Se aíslan 60 mg de un sólido blancuzco con un rendimiento total de 39%. EM (ES, *m/z*): $(M+H)^+$ 439. RMN ^1H (300 MHz, $CDCl_3$): δ 1.41 (t, J = 7.2, 3H), 2.87 (s, 3H), 3.06 (t, J = 7 .8, 2H), 3.90 (t, J = 5.4, 2H), 4.14 (t, J = 8.1, 2H), 4.28 (t, J = 8.1, 2H), 4.38 (c, J = 7.2, 2H), 6.69-6.84 (m, 3H).

Ejemplo 172: Síntesis de 3-(2-hidroxietil)-5-metil-2,4-dioxo-1-(1-fenilpropan-2-il)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxilato de etilo (I-36).

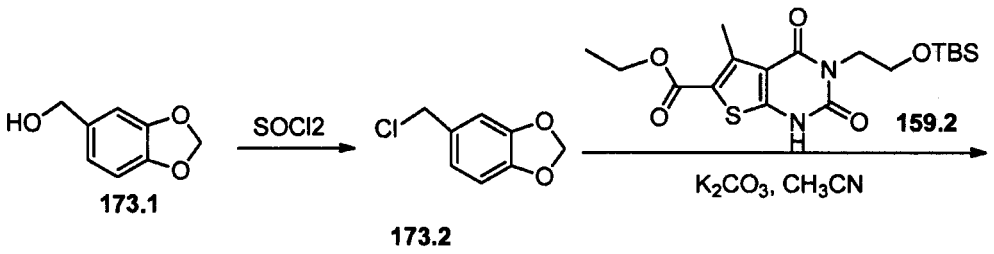


Síntesis del compuesto 172.2. En un matraz de fondo redondo de 3 cuellos de 100 ml, mantenido en una atmósfera inerte de nitrógeno se coloca 1-fenilpropan-2-ona (3 g, 22.36 mmol, 1.00 equivalentes) y 50 ml de etanol. Esto es seguido por la adición de $NaBH_4$ (1.7 g, 44.94 mmol, 2.01 equivalentes) a 5°C. La solución resultante se agita durante la noche a temperatura ambiente. La reacción después se suspende por la adición de 10 ml de cloruro de amonio (saturado). La solución resultante se extrae con 2 x 50 ml de acetato de etilo y las capas orgánicas se combinan y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:2).

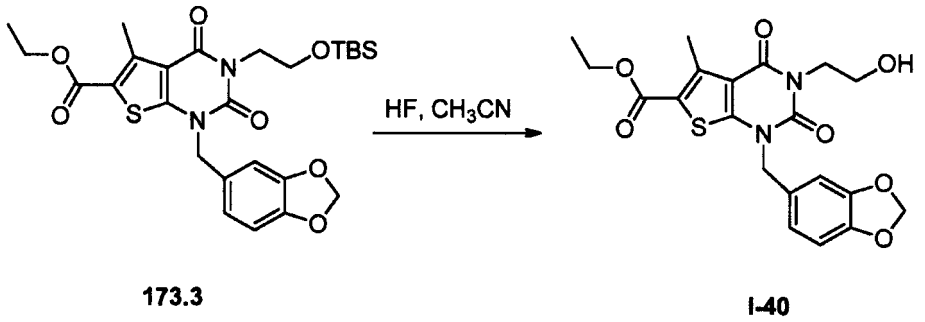
Esto resulta en 2.8 g (92%) de 1-fenilpropan-2-ol como un aceite incoloro.

Síntesis del compuesto I-36. Se prepara el compuesto I-36 a partir de 172.2 y 159.2 de una manera análoga a la síntesis de I-30 (Ejemplo 161). Se aíslan 23.4 mg de un sólido blanco con un rendimiento total de 45%. EM (ES): *m/z* 417$(M+H)^+$ 439 $(M+Na)^+$, 480 $(M+Na+CH_3CN)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.36 (t, J = 7.2, 3H), 1.70 (t, J = 6.6, 3H), 2.75 (s, 3H), 3.10-3.17 (m, 1H), 3.56-3.63 (m, 4H), 4.13 (s, 2H), 4.32 (c, J = 6.6, 2H), 7.12-7.21 (m, 5H).

Ejemplo 173: Síntesis de 1-(2H-1,3-benzodioxol-4-ilmetil)-3-(2-hidroxietil)-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxilato de etilo (I-40).



173.1 173.2

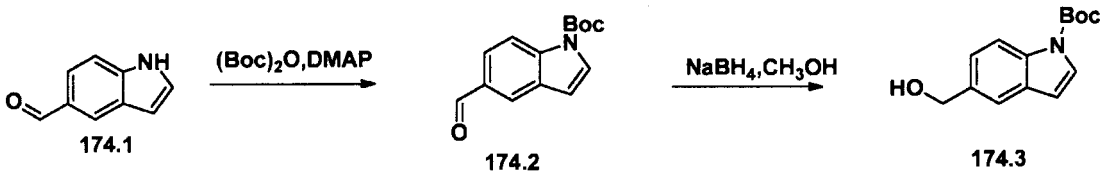


173.3 I-40

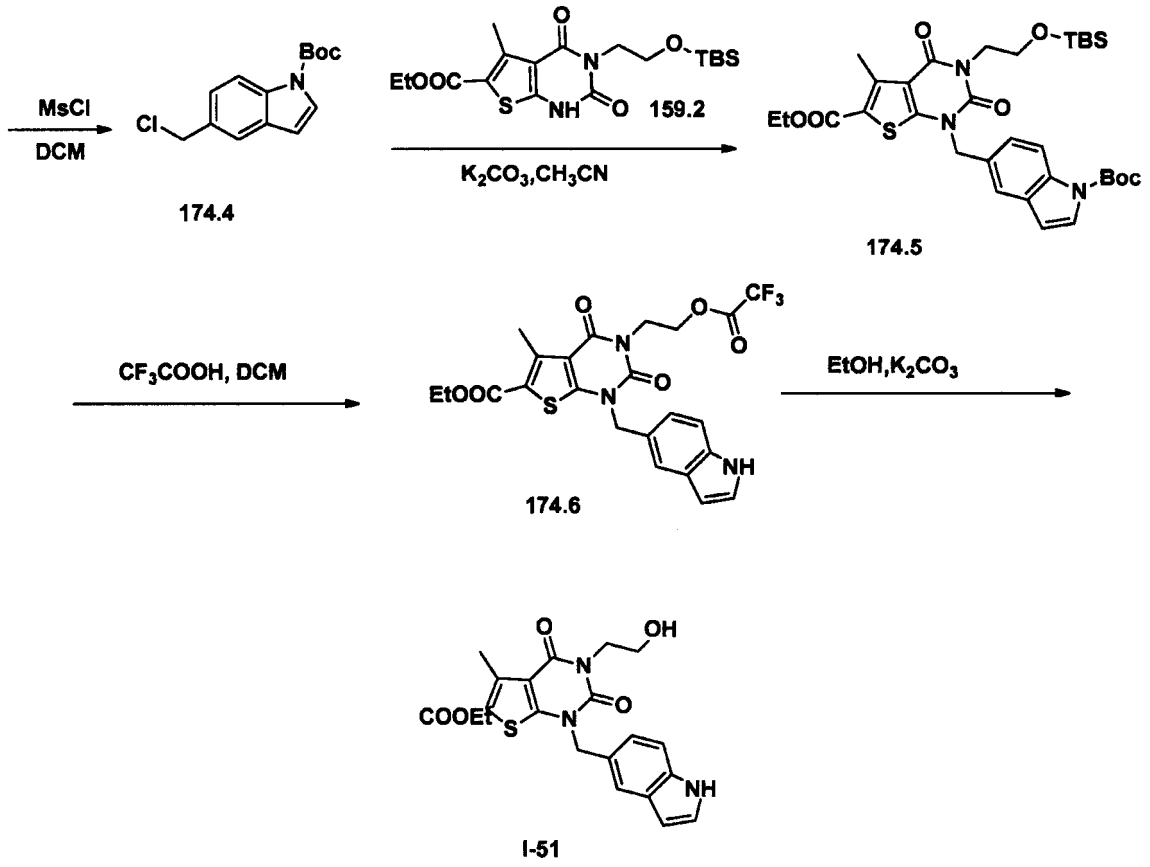
Síntesis del compuesto 173.2. En un matraz de fondo redondo de 50 ml, purgado y mantenido con una atmósfera inerte de nitrógeno se coloca 173.1 (400 mg, 2.63 mmol, 1.00 equivalentes), cloruro de tionilo (626 mg, 5.26 mmol, 2.00 equivalentes) y 20 ml de diclorometano. La solución resultante se agita durante 1 h a temperatura ambiente. La mezcla resultante se concentra bajo vacío. Esto resulta en 460 mg (97%) de 173.2 como un aceite amarillo.

Síntesis del compuesto I-40. Se sintetiza I-40 a partir de 173.2 y 159.2 de una manera consistente con la síntesis del compuesto I-30 (Ejemplo 161). Se aíslan 27.5 mg de un sólido blanco con un rendimiento total de 39%. EM (ES): *m/z* $(M+H)^+$ 433, 455 $(M+Na)^+$, 496 $(M+Na+CH_3CN)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 1.26 (t, J = 7.2, 3H), 2.77 (s, 3H), 3.59 (t, J = 6.0, 2H), 4.01 (t, J = 6.6, 2H), 4.25 (c, J = 7.2, 3H), 4.79 (t, J = 6.0, 1H), 5.10 (s, 2H), 6.01 (s, 2H), 6.85-6.95 (m, 3H).

Ejemplo 174: Síntesis de 3-(2-hidroxietil)-1-(1H-indol-5-ilmetil)-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxilato de etilo (I-51).



174.1 174.2 174.3



Síntesis del compuesto 174.2. En un matraz de fondo redondo de 50 ml se colocan 20 ml de tetrahidrofurano, 4-dimetilaminopiridina (1.32 g, 10.80 mmol, 1.08 equivalentes), 1H-indol-5-carbaldehído (1.45 g, 9.99 mmol, 1.00 equivalentes) y $(Boc)_2O$ (2.18 g, 9.99 mmol, 1.00 equivalentes). La solución resulante se agita durante 12 h a temperatura ambiente. La reacción después se suspende por la adición de 10 ml de agua. La solución resultante se extrae con 3 x 50 ml de acetato de etilo y las capas orgánicas se combinan y se secan sobre sulfato de sodio anhidro y se concentran bajo vacío. Esto resulta en 2.1 g (86%) de 174.2 como un sólido amarillo.

Síntesis del compuesto 174.3. En un matraz de fondo redondo de 50 ml se coloca una solución de 174.2 (2.1 g, 8.56 mmol, 1.00 equivalentes) en 20 ml de metanol. Después se agrega a 0°C $NaBH_4$ (740 mg, 19.56 mmol, 2.28 equivalentes). La solución resultante se agita durante 4 h a 0°C en un baño de agua/hielo. La reacción después se suspende por la adición de 10 ml de agua. La solución resultante se extrae con 3 x 50 ml de acetato de etilo y las capas orgánicas se combinan y se secan sobre sulfato de sodio anhidro y se concentran bajo vacío. Esto resulta en 1.85 g (87%) de 174.3 como un sólido amarillo.

Síntesis del compuesot 174.4. En un matraz de fondo redondo de 50 ml se coloca una solución de 174.3 (320 mg, 1.29 mmol, 1.00 equivalentes) en 20 ml de diclorometano. Después se agregan a la mezcla anterior, a 0°C, Et_3N (0.223 g, 2.21 mmol, 1.70 equivalentes) y cloruro de metansulfonilo (222 mg, 1.94 mmol, 1.50 equivalentes). La solución resultante se agita durante 5 h a °C en un baño de agua/hielo. La reacción después se suspende por la adición de 15 ml de agua. La solución resultante se extrae con 3 x 40 ml de acetato de etilo y las capas orgánicas y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:4). La purificación proporciona 0.112 g (33%) de 174.4 como un aceite amarillo.

Síntesis del compuesto 174.5. En un matraz de fondo

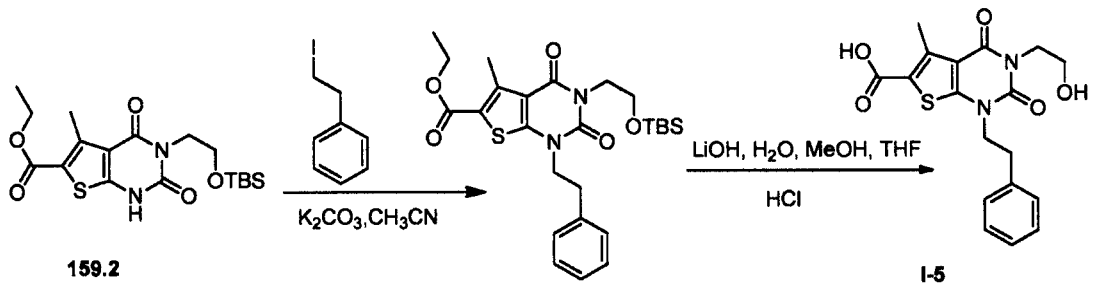
redondo de 25 ml se colocan 5 ml de CH_3CN, 0.005 g de NaI, carbonato de potasio (105 mg, 0.76 mmol, 2.02 equivalentes), 159.2 (155 mg, 0.38 mmol, 1.00 equivalentes) y 174.4 (100 mg, 0.38 mmol, 1.00 equivalentes). La solución resultante se agita durante la noche a 50°C en un baño de aceite. La reacción después se suspende por la adición de 40 ml de agua. La solución resultante se extrae con 3 x 60 ml de acetato de etilo y las capas orgánicas se combinan y se secan sobre sulfato de sodio anhidro y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:5). La purificación proporciona 0.143 g (59%) de 174.5 como un sólido blanco.

Síntesis del compuesto 174.6. En un matraz de fondo redondo de 25 ml se colocan 10 ml de diclorometano, 174.5 (143 mg, 0.22 mmol, 1.00 equivalentes) y 2 ml de CF_3COOH. La solución resultante se agita durante la noche a temperatura ambiente y después se concentra bajo vacío. Esto resulta en 0.126 g (crudo) de 174.6 crudo como un sólido amarillo.

Síntesis del compuesto I-51. En un matraz de fondo redondo de 25 ml se colocan 5 ml de etanol, carbonato de potasio (276 mg, 2.00 mmol, 8.30 equivalentes) e I-51 (126 mg, 0.24 mmol, 1.00 equivalentes). La solución resultante se agita durante la noche a temperatura ambiente, se concentra bajo vacío y se diluye con 50 ml de H_2O. La solución resultante se extrae con 3 x 50 ml de acetato de etilo y las capas orgánicas

se combinan, se secan sobre sulfato de sodio anhidro y se concentran bajo vacío. El producto crudo se purifica por recristalización a partir de acetato de etilo:hexano (1/10). Esto resulta en 0.043 g (42%) de I-51 como un sólido blanco. EM (ES): *m/z* 428 $(M+H)^+$ RMN ^1H ($CDCl_3$, 300 MHz): δ 1.27 (t, 3H), 2.85 (s, 3H), 3.96 (m, 2H), 4.34 (m, 4H), 5.29 (s, 2H), 6.56 (s, 1H), 7.25 (m, 2H), 7.38 (m, 1H), 7.70 (s, 1H), 8.23 (s, 1H).

Ejemplo 175: Síntesis del ácido 3-[2-[(terbutildimetilsilil)oxi]etil]-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxílico (I-5).



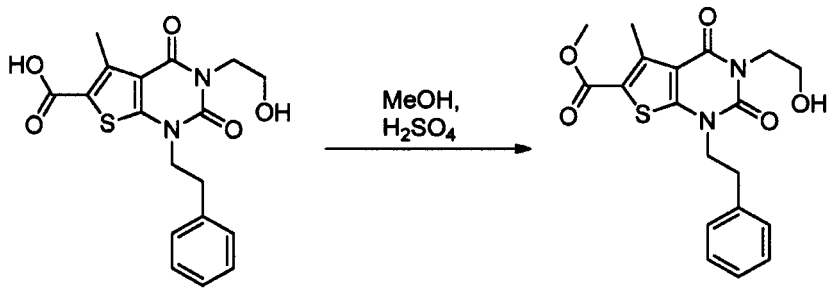
159.2 175.1 I-5

Síntesis del compuesto 175.1. En un matraz de fondo redondo de 100 ml se coloca una solución de 159.2 (1.2 g, 2.91 mmol, 1.00 equivalentes) en 50 ml de CH_3CN, 2-yodoetilbenceno (1.35 g, 5.82 mmol, 2.00 equivalentes) y 1.2 g de carbonato de potasio. La solución resultante se calienta a reflujo durante la noche. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de

sílice con acetato de etilo/éter de petróleo (1:20). La purificación proporciona 1.5 g (95%) de 175.1 como un sólido blanco.

Síntesis del compueso I-5. En un matraz de fondo redondo de 100 ml se colocan 175.1 (500 mg, 0.9676 mmol, 1.00 equivalentes), 5 ml de tetrahidrofurano, 5 ml de metanol, 5 ml de agua y 0.07 g de LiOH. La solución resultante se agita durante la noche a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El valor de pH de la solución se ajusta a 1 con cloruro de hidrógeno. La mezcla se agita durante 1 h a temperatura ambiente. Los sólidos se recolectan por filtración. La torta de filtro se lava con etanol. Se obtienen 300 mg (63%) de I-5 como un sólido blanco. EM (ES): *m/z* 375 $(M+H)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 2.74 (s, 3H), 3.00 (t, J = 7 .2, 2H), 3.51 (t, J = 6.3, 2H), 3.96 (t, J = 6.6, 2H), 4.09 (t, J = 7.2, 2H), 4.78 (s, 1H), 7.20-7.33 (m, 5H).

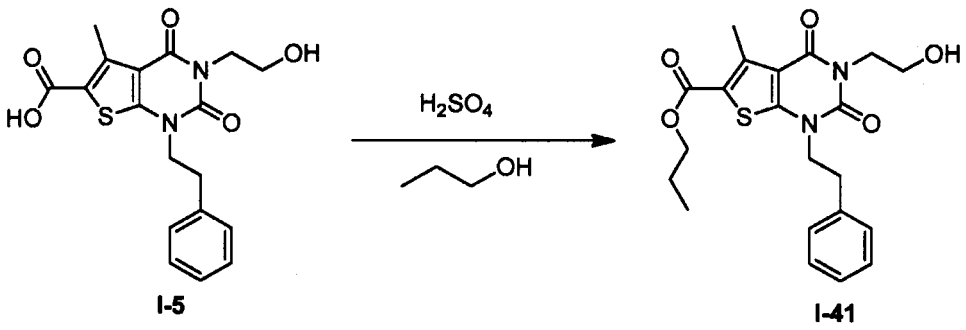
Ejemplo 176: Síntesis de 3-(2-hidroxietil)-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxilato de metilo (I-37).



I-5 I-32

En un matraz de fondo redondo de 100 ml se coloca I-5 (200 mg, 0.53 mmol, 1.00 equivalentes), 20 ml de metanol y 0.1 ml del ácido sulfúrico. La solución resultante se agita durante 4 días a 50°C. La reacción después se suspende por la adición de 5 ml de agua. El valor de pH de la solución se ajusta a >7 con carbonato de sodio (acuoso). La solución resultante se extrae con 3 x 20 ml de acetato de etilo y las capas orgánicas se combinan y se concentran bajo vacío. Se purifican 200 mg del producto crudo por *HPLC* preparativa bajo las siguientes condiciones: (SHIMADZU): columna: SunFire Prep C18, 19*150mm 5 µm; fase móvil: agua con 0.05% de NH_4HCO_3 y CH_3CN (8.0% de CH_3CN hasta 55.0% en 20 min); detector; 254/220 nm. 20.2 mg (10%) de I-32 se obtienen como un sólido blanco. EM (ES): *m/z* 389 $(M+H)^+$. RMN ^1H (400 MHz, CD_3OD): δ 2.83 (s, 3H), 3.10 (t, J = 7.5, 2H), 3.74 (t, J = 6.3, 2H), 3.87 (s, 3H), 4.14-4.20 (m, 4H), 7.22-7.30 (m, 5H).

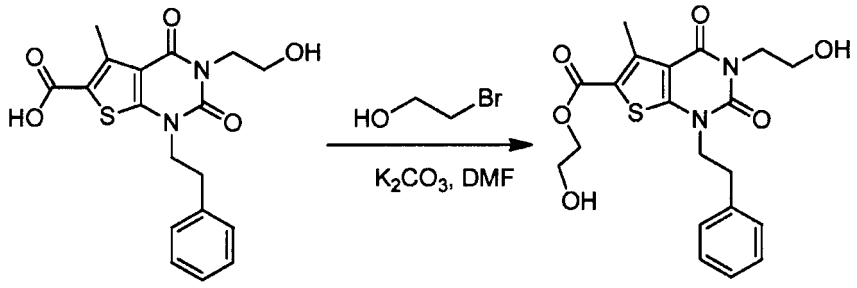
Ejemplo 177: Síntesis de 3-(2-hidroxietil)-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxilato de propilo (I-41).



I-5 I-41

Se prepara el compuesto I-41 a partir de I-5 y 1-propanol de una manera análoga a la síntesis del compuesto I-32 (Ejemplo 176). Esto resulta en 4.7 mg (2%) de I-41 como un sólido blanco. EM (ES): *m/z* 417 $(M+H)^+$. RMN ^1H (400 MHz, CD_3OD): δ 1.05 (t, J = 7.6, 3H), 1.78 (m, J = 7.2, 2H), 2.83 (s, 3H), 3.11 (t, J = 7.6, 2H), 3.75 (t, J = 6.8, 2H), 4.15-4.21 (m, 4H), 4.25 (t, J = 6.4, 2H), 7.23-7.32 (m, 5H).

Ejemplo 178: Síntesis de 3-(2-hidroxietil)-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxilato de 2-hidroxietilo (I-42).

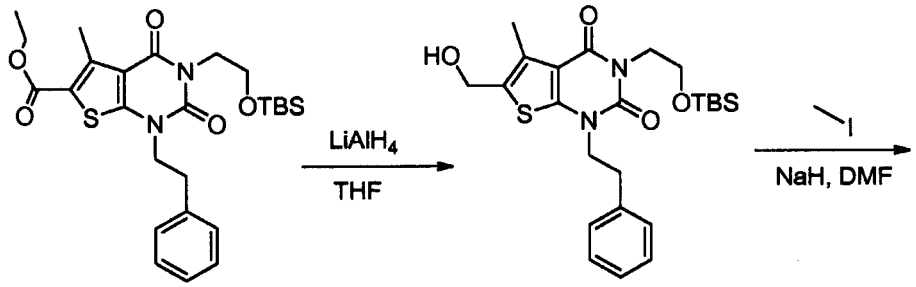


I-5 I-42

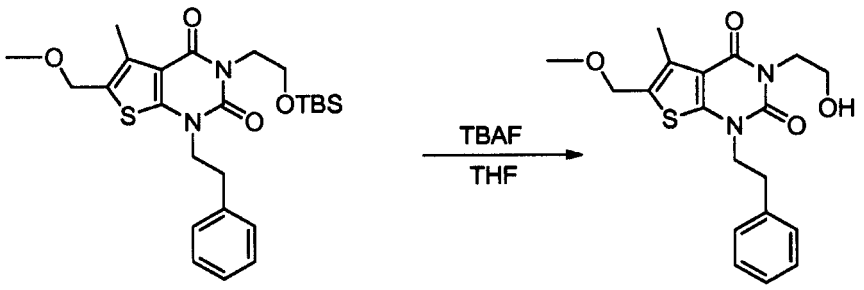
En un matraz de fondo redondo de tres cuellos de 100 ml se coloca I-5 (200 mg, 0.53 mmol, 1.00 equivalentes), carbonato de potasio (221 mg, 1.60 mmol, 2.99 equivalentes), 2-bromoetan-1-ol (100 mg, 0.80 mmol, 1.50 equivalentes) y 10 ml de N,N-dimetilformamida. La solución resultante se agita durante la noche a 80°C. La mezcla de reacción se enfría. La mezcla resultante se concentra bajo vacío. Se purifican 200 mg del producto crudo por *HPLC* preparativa bajo las siguientes condiciones (SHIMADZU): columna: SunFire Prep C18, 19*150 mm

5 µm; fase móvil; agua con NH_4HCO_3 0.05% y CH_3CN (CH_3CN 6.0% hasta 60.0% en 14 min); detector 245/220 nm. Esto resulta en 30.7 mg (14%) de I-42 como un sólido blanco. EM (ES): *m/z* 419 $(M+H)^+$, 441, $(M+Na)^+$, 482 $(M+Na+CH_3CN)^+$. RMN ^1H (400 MHz, DMSO-d_6): δ 2.77 (s, 3H), 3.01 (t, J = 7.6, 2H), 3.52 (t, J = 6.0, 2H), 3.68 (t, J = 4.8, 2H), 4.11 (t, J = 7.6, 2H), 3.02 (t, J = 7.6, 2H), 4.26 (t, J = 4.8, 2H), 3.02 (t, J = 7.6, 2H), 4.78 (t, 1H), 4.92 (t, 1H), 7.24-7.33 (m, 5H).

Ejemplo 179: Síntesis de 3-(2-hidroxietil)-6-(metoximetil)-5-metil-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-2,4-diona (I-39).



175.1 **179.1**



179.2 **I-39**

Síntesis del compuesto 179.1. En un matraz de fondo redondo de 3 cuellos de 100 ml, purgado y mantenido con una

atmósfera inerte de nitrógeno se coloca una solución de 175.1 (1 g, 1.94 mmol, 1.00 equivalentes) en 20 ml de tetrahidrofurano. Esto es seguido por la adición de $LiAlH_4$ (100 mg, 2.63 mmol, 1.36 equivalentes) a −78°C. La solución resultante se agita durante 2 h a temperatura ambiente. La reacción después se suspende por la adición de 50 ml de NH_4Cl (acuoso). La solución resultante se extrae con 3 x 50 ml de acetato de etilo y las capas orgánicas se combinan y concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:2). Esto resulta en 0.5 g (54%) de 179.1 como un sólido amarillo claro.

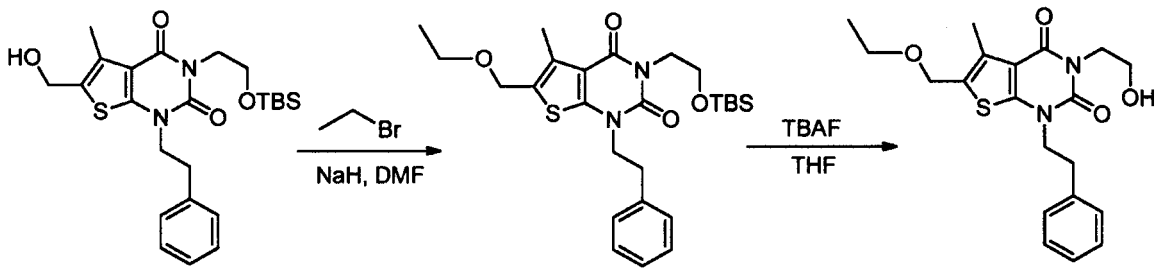
Síntesis del compuesto 179.2. En un tubo sellado de 10 ml se coloca una solución de 179.1 (150 mg, 0.31 mmol, 1.00 equivalentes), 5 ml de N,N-dimetilformamida e hidruro de sodio (19 mg, 0.55 mmol, 1.76 equivalentes, 70%). La solución resultante se agita durante 10 min a temperatura ambiente. Esto es seguido por la adición de yodometano (67 mg, 0.47 mmol, 1.50 equivalentes) a gotas, con agitación. La solución resultante se permite que reaccione con agitación durante 2 h adicionales a temperatura ambiente. La reacción después se suspende por la adición de 5 ml de NH_4Cl (acuoso). La solución resultante se extrae con 3 x 10 ml de acetato de etilo y las capas orgánicas se combinan y concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con

acetato de etilo/éter de petróleo (1:10). La purificación proporciona 90 mg (59%) de 179.2 como un sólido blanco.

Síntesis del compuesto I-39. En un tubo sellado de 10 ml se coloca una solución de 179.2 (90 mg, 0.18 mmol, 1.00 equivalentes) en 2.5 ml de tetrahidrofurano y 200 mg de TBAF. La solución resultante se agita durante la noche a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:2). La purificación proporciona 34.7 mg (50%) de I-39 como un sólido blanco. EM (ES): *m/z* 375 $(M+H)^+$ 397 $(M+Na)^+$.

RMN ^1H (300 MHz, DMSO-d_6): δ 2.37 (s, 3H), 2.98 (t, J = 7.5, 2H), 3.26 (s, 3H), 3.50 (c, J = 6.6, 2H), 3.96 (t, J = 6.6, 2H), 4.06 (t, J = 7.5, 2H), 4.51 (s, 2H), 4.76 (t, J = 6.0, 1H), 7.20-7.33 (m, 5H).

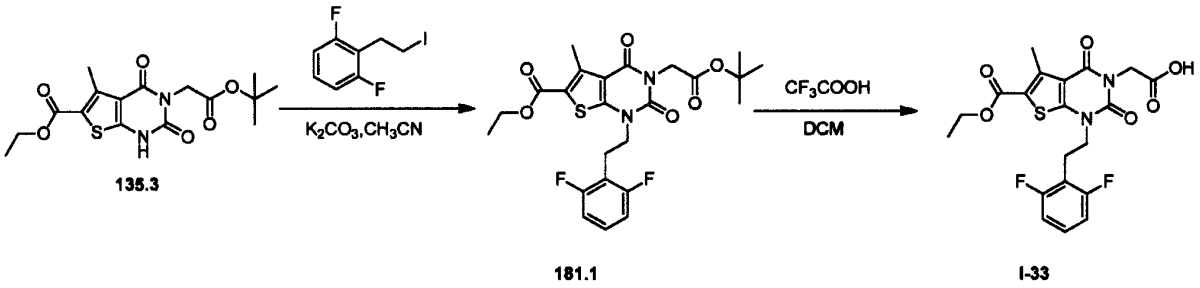
Ejemplo 180: Síntesis de 6-(etoximetil)-3-(2-hidroxietil)-5-metil-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-2,4-diona (I-38).



179.1 180.1 I-38

Se prepara el compuesto I-38 a partir de 179.1 y bromuro de etilo de una manera análoga a la síntesis del compuesto I-39 (Ejemplo 179). Se aíslan 50.5 mg de un sólido blanco con un rendimiento total de 42%. EM (ES): *m/z* 389 $(M+H)^+$ 411 $(M+Na)^+$, 452 $(M+Na+CH_3CN)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 1.13 (t, J = 7.2, 3H), 2.35 (s, 3H), 2.98 (t, J = 7.5, 2H), 3.42-3.51 (m, 4H), 4.14-4.20 (m, 4H), 4.54 (s, 2H), 4.74 (s, 1H), 7.20-7.32 (m, 5H).

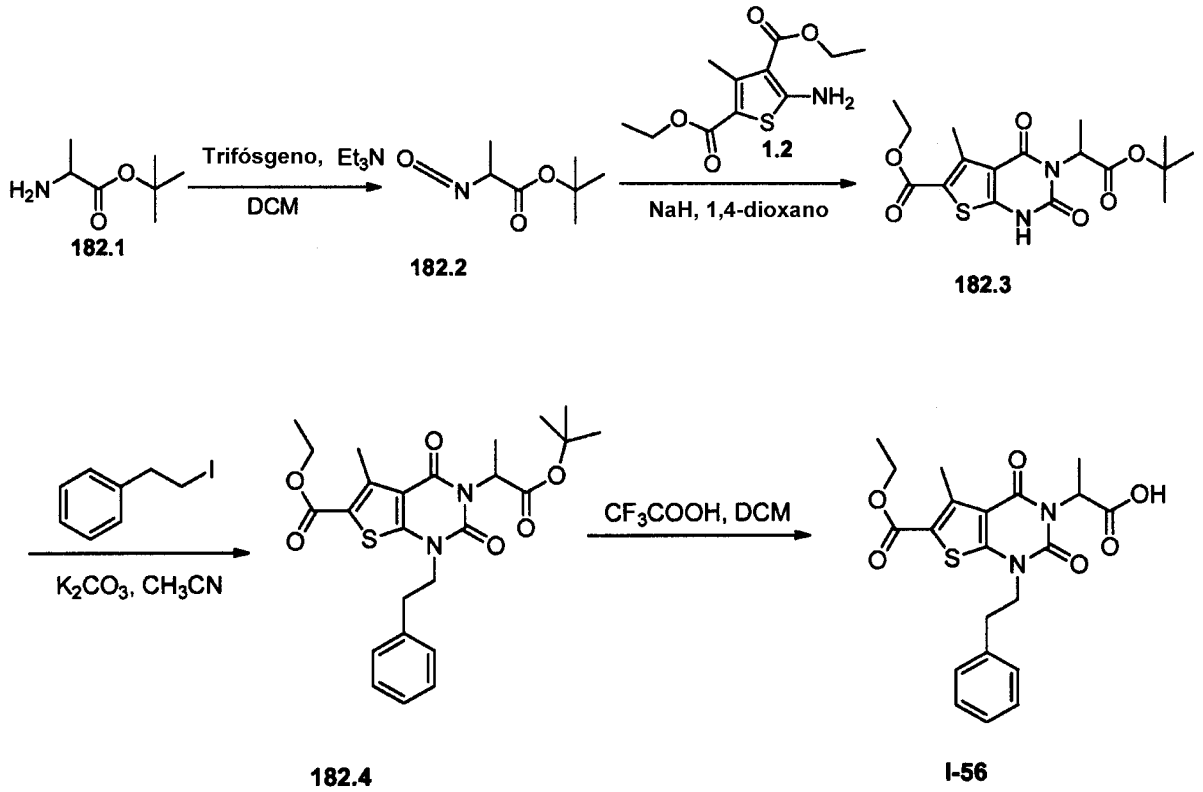
Ejemplo 181: Síntesis del ácido 2-[1-[2-(2,6-difluorofenil)etil]-6-(etoxicarbonil)-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acético (I-33).



Se prepara el compuesto I-33 a partir de 135.3 y 1,3-difluoro-2-(2-yodoetil)benceno de una manera análoga a la síntesis de 136.2. Se aíslan 36 mg de un sólido blanco con un rendimiento general de 30%. EM (ES): *m/z* 453 $(M+H)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.32-1.40 (t, 3H), 2.82 (s, 3H), 3.21-3.26 (t,2H), 4.22-4.27 (t, 2H), 4.31-4.38 (c, 2H), 4.67 (s, 2H), 6.91-6.96 (t, 2H), 7.26-7.31 (m, 1H). RMN ^{19}F (400 MHz, CD_3OD): δ 117.76.

Ejemplo 182: Síntesis del ácido 2-[6-

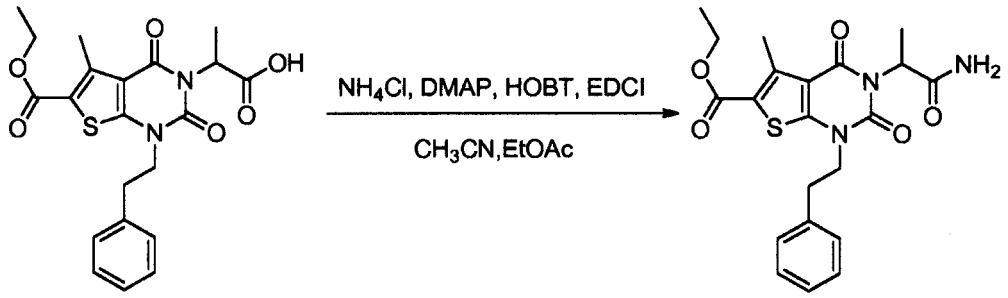
(etoxicarbonil)-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-56).



Se prepara el compuesto I-56 a partir de 182.1 y 1.2 de una manera análoga al compuesto 136.2 (Ejemplos 135 y 136). Se aíslan 1.4 g de un sólido blanco con un rendimiento total de 42%. EM (ES): *m/z* 431 $(M+H)^+$. RMN ^1H (400 MHz, DMSO-d_6): δ 1.30 (t, J = 7.2, 3H), 1.41 (d, J = 6.8, 3H), 2.75 (s, 3H), 3.01 (t, J = 7.2, 2H), 4.13 (t, J = 7.2, 2H), 4.29 (c, J = 7.2, 2H), 5.39 (c, J = 6.8, 1H), 7.20-7.30 (m, 5H), 12.70 (s, 1H).

Ejemplo 183: Síntesis de 3-(1-carbamoiletil)-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-

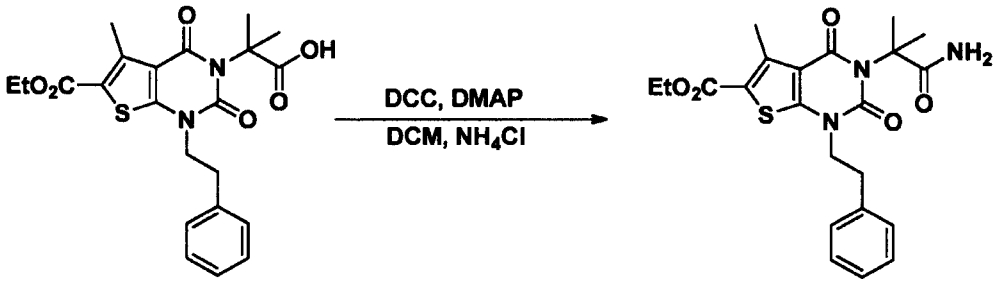
d]pirimidin-6-carboxilato de etilo (I-69).



182.4 I-69

En un matraz de fondo redondo de 100 ml se colocan 4-dimetilaminopiridina (82 mg, 0.67 mmol, 1.44 equivalentes), 182.4 (200 mg, 0.46 mmol, 1.00 equivalentes), NH_4Cl (1 g, 18.70 mmol, 40.24 equivalentes), EDCI (130 mg, 0.68 mmol, 1.46 equivalentes), 10 ml de CH_3CN, 10 ml de acetato de etilo y HOBT (100 mg, 0.74 mmol, 1.59 equivalentes). La solución resultante se agita durante 5 h a temperatura ambiente. La reacción después se detiene por la adición de 20 ml de agua. La solución resultante se extrae con 3 x 50 ml de acetato de etilo y las capas orgánicas se combinan y se secan sobre sulfato de magnesio anhidro y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con diclorometano/metanol (20:1). Esto resulta en 0.12 g (60%) de I-69 como un sólido blanco. EM (ES): *m/z* 430 $(M+H)^+$. RMN ^1H (400 MHz, DMSO-d_6): δ 1.25 (t, J = 7.2 Hz, 3H), 1.36 (d, J = 6.8 Hz, 3H), 2.68 (s, 3H), 2.97 (t, J = 7.2 Hz, 2H), 4.07 (t, J = 7.2 Hz, 2H), 4.23 (c, J = 7.2 Hz, 2H), 5.30 (c, J = 7.2 Hz, 1H), 7.15-7.24 (m, 5H).

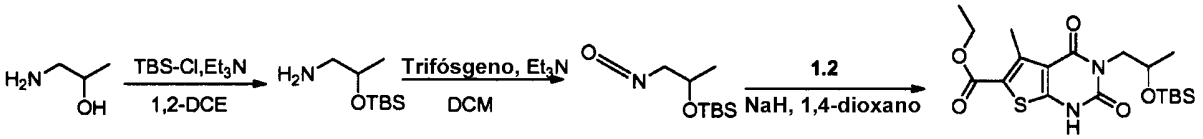
Ejemplo 184: Síntesis de 3-(1-carbamoil-1-metiletil)-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxilato de etilo (I-107).



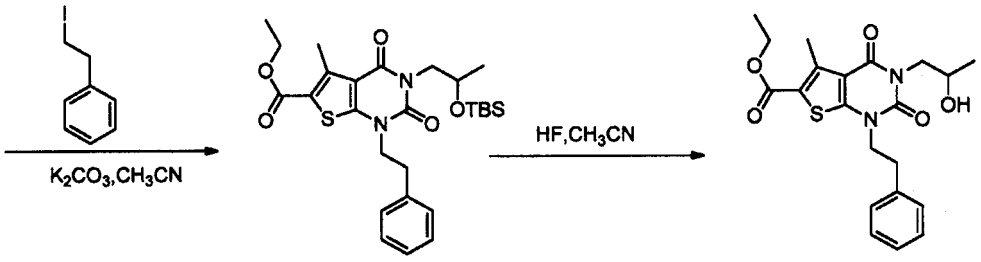
I-70 I-107

Se prepara el compuesto I-107 a partir de I-70 (Ejemplo 120) y cloruro de amonio de una manera análoga a la síntesis del compuesto I-121 (Ejemplo 4). Se aíslan 70 mg de un sólido blanco con 70% de rendimiento. EM (ES): *m/z* 466 $(M+Na)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.37 (t, J = 7.2, 3H), 1.80 (s, 6H), 2.76 (s, 3H), 3.07 (t, J = 7.2, 2H), 4.12 (t, J = 7.2, 2H), 4.33 (c, J = 7.2, 2H), 7.22-7.34 (m, 5H).

Ejemplo 185: Síntesis de 3-(2-hidroxipropil)-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxilato de etilo (I-62).



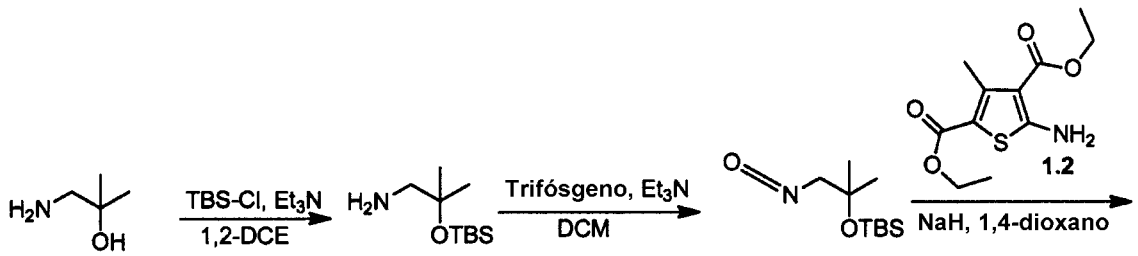
185.1 185.2 185.3 185.4



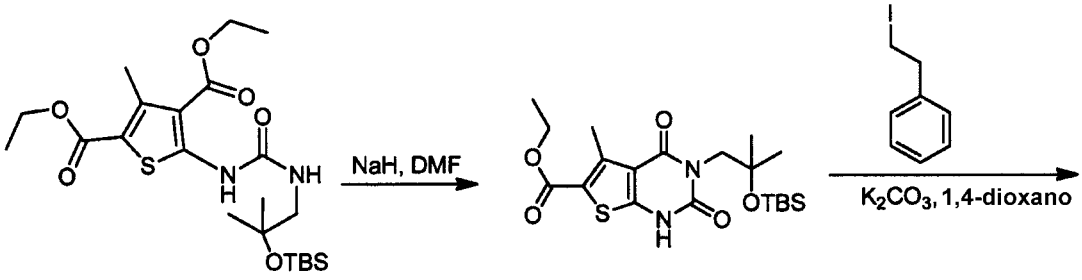
185.5 I-62

Se prepara el compuesto I-62 a partir de 185.1 y 1.2 de una manera análoga a la síntesis del compuesto I-34 (Ejemplo 169). Se aíslan 0.34 g de un sólido blanco con un rendimiento total de 8%. EM (ES): *m/z* 417 $(M+H)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 1.02 (d, J = 7.6 Hz, 3H), 1.29 (t, J = 9.6 Hz, 3H), 2.75 (s, 3H), 2.99 (t, J = 9.6 Hz, 2H), 3.69 (c, J = 10.8 Hz, 1H), 3.94 (m, J = 7.2 Hz, 2H), 4.27 (c, J = 9.2 Hz, 2H), 4.15 (t, J = 10.0 Hz, 2H), 4.77 (s, 1H), 7.19-7.32 (m, 5H).

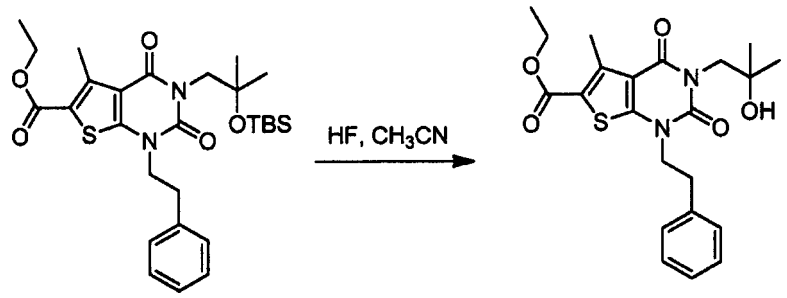
Ejemplo 186: Síntesis de 3-(2-hidroxi-2-metilpropil)-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxilato de etilo (I-79).



186.1 186.2 186.3



186.4 186.5

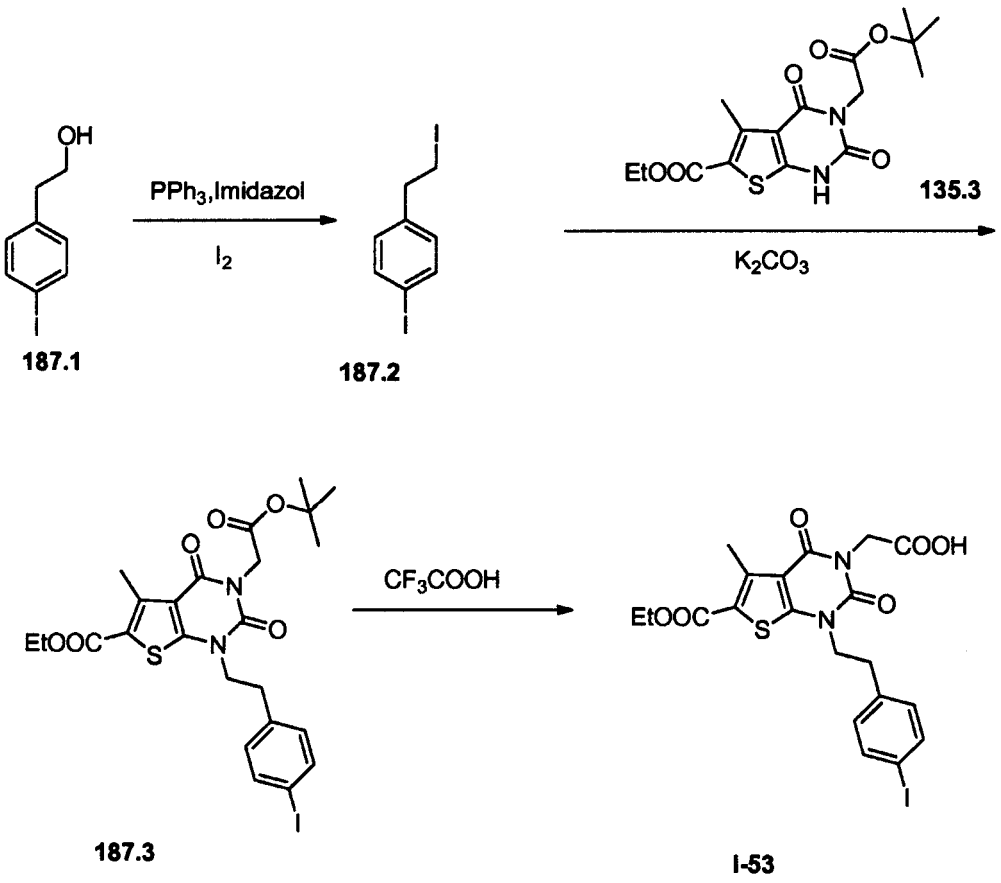


186.6 I-79

Se prepara el compuesto I-79 a partir de 186.1 y 1.2 de una manera análoga a la síntesis del compuesto I-34 (Ejemplo 169). Se aíslan 80 mg de un sólido blanco con un rendimiento total de 10%. EM (ES): *m/z* 431 $(M+H)^+$. RMN ^1H (400 MHz, DMSO-d_6): δ 1.07 (s, 6H), 1.30 (t, J = 7.2 Hz, 3H), 2.76 (s, 3H), 3.01 (t, J = 7.2 Hz, 2H), 3.96 (s, 2H), 4.13 (t, J = 7.2 Hz, 2H), 4.29 (c, 2H), 4.41 (s, 1H), 7.20-7.32 (m, 5H).

Ejemplo 187: Síntesis del ácido 2-[6-(etoxicarbonil)-1-[2-(4-yodofenil)etil]-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acético

(I-53).

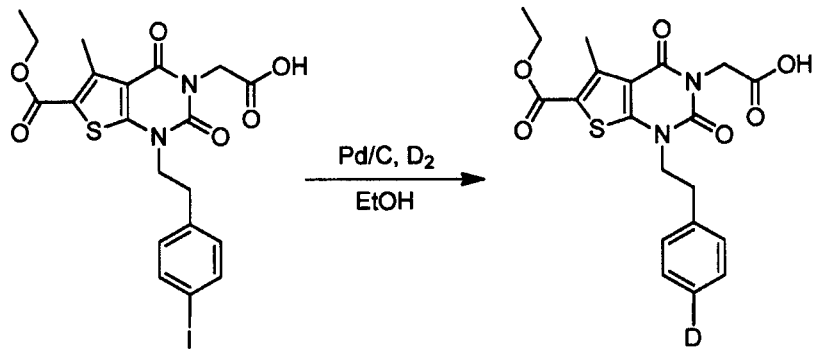


Síntesis del compuesto 187.2. Se preparan 187.2 a partir de 187.1 de una manera análoga a la síntesis de 160.2. Se aíslan 2.23 g de un sólido blanco con un rendimiento de 78%.

Ejemplo 188: Síntesis del compuesto I-53. Se prepara I-53 a partir de 187.2 y 135.3 de una manera análoga a la síntesis de 136.2. Se aíslan 0.134 g de un sólido blancuzco con un rendimiento total de 57% para 135.3. EM (ES): *m/z* 543 $(M+H)^+$. RMN ^1H ($CDCl_3$, 400 MHz): δ 1.43 (t, 3H), 2.88 (s, 3H), 3.04 (m, 2H), 4.14 (m, 2H), 4.38 (m, 2H), 4.85 (s, 2H), 7.03

(d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H).

Ejemplo 188: Síntesis del ácido 2-(1-(4-deuterofenetil)-6-(etoxicarbonil)-5-metil-2,4-dioxo-1,2-dihidrotieno[2,3-d]pirimidin-3(4H)-il)acético (I-66).

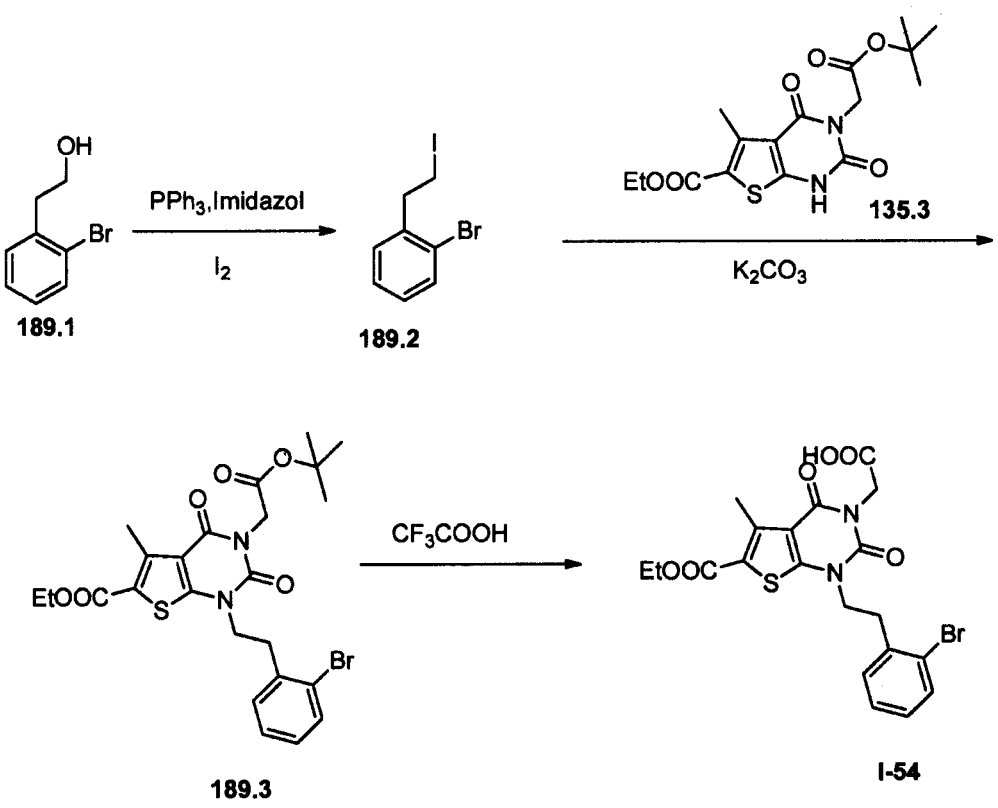


I-53 I-66

En un matraz de fondo redondo de 50 ml se colocan 20 ml de etanol, I-53 (Ejemplo 187; 73 mg, 0.13 mmol, 1.00 equivalentes). Esto es seguido por la adición de 100 mg de paladio 10% sobre carbono, bajo nitrógeno. El matraz se evacua y se purga tres veces con nitrógeno, seguido por purgado con deuterio gaseoso. La mezcla se agita durante la noche a temperatura ambiente bajo una atmósfera de gas de deuterio. Los sólidos se separan por filtración. La mezcla resultante se concentra bajo vacío. Se purifican 80 mg del producto crudo por CLAP preparativa bajo las siguientes condiciones (SHIMADZU): columna: SunFire Prep C18, 19*150 mm 5 µm; fase móvil: agua con NH_4HCO_3 0.05% y CH_3CN (CH_3CN 5.0% hasta 53.0% en 16 min); detector: 254/220 nm. Esto resulta en 0.04 g (71%) de I-66 como un sólido blanco. EM (ES): *m/z*

$(M+H)^+$ 418. RMN ^1H (300 MHz, $CDCl_3$): δ 1.41 (t, J = 7.2, 3H), 2.87 (s, 3H), 3.09 (t, J = 8.1, 2H), 4.16 (t, 2H), 4.38 (c, J = 7.2, 2H), 4.82 (s, 2H), 7.26-7.35 (m, 4H).

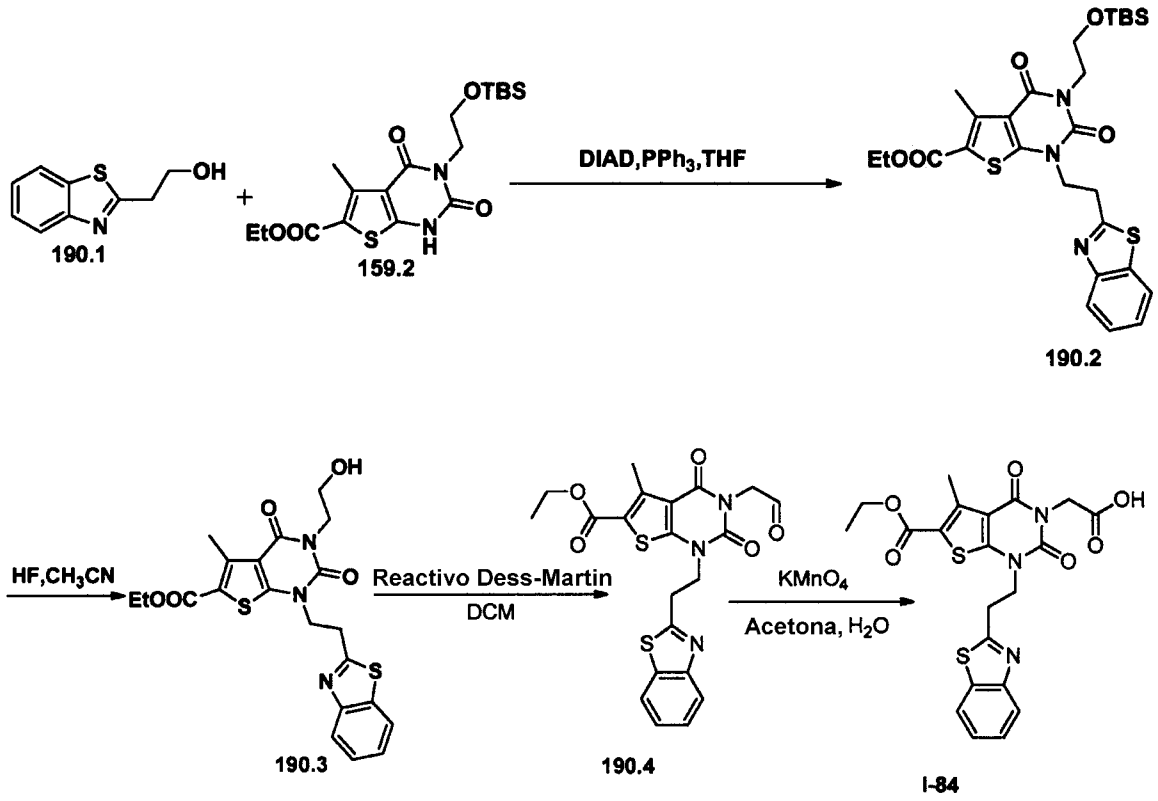
Ejemplo 189: Síntesis del ácido 2-[1-[2-(2-bromofenil)etil]-6-(etoxicarbonil)-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acético (I-54).



Se prepara el compuesto I-54 a partir de 189.1 y 135.3 de una manera análoga a la síntesis de I-53 (Ejemplo 187). Se aíslan 0.2 g de un sólido blanco con un rendimiento total de 38% a partir de 135.3. EM (ES): *m/z* 495 $(M+H)^+$. RMN ^1H ($CDCl_3$, 300 MHz): δ 1.38 (t, 3H), 2.85 (s, 3H),

3.24 (t, 2H), 4.24 (t, 2H), 4.37 (t, 2H), 4.81 (s, 2H), 7.11 (m, 1H), 7.20 (m, 2H), 7.54 (m,1 H).

Ejemplo 190: Síntesis del ácido 2-[1-[2-(1,3-benzotiazol-2-il)etil]-6-(etoxicarbonil)-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acético (I-84).



Síntesis del compuesto 190.2. En un matraz de fondo redondo de 25 ml purgado con N_2 se colocan 5 ml de tetrahidrofurano, 2-(1,3-benzotiazol-2-il)etan-1-ol (358 mg, 2.00 mmol, 2.00 equivalentes), PPh_3 (524 mg, 2.00 mmol, 2.00 equivalentes), DIAD (292 mg, 1.44 mmol, 1.45 equivalentes) y 159.2 (412 mg, 1.00 mmol, 1.00 equivalentes). La solución resultante se agita durante la noche a temperatura ambiente.

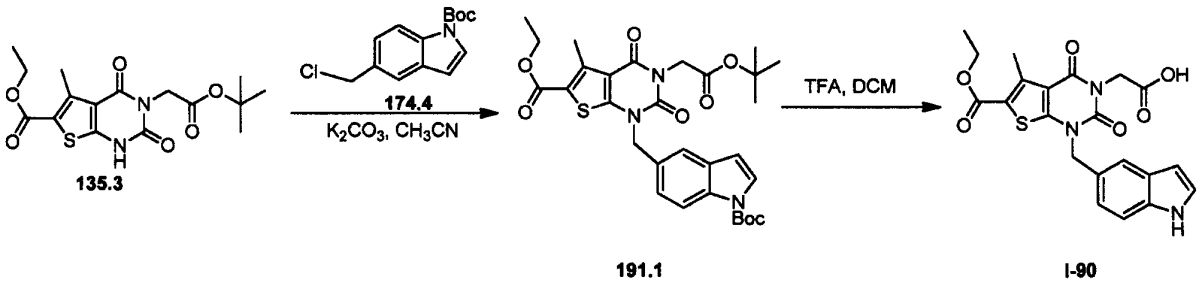
La reacción después se suspende por la adición de 50 ml de agua. La solución resultante se extrae con 3 x 50 ml de acetato de etilo y las capas orgánicas se combinan, se secan sobre sulfato de sodio anhidro y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:10). Esto resulta en 0.350 g (61%) de 190.2 como un sólido blanco.

Síntesis del compuesto 190.3. En un matraz de fondo redondo de 50 ml se colocan 15 ml de CH_3CN, 190.2 (352 mg, 0.61 mmol, 1.00 equivalentes) y 5 ml de HF. La solución resultante se agita durante 2 h a temperatura ambiente. La reacción después se suspende por la adición de 20 ml de bicarbonato de sodio (saturado). La solución resultante se extrae con 3 x 50 ml de acetato de etilo y las capas orgánicas se combinan y se secan sobre sulfato de sodio anhidro y se concentran bajo vacío. El producto crudo (50 mg) se purifica por CLAP preparativa bajo las siguientes condiciones (SHIMADZU): columna: SunFire Prep C18, 19*150 nm 5 µm; fase móvil; agua con TFA 0.05% y CH_3CN (CH_3CN 12.0% hasta 58.0% en 10 min); detector; 254/220 nm. Se obtienen 142 mg de producto. Esto resulta en 14.7 mg (5%) de 190.3 como un sólido blanco. EM (ES): *m/z* 460 $(M+H)^+$. RMN ^1H ($CDCl_3$, 400 MHz): δ 1.39 (m, 3H), 2.89 (s, 3H), 3.62 (m, 2H), 3.90 (m, 2H), 4.28 (m, 2H), 4.36 (m, 2H), 4.53 (m, 2H), 7.42 (m, 1H), 7.49 (m, 1H), 7.88 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H).

Síntesis del compuesto 190.4. En un matraz de fondo redondo de 50 ml se coloca 190.3 (74 mg, 0.16 mmol, 1.00 equivalentes), 10 ml de diclorometano y reactivo de Dess-Martin (740 mg, 1.75 mmol, 10.84 equivalentes). La solución resultante se agita durante la noche a 40°C en un baño de aceite. Los sólidos se separan por filtración. El filtrado se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:2). Esto resulta en 87 mg (crudo) de 190.4 como un sólido blanco.

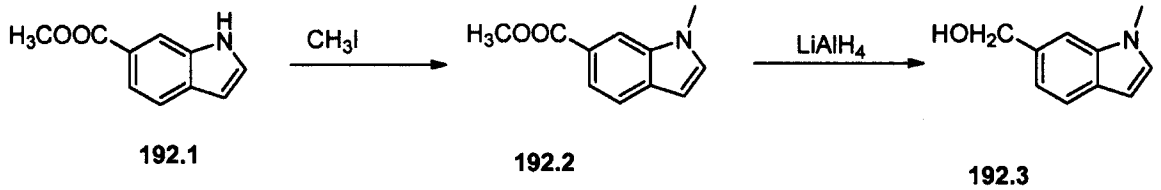
Síntesis del compuesto I-84. En un matraz de fondo redondo se coloca 190.4 (87 mg, 0.19 mmol, 1.00 equivalentes), 3 ml de acetona, 2 ml de H_2O y tetraoxo (potasio) manganeso (25.4 mg, 0.16 mmol, 0.85 equivalentes). La solución resultante se agita durante 4 h a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:2). Esto resulta en 16 mg (18%) de I-84 como un sólido blanco. EM (ES): *m/z* 474 $(M+H)^+$. RMN ^1H (400 MHz, DMSO-d_6): δ 1.27 (t, J = 7.2, 3H), 2.76 (s, 3H), 3.57 (t, J = 7.2, 2H), 4.27 (c, J = 7.2, 2H), 4.44 (t, J = 7.2, 2H), 4.53 (s, 3H), 7.43 (t, J = 7.6, 1H), 7.51 (t, J = 7.2, 1H), 7.95 (d, J = 8.0, 1H), 8.08 (d, J = 7.6, 1H).

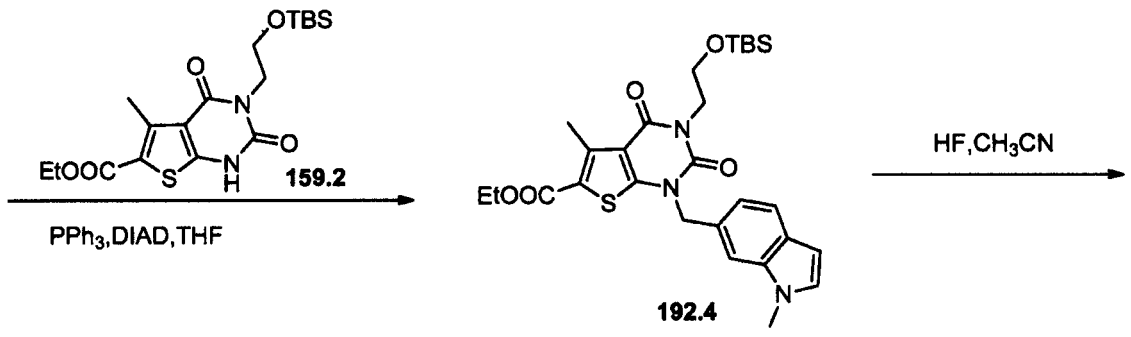
Ejemplo 191: Síntesis del ácido 2-[6-(etoxicarbonil)-1-(1H-indol-5-ilmetil)-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acético (I-90).

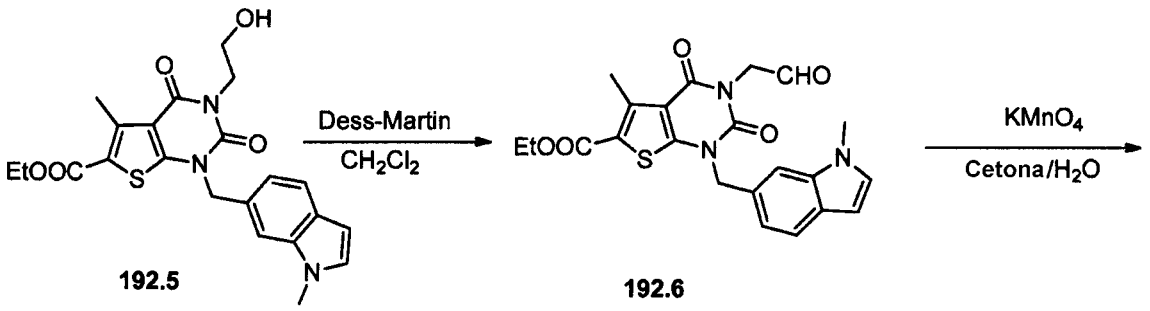


Se prepara el compuesto I-90 a partir de 135.3 y 174.4 de una manera análoga a la síntesis de 136.2. Se aíslan 11 mg de un sólido blancuzco con un rendimiento de 12% a partir de 135.3. EM (ES): *m/z* 442 $(M+H)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 1.25 (t, J = 7.2, 3H), 2.75 (s, 3H), 4.23 (c, J = 7.2, 2H), 4.46 (s, 2H), 5.28 (s, 2H), 6.40 (s, 1H), 7.08 (d, J = 6.6, 1H), 7.34-7.39 (m, 2H), 7.52 (s, 1H), 11.14 (s, 3H).

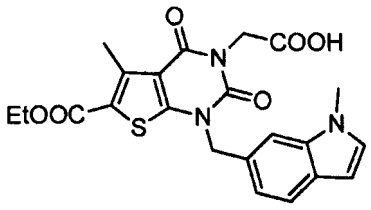
Ejemplo 192: Síntesis del ácido 2-[6-(etoxicarbonil)-5-metil-1-[(1-metil-1H-indol-6-il)metil]-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acético (I-74).







192.5 192.6



I-74

Síntesis del compuesto 192.2. En un matraz de fondo redondo de 500 ml se colocan 200 ml de N,N-dimetilformamida y 1H-indol-6-carboxilato de metilo (7 g, 39.96 mmol, 1.00 equivalentes). Se agrega hidruro de sodio (1.9 g, 47.50 mmol, 1.19 equivalentes, 60%) a 0°C y se continúa agitando durante 30 minutos a esta temperatura después de lo cual se agrega CH_3I (6.8 g, 47.91 mmol, 1.20 equivalentes). La solución resultante se agita durante 2 h a 0°C en un baño de agua/hielo. La reacción después se suspende por la adición de 120 ml de agua. La solución resultante se extrae con 3 x 150 ml de acetato de etilo y las capas orgánicas se combinan y se secan sobre sulfato de sodio anhidro y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:5). La purificación

proporciona 7.2 g (95%) de 192.2 como un sólido amarillo.

Síntesis del compuesto 192.3. En un matraz de fondo redondo de 500 ml se colocan 300 ml de tetrahidrofurano y 192.2 (5.67 g, 29.97 mmol, 1.00 equivalentes). A esta solución se le agrega, a −5°C, $LiAlH_4$ (2.28 g, 60.08 mmol, 2.00 equivalentes). La solución resultante se agita durante 2 h a −5°C en un baño de hielo/sal. La reacción después se suspende por la adición de 10 ml de acetato de etilo y 150 ml de NH_4Cl (acuoso). La solución resultante se extrae con 3 x 150 ml de acetato de etilo y las capas orgánicas se combinan y se secan sobre sulfato de sodio anhidro y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:2). La purificación proporciona 5.0 g (98%) de 192.3 como un aceite amarillo claro.

Síntesis del compuesto 192.4. En un matraz de fondo redondo de 25 ml se coloca una solución de 192.3 (322 mg, 2.00 mmol, 2.00 equivalentes) en 5 ml de tetrahidrofurano, PPh_3 (524 mg, 2.00 mmol, 2.00 equivalentes), DIAD (292 mg, 1.44 mmol, 1.45 equivalentes) y 159.2 (412 mg, 1.00 mmol, 1.00 equivalentes). La solución resultante se agita durante la noche a temperatura ambiente. La reacción después se suspende por la adición de 50 ml de agua. La solución resultante se extrae con 3 x 50 ml de acetato de etilo y las capas orgánicas se combinan y se secan sobre sulfato de sodio anhidro y se

concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:10). Esto resulta en 0.12 g (22%) de 192.4 como un sólido blanco.

Síntesis del compuesto 192.5. En un matraz de fondo redondo de 50 ml se colocan 15 ml de CH_3CN, 192.4 (120 mg, 0.22 mmol, 1.00 equivalentes) y 3 ml de HF. La solución resultante se agita durante 4 h a temperatura ambiente. La reacción después se suspende por la adición de 10 ml de $NaHCO_3$ saturado. La solución resultante se extrae con 3 x 50 ml de acetato de etilo y las capas orgánicas se combinan, se lavan con carbonato de sodio acuoso y salmuera, se secan y se concentran bajo vacío. Se purifican 80 mg del producto crudo por CLAP preparativa bajo las siguientes condiciones (SHIMADZU): columna: SunFire Prep C18, 19*150 mm 5 µm; fase móvil: agua con NH_4HCO_3 0.05% y CH_3CN (CH_3CN 7.0% hasta 63.0% en 18 min); detector: 254/220 nm. Esto resulta en 0.075 g (79%) de 192.5 como un sólido blanco. EM (ES): *m/z* 442 $(M+H)^+$. RMN ^1H ($CDCl_3$, 400 MHz): δ 1.38 (t, 3H), 2.86 (s, 3H), 3.81 (s, 3H), 3.97 (m, 2H), 4.36 (m, 4H), 5.34 (s, 2H), 6.48 (d, J = 2.8 Hz, 1H), 7.09 (d, J = 3.2 Hz, 1H), 7.16 (m, 1H), 7.39 (s, 1H), 7.61 (d, J = 8.0 Hz, 1H).

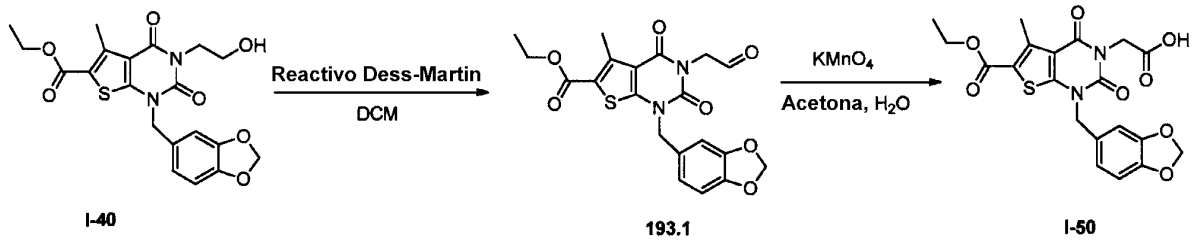
Síntesis del compuesto 192.6. En un matraz de fondo redondo de 50 ml se colocan 20 ml de diclorometano, 192.5 (61 mg, 0.14 mmol, 1.00 equivalentes) y reactivo de Dess-Martin (157 mg, 0.37 mmol, 2.68 equivalentes). La solución

resultante se calienta a reflujo durante la noche en un baño de aceite. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:2). Esto resulta en 0.035 g (58%) de 192.6 como un sólico blanco.

Síntesis del compuesto I-74. En un matraz de fondo redondo de 50 ml se colocan 4 ml de agua, 20 ml de acetona y 192.6 (35 mg, 0.08 mmol, 1.00 equivalentes). Esto es seguido por la adición de $KMnO_4$ (13 mg, 0.08 mmol, 1.00 equivalentes). La solución resultante se agita durante 1 h a temperatura ambiente. La reacción después se suspende por la adición de 2 ml de acetato de etilo. La mezcla resultante se concentra bajo vacío. Se purifican 50 mg del producto crudo por CLAP preparativa bajo las siguientes condiciones (SHIMADZU): columna: SunFire Prep C18, 19*150 mm 5 µm; fase móvil; agua con TFA 0.05% y CH_3CN (CH_3CN 8.0% hasta 57.0% en 16 min); detector: 254/220 nm. Esto resulta en 0.011 g (30%) de I-74 como un sólido blanco. EM (ES): *m/z* 456 $(M+H)^+$. RMN ^1H (DMSO-d_6, 400 MHz): δ 1.25 (t, 3H), 2.76 (s, 3H), 3.76 (s, 3H), 4.23 (m, 2H), 4.65 (s, 2H), 5.36 (s, 2H), 6.41 (d, J = 2.8 Hz, 1H), 7.00 (d, J = 7.2 Hz, 1H), 7.34 (d, J = 3.2 Hz, 1H), 7.42 (s, 1H), 7.52 (d, J = 8.0 Hz, 1H).

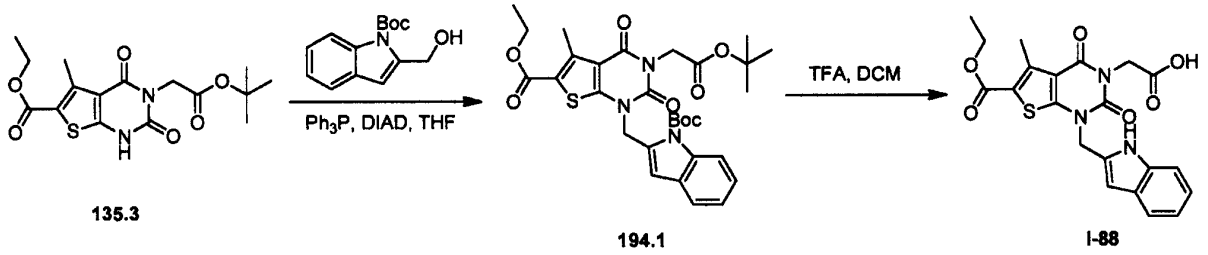
Ejemplo 193: Síntesis del ácido 2-[1-(2H-1,3-benzodioxol-5-ilmetil)-6-(etoxicarbonil)-5-metil-2,4-dioxo-

1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acético (I-50).



Se prepara el compuesto I-50 a partir del compuesto I-40 (Ejemplo 173) de una manera análoga a la síntesis del compuesto I-74 (Ejemplo 192). Se aíslan 7.6 mg de un sólido blanco con un rendimiento de 6% a partir de I-40. EM (ES): 447 *m/z* $(M+H)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.35 (t, J = 7.2, 3H), 2.81 (s, 3H), 4.32 (c, J = 7.2, 3H), 4.76 (s, 2H), 5.15 (s, 2H), 5.94 (s, 3H), 6.79-6.91 (m, 3H).

Ejemplo 194: Síntesis del ácido 2-[6-(etoxicarbonil)-1-(1H-indol-2-ilmetil)-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acético (I-88).



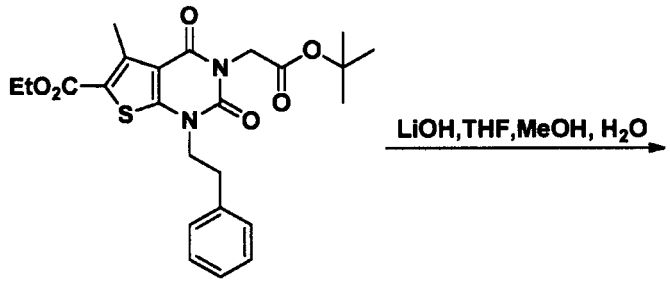
Síntesis del compuesto 194.1. En un matraz de fondo redondo de 25 ml se coloca una solución de 174.4 (322 mg, 1.30 mmol, 1.30 equivalentes) en 5 ml de

tetrahidrofurano, PPh_3 (524 mg, 2.00 mmol, 2.00 equivalentes), DIAD (292 mg, 1.44 mmol, 1.45 equivalentes) y 135.3 (368 mg, 1.00 mmol, 1.00 equivalentes). La solución resultante se agita durante 48 h a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:15). La purificación proporciona 0.244 g (41%) de 194.1 como un sólido blanco.

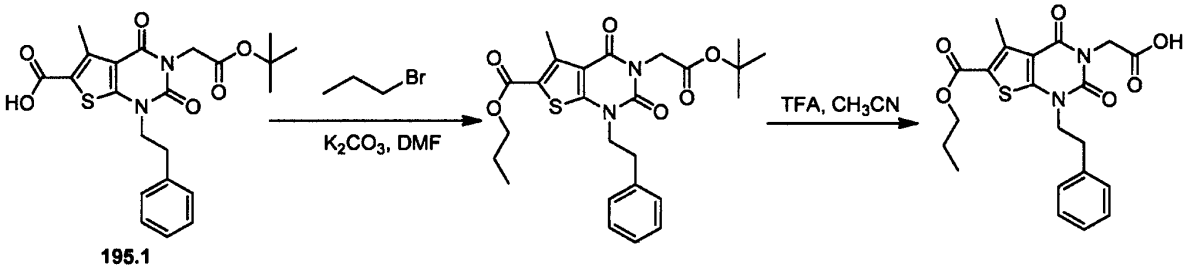
Síntesis del compuesto I-88. En un matraz de fondo redondo de 25 ml se colocan 10 ml de diclorometano, 194.1 (20 mg, 0.03 mmol, 1.00 equivalentes) y 4 ml de CF_3COOH. La solución resultante se agita durante la noche a temperatura ambiente. La mezcla resultante se concentra bajo vacío. Se purifica el producto crudo (30 mg) por *HPLC* preparativa bajo las siguientes condiciones (SHIMADZU): columna: SunFire Prep C18, 19*150 mm, 5 µm; fase móvil:agua con NH_4 HCO_3 0.05% y CH_3CN (CH_3CN 6.0% hasta 55.0% en 13 min); detector: 254/220 nm. Esto resulta en 0.0065 g (44%) de I-88 como un sólido blanco. EM (ES): *m/z* 442 $(M+H)^+$. RMN ^1H (400 MHz, $CDCl_3$): δ 1.44 (t, J = 7.2, 3H), 2.85 (s, 3H), 4.40 (c, J = 7.2, 2H), 4.89 (s, 2H), 5.25 (s, 2H), 6.71 (s, 1H), 7.11 (t, J = 7.2, 1H), 7.20 (t, J = 7.6, 1H), 7.36 (d, J = 8.4, 1H), 7.60 (d, J = 8.0, 1H), 8.79 (s, 1H).

Ejemplo 195: Síntesis del ácido 2-[5-metil-2,4-dioxo-1-(2-feniletil)-6-(propoxicarbonil)-1H,2H,3H,4H-

tieno[2,3-d]pirimidin-3-il]acético (I-68).



136.1



195.1 195.2 I-68

Síntesis del compuesto 195.1. En un matraz de fondo redondo de 100 ml se coloca 136.1 (5.1 g, 10.79 mmol, 1.00 equivalentes), 5 ml de tetrahidrofurano, 10 ml de metanol, 10 ml de agua y LiOH (770 mg, 32.15 mmol, 2.98 equivalentes). La solución resultante se agita durante la noche a temperatura ambiente. La mezcla resultante se diluye con 100 ml de H_2O. El valor de pH de la solución se ajusta a 3 con cloruro de hidrógeno 10%. La solución resultante se extrae con 3 x 100 ml de acetato de etilo y las capas orgánicas se combinan y concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con diclorometano/metanol (100:1). Esto resulta en 2.3 g (48%) de 195.1 como un

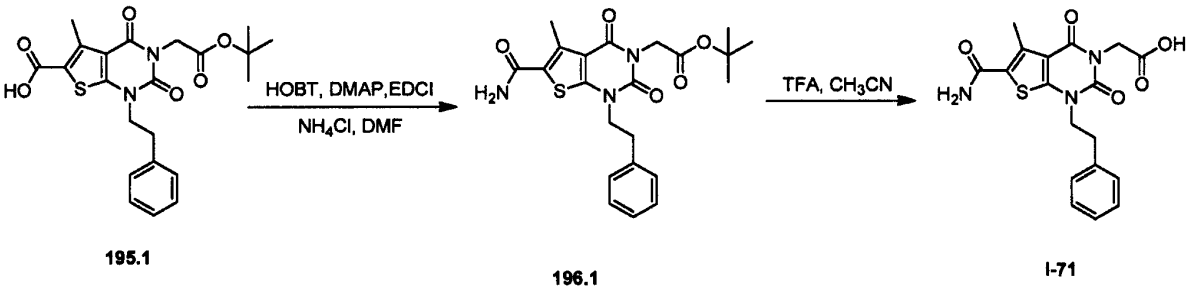
sólido blanco.

Síntesis del compuesto 195.2. En un matraz de fondo redondo de 50 ml se coloca 195.1 (150 mg, 0.34 mmol, 1.00 equivalentes), 10 ml de N,N-dimetilformamida, carbonato de potasio (140 mg, 1.01 mmol, 3.00 equivalentes) y 1-bromopropano (83 mg, 0.67 mmol, 2.00 equivalentes). La solución resultante se agita durante la noche a 50°C. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:50). Esto resulta en 130 mg (79%) de 195.2 como un sólido blanco.

Síntesis del compuesto I-68. En un matraz de fondo redondo de 25 ml se colocan 195.2 (130 mg, 0.27 mmol, 1.00 equivalentes), 2 ml de CF_3COOH y 5 ml de CH_3CN. La solución resultante se agita durante 5 h a temperatura ambiente y después se concentra bajo vacío. El producto crudo se recristaliza a partir de EA:n-hexano en la relación de 1:5. Esto resulta en 40.9 mg (36%) de I-68 como un sólido blanco. EM (ES): *m/z* 431 $(M+H)^+$. RMN ^1H (400 MHz, DMSO-d_6): δ 0.87 (t, J = 6.4, 3H), 1.65-1.74 (m, 2H), 2.75 (s, 3H), 3.01 (t, J = 7.2, 2H), 4.14 (t, J = 7.2, 2H), 4.21 (t, J = 6.8, 3H), 2.75 (s, 2H), 7.20-7.31 (m, 5H).

Ejemplo 196: Síntesis del ácido 2-[6-carbamoil-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-

d]pirimidin-3-il]acético (I-71).

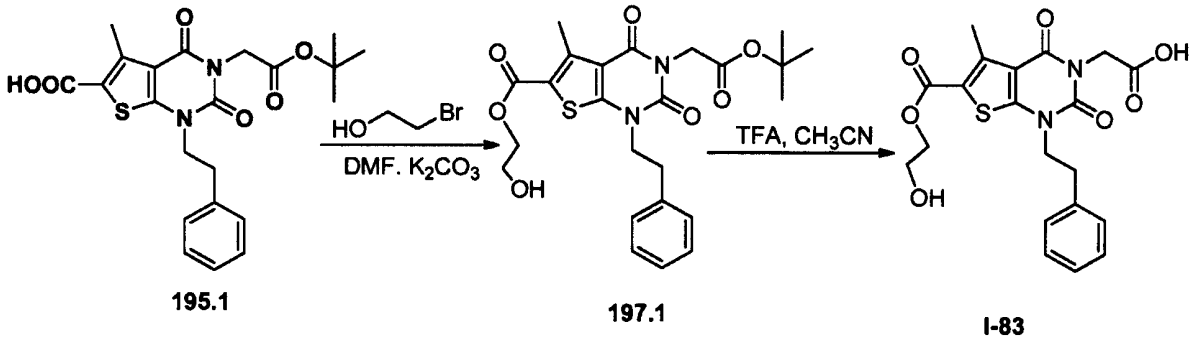


Síntesis del compuesto 196.1. En un matraz de fondo redondo de 50 ml se coloca HOBT (50 mg, 0.37 mmol, 1.10 equivalentes), 195.1 (150 mg, 0.34 mmol, 1.00 equivalentes), 4-dimetilaminopiridina (45 mg, 0.37 mmol, 1.09 equivalentes), NH_4Cl (72 mg, 1.35 mmol, 3.99 equivalentes), 10 ml de N,N-dimetilformamida y EDC (71 mg, 0.46 mmol, 1.36 equivalentes). La solución resultante se agita durante la noche a temperatura ambiente. La reacción después se suspende por la adición de 20 ml de agua. La solución resultante se extrae con 3 x 20 ml de acetato de etilo y las capas orgánicas se combinan, se secan y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:5). Esto resulta en 500 mg (crudo) de 196.1 como un sólido blanco.

Síntesis del compuesto I-71. Se prepara el compuesto I-71 a partir de 196.1 de una manera análoga a la síntesis del compuesto I-68 (Ejempl 195). Se aíslan 27 mg de un sólido blanco con un rendimiento de 6%. EM (ES): *m/z* 388 $(M+H)^+$ 410, $(M+Na)^+$, 429 $(M+H+CH_3CN)^+$. RMN ^1H (400 MHz, DMSO-d_6): δ 2.66

(s, 3H), 2.99 (t, J = 8.0, 2H), 4.07 (t, J = 7.6, 2H), 4.37 (s, 2H), 7.22-7.34 (m, 5H), 7.55 (s, 2H).

Ejemplo 197: Síntesis de 2-[6-[(2-hidroxietoxi)carbonil]-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acético (I-83).



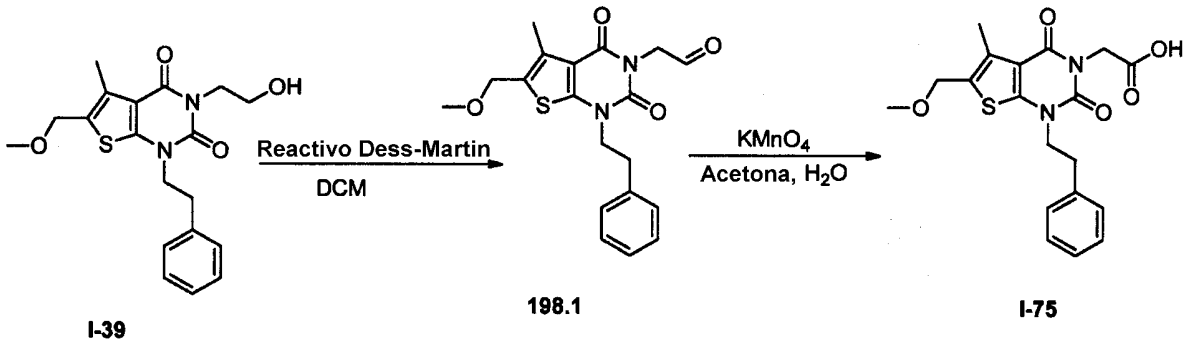
195.1 197.1 I-83

Síntesis del compuesto 197.1. Se prepara 197.1 a partir de 195.1 de una manera análoga a la síntesis de I-42 (Ejemplo 178). Se aíslan 140 mg (85%) de un sólido blanco.

Síntesis del compuesto I-83. Se prepara el compuesto I-83 a partir de 197.1 de una manera análoga al compuesto I-68 (Ejemplo 195). Se aíslan 35.2 mg de un sólido blanco con un rendimiento de 28%. EM (ES): *m/z* 433 $(M+H)^+$ 455 $(M+Na)^+$, 496 $(M+H+CH_3CN)^+$. RMN ^1H (400 MHz, DMSO-d_6): δ 2.76 (s, 3H), 3.02 (t, J = 7.6, 2H), 3.68 (t, J = 4.8, 2H), 4.14 (t, J = 7.6 2H), 4.27 (t, J = 4.8, 2H), 4.56 (s, 2H), 7.21-7.32 (m, 5H).

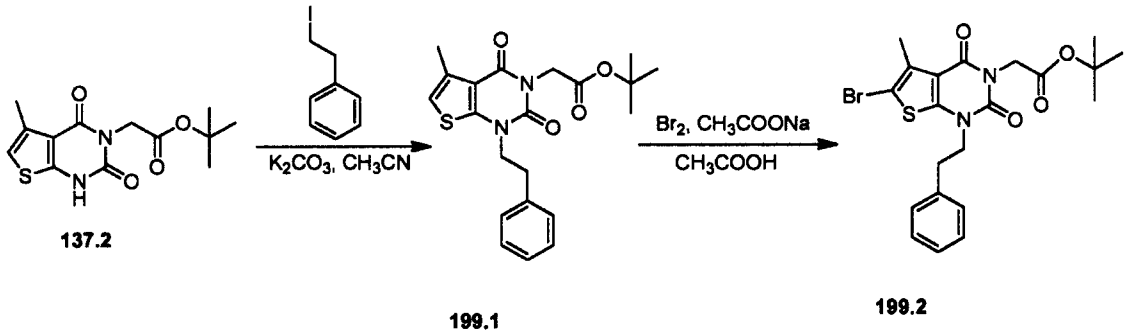
Ejemplo 198: Síntesis del ácido 2-[6-(metoximetil)-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-

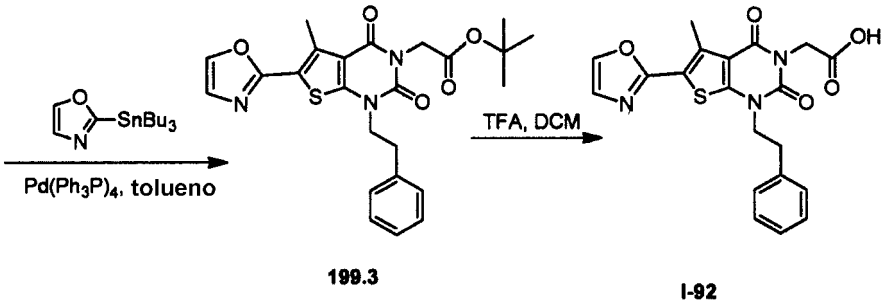
d]pirimidin-3-il]acético (I-75).



Se prepara el compuesto I-75 a partir de I-39 (Ejemplo 179) de una manera análoga a la síntesis del Compuesto I-84 (Ejemplo 190). Se aísla 49.5 mg de un sólido blanco con un rendimiento de 40% a partir de I-39. EM (ES): *m/z* 389 $(M+H)^+$ 411 $(M+Na)^+$, 452 $(M+Na+CH_3CN)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 2.35 (s, 3H), 2.99 (t, J = 7.5, 2H), 3.32 (s, 3H), 4.08 (t, J = 7.2, 2H), 4.51 (s, 2H), 7.19-7.32 (m, 5H), 12.94 (s, 1H).

Ejemplo 199: Síntesis del ácido 2-[5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acético (I-92).





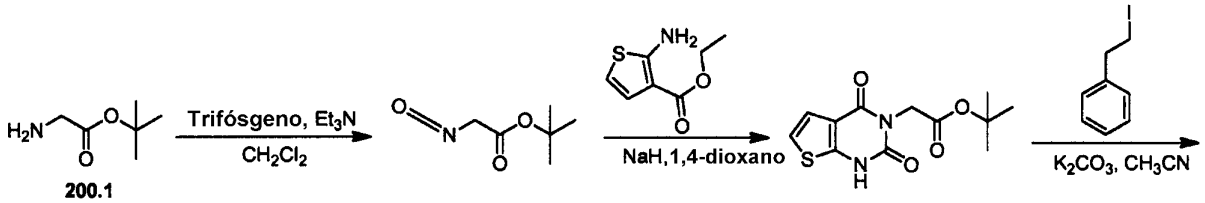
199.3 I-92

Síntesis del compuesto 199.1. Se prepara el compuesto 199.1 a partir de 137.2 de una manera análoga a la síntesis de 136.1. Se aíslan 0.87 g de un sólido amarillo con un rendimiento de 64%.

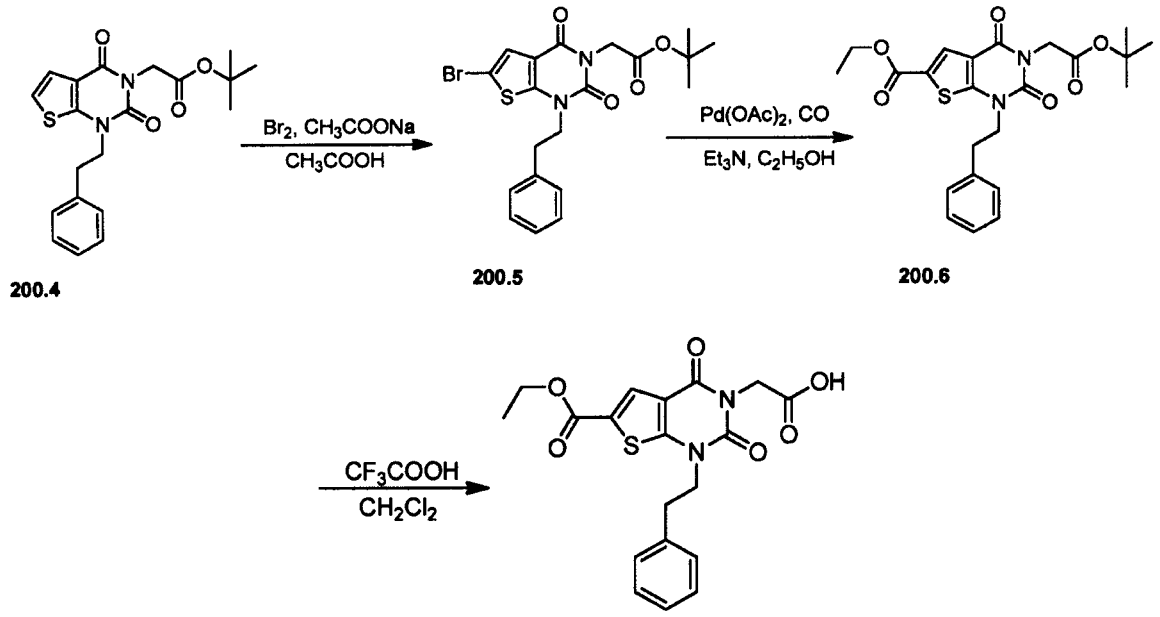
Síntesis del compuesto 199.2. Se prepara el compuesto 199.2 a partir de 199.1 de una manera análoga a la síntesis del compuesto 137.3. Se aíslan 0.56 g de un sólido blanco con un rendimiento de 94%.

Síntesis del compuesto I-92. Se prepara el compuesto I-92 a partir de 199.2 de una manera análoga al compuesto I-141 (Ejemplo 7). Se aíslan 24 mg (52%) de un sólido blanco.

Ejemplo 200: Síntesis del ácido 2-[6-(etoxicarbonil)-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acético (I-91).



200.1 200.2 200.3



200.4 200.5 200.6

I-91

Síntesis del compuesto 200.4. El compuesto 200.4 se prepara a partir de 200.1 y 2-aminotiofeno-3-carboxilato de etilo de una manera análoga a la síntesis de 136.1 (Ejemplos 135 y 136). Se aíslan 1.1 g de un sólido amarillo con un rendimiento total de 12%.

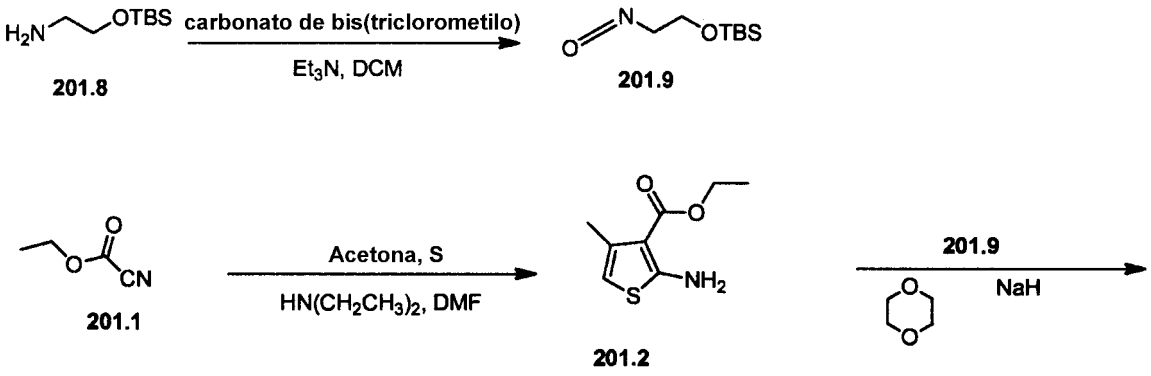
Síntesis del compuesto 200.5. Se prepara el compuesto 200.5 a partir de 200.4 de una manera consistente con la síntesis de 137.3. Se aíslan 1.1 g de un sólido blanco con un rendimiento de 83%.

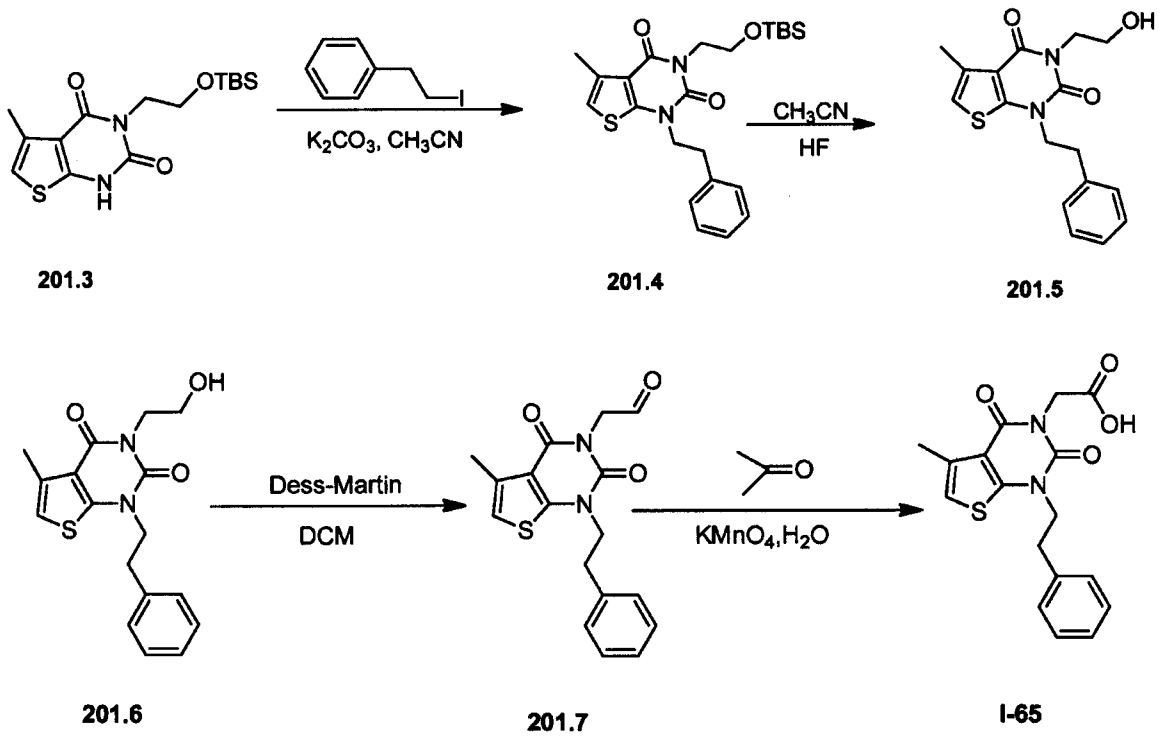
Síntesis del compuesto 200.6. En un reactor de tanque a presión de 100 ml (7 atmósferas) se coloca $Pd(OAc)_2$ (100 mg, 0.45 mmol, 0.41 equivalente), 200.5 (500 mg, 1.07 mmol, 1.00 equivalentes), 50 ml de etanol y trietilamina (220

mg, 2.17 mmol, 2.02 equivalentes). Después se introduce CO (gaseoso) para mantener la presión a 7 atmósferas. La solución resultante se agita durante la noche a 100°C. Después de enfriar, la mezcla resultante se concentra bajo vacío. El residuo es aplicado sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:20). La purificación proporciona 130 mg (26%) de 200.6 como un sólido blanco.

Síntesis del compuesto I-91. Se prepara el compuesto I-91 a partir de 200.6 de una manera análoga a la síntesis del compuesto 2.5. EM (ES): *m/z* 403 $(M+H)^+$, 425 $(M+Na)^+$, 444 $(M+H+CH_3CN)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 1.29 (t, *J*=6.9, 3H), 3.02 (t, *J*=7.2, 2H), 4.15 (t, *J*=7.2, 2H), 4.30 (c, *J*=6.9, 2H), 4.56 (s, 2H), 7.18-7.30 (m, 5H), 7.81 (s, 1H), 13.09 (s, 1H).

Ejemplo 201: Síntesis del ácido 2-[2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acético (I-65).





Síntesis del compuesto 201.9. Se prepara el compuesto 201.9 a partir de (2-aminoetoxi)(terbutil)dimetilsilano de una manera análoga al compuesto 169.3. Se aíslan 13 g (crudo) de un líquido amarillo.

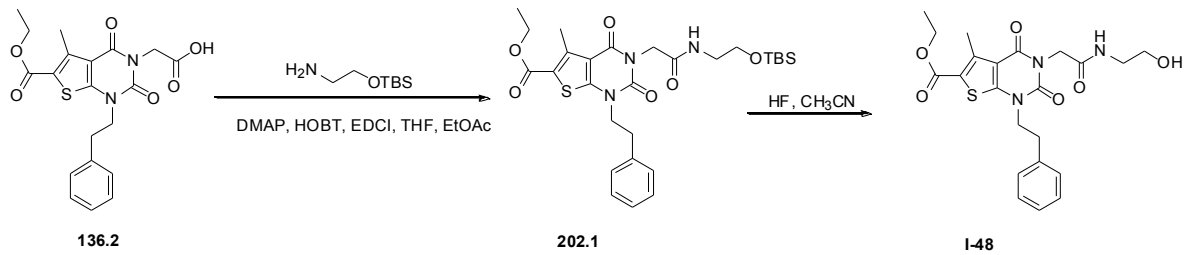
Síntesis del compuesto 201.2. En un matraz de fondo redondo de 3 cuellos de 500 ml purgado y mantenido con una atmósfera inerte de nitrógeno se coloca 2-cianoacetato de etilo (22.6 g, 199.80 mmol, 1.00 equivalentes), 200 ml de etanol, propan-2-ona (11.6 g, 199.73 mmol, 1.00 equivalentes), 14.6 g de dietilamina y 6.4 g de S. La solución resultante se agita durante la noche a 50°C. Los sólidos se separan por filtración. El filtrado se concentra bajo vacío. El residuo se

aplica sobre una columna de gel de sílice con acetato de etilo/PE (1:100-1:20). Esto resulta en 6.47 g (17%) de 201.2 como un sólido blanco.

Síntesis del compuesto 201.5. Se prepara el compuesto 201.5 a partir de 201.2 de una manera análoga al compuesto I-34 (Ejemplo 169). Se aíslan 12.6 mg de un sólido blanco con un rendimiento total de 0.03%. EM (ES): *m/z* 331.1 $(M+H)^+$. RMN ^1H ($CDCl_3$, 400 MHz): δ 2.37 (s,3H), 2.96-3.01 (t, 2H), 3.58-3.62 (t, 2H), 3.92-3.96 (t, 2H), 4.04-4.09 (t, 2H), 6.81 (s, 1H), 7.21-7.32 (m, 5H).

Síntesis del compuesto I-65. Se prepara el compuesto I-65 a partir de 201.5 de una manera análoga al compuesto I-84 (Ejemplo 190). Se aíslan 30.8 mg de un sólido blanco con un rendimiento de 29% a partir de 201.5. EM (ES): *m/z* 367.1 $(M+Na)^+$. RMN ^1H ($CDCl_3$, 300 MHz): δ 2.36 (s, 3H), 2.97-3.02 (t, 2H), 4.06-4.11 (t, 2H), 4.55 (s, 2H), 6.90 (s, 1H), 7.19-7.32 (m, 5H).

Ejemplo 202: Síntesis de 3-[[(2-hidroxietil)carbamoil]metil]-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxilato de etilo (I-48).



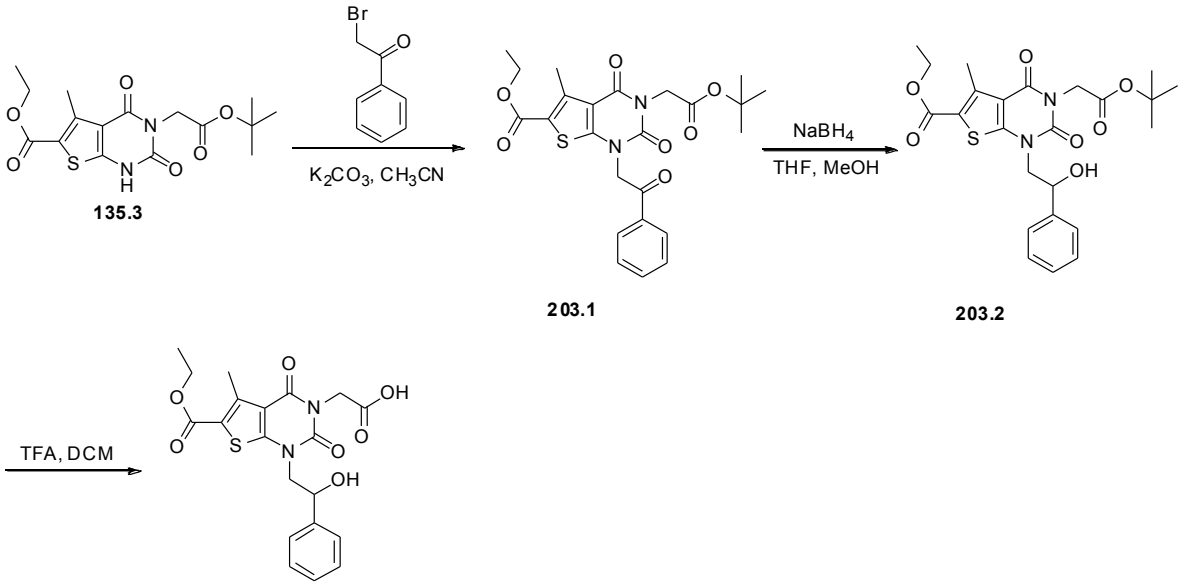
Síntesis del compuesto 202.1. Se prepara el

compuesto 202.1 a partir de 136.2 y (2-aminoetoxi)(terbutil)dimetilsilano de una manera análoga a 136.3. Se aíslan 0.7 g de un sólido blanco con un rendimiento de 98%.

Síntesis del compuesto I-48. Se prepara el compuesto I-48 a partir de 202.1 de una manera análoga al compuesto I-20. (Ejemplo 160). Se aíslan 0.46 g de un sólido blanco con un rendimiento de 80%. EM (ES): *m/z* 460 $(M+H)^+$.

RMN ^1H (CD_3OD, 400 MHz): δ 1.38 (t, *J*=7.2 Hz, 3H), 2.82 (s, 3H), 3.10 (t, *J*=7.2 Hz, 2H), 3.37 (t, *J*=5.6 Hz, 2H), 3.64 (t, *J*=5.6 Hz, 2H), 4.18 (t, *J*=7.2 Hz, 2H), 4.34 (c, 2H), 4.69 (s, 2H), 7.23-7.33 (m, 5H).

Ejemplo 203: Síntesis del ácido 2-[6-(etoxicarbonil)-1-(2-hidroxi-2-feniletil)-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acético (I-60).



135.3 203.1 203.2 I-60

Síntesis de 203.1. Se prepara el compuesto 203.1 a partir de 135.3 y 2-bromo-1-pentiletan-1-ona de una manera análoga a 136.1. Se aíslan 0.34 g de un sólido amarillo claro con un rendimiento de 51%.

Síntesis de 203.2. En un matraz de fondo redondo de 50 ml se colocan 203.1 (300 mg, 0.62 mmol, 1.00 equivalentes), 5 ml de metanol, 5 ml de tetrahidrofurano y $NaBH_4$ (25 mg, 0.66 mmol, 1.07 equivalentes). La solución resultante se agita durante 2 h a temperatura ambiente. La reacción después se suspende por adición de 5 ml de NH_4Cl acuoso. La solución resultante se extrae con 2 x 5 ml de acetato de etilo y las capas orgánicas se combinan, se secan sobre sulfato de sodio anhidro y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:5). Esto resulta en 160 mg (53%) de 203.2 como un sólido blanco.

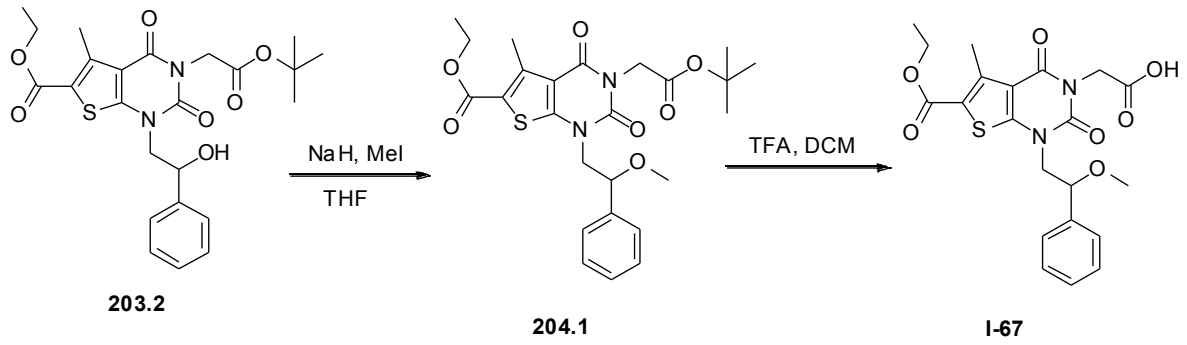
Síntesis del compuesto I-60. El compuesto I-60 se prepara a partir de 203.2 de una manera consistente con la síntesis del compuesto 2.5. Se aíslan 20.4 mg de un sólido blanco con un rendimiento de 38%.

EM (ES): *m/z* 433 $(M+H)^+$, 455 $(M+Na)^+$, 496 $(M+Na+CH_3CN)^+$.

RMN ^1H (300 MHz, DMSO-d_6): δ 1.31 (t, *J*=7.2, 3H), 2.76 (s, 3H), 3.77-3.85 (m, 1H), 4.12-4.15 (m, 1H), 4.29 (c, *J*=6.9, 2H), 4.44 (s, 2H), 4.99 (d, *J*=7.2, 1H), 5.89(s, 1H),

7.30-7.43 (m, 5H).

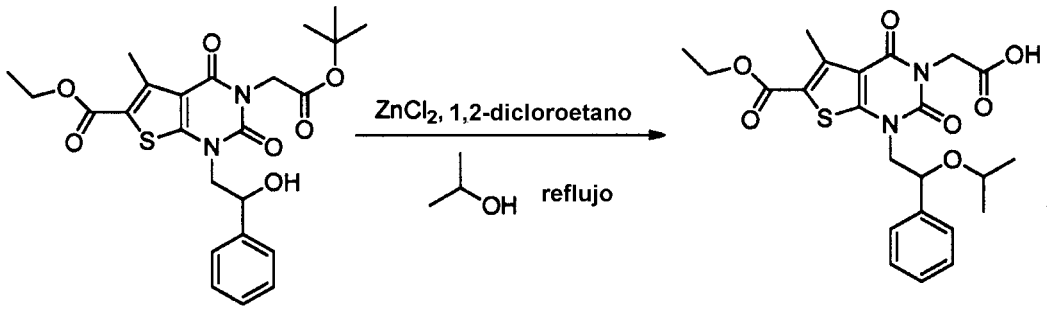
Ejemplo 204: Síntesis del ácido 2-[6-(etoxicarbonil)-1-(2-metoxi-2-feniletil)-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acético (I-67).



Síntesis del compuesto 204.1. En un matraz de fondo redondo de 50 ml, purgado y mantenido con una atmósfera inerte de nitrógeno se colocan 203.2 (100 mg, 0.20 mmol, 1.00 equivalentes), 10 ml de tetrahidrofurano. Esto es seguido por la adición de hidruro de sodio (8.2 mg, 0.20 mmol, 1.00 equivalentes). La mezcla se agita durante 15 min a 0°C. A esto se agrega CH_3I (43.6 mg, 0.31 mmol, 1.50 equivalentes). La solución resultante se agita durante la noche a temperatura ambiente. La reacción después se suspende por la adición de 5 ml de NH_4Cl acuoso. La solución resultante se extrae con 2 x 5 ml de acetato de etilo. Las capas orgánicas se combinan, se secan sobre sulfato de sodio y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/PE (1:10). Esto resulta en 70 mg (68%) de 204.1 como un sólido blanco.

Síntesis del compuesto I-67. Se prepara el compuesto I-67 a partir de 204.1 de una manera consistente con la síntesis del compuesto 2.5. Se aíslan 30.5 mg de un sólido blanco con un rendimiento de 49%. EM (ES): *m/z* 447 $(M+H)^+$, 469 $(M+Na)^+$, 469 $(M+Na+CH_3CN)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 1.31 (t, *J*=7.2, 3H), 2.76 (s, 3H), 3.09 (s, 3H), 3.94-4.15 (m, 2H), 4.30 (c, *J*=6.6, 2H), 4.56-4.65 (m, 3H), 7.34-7.46 (m, 5H), 12.98 (s, 1H).

Ejemplo 205: Síntesis del ácido 2-[6-(etoxicarbonil)-5-metil-2,4-dioxo-1-[2-fenil-2-(propan-2-iloxi)etil]-1H,2H,3H,4H-tieno[2,3-d]pirmidin-3-il]acético (I-89).

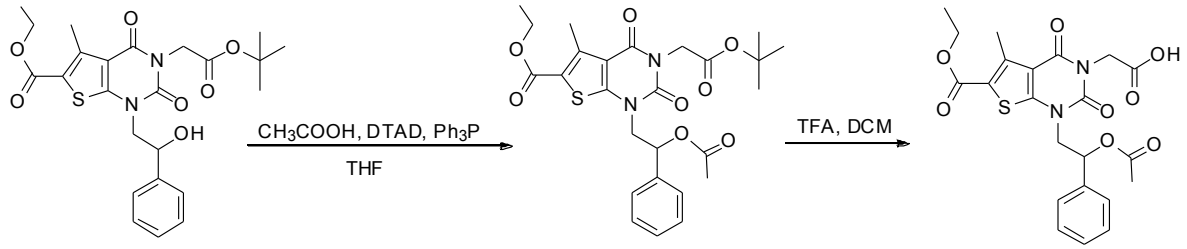


203.2 **I-89**

En un matraz de fondo redondo de 50 ml se coloca 203.2 (100 mg, 0.20 mmol, 1.00 equivalentes), 20 ml de 1,2-dicloroetano, $ZnCl_2$ (33 mg, 0.24 mmol, 1.18 equivalentes) y propan-2-ol (25 mg, 0.42 mmol, 2.03 equivalentes). La solución resultante se agita durante la noche a 50°C. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de

petróleo (1:10). Se purifican 110 mg del producto crudo por *HPLC* preparativa bajo las siguientes condiciones (SHIMADZU): columna: SunFire Prep C18, 19*150 mm 5 µm; fase móvil: agua con NH_4HCO_3 0.05% y CH_3CN (CH_3CN 6.0% hasta 49% en 19 min); detector: 254/220 nm. La purificación proporciona 23.8 mg (25%) de I-89 como un sólido blanco. EM (ES): *m/z* 475 $(M+H)^+$, 497 $(M+Na)^+$, 538 $(M+Na+CH_3CN)^+$. RMN ^1H (400 MHz, DMSO-d_6): δ 0.85 (d, 3H), 0.95 (d, 3H), 1.33 (t, 3H), 2.77 (s, 3H), 3.46 (m, 1H), 3.78 (m, 1H), 3.91 (m, 1H), 4.14 (m, 1H), 4.34 (m, 2H), 4.61 (m, 2H), 4.81 (m, 1H), 7.34-7.42 (m, 5H).

Ejemplo 206: Síntesis del ácido 2-[1-[2-(acetiloxi)-2-feniletil]-6-(etoxicarbonil)-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acético (I-85).



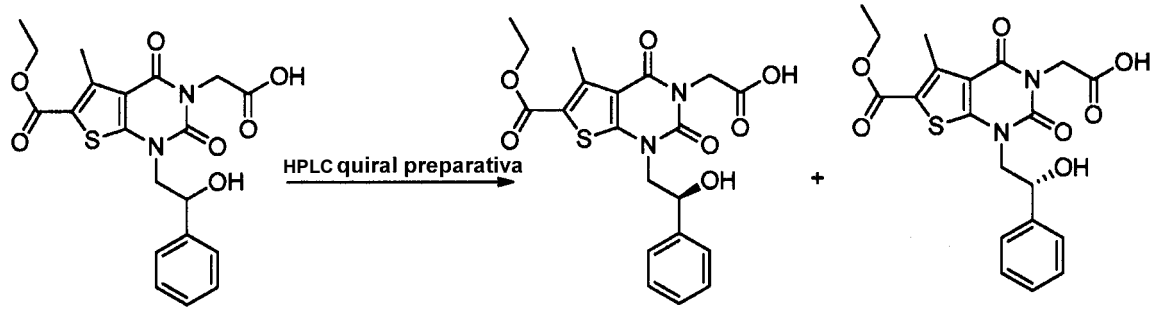
203.2 **206.1** **I-85**

Síntesis del compuesto 206.1. En un tubo de sellado de 10 ml, purgado y mantenido con una atmósfera inerte de nitrógeno se coloca 203.2 (200 mg, 0.41 mmol, 1.00 equivalentes), DTAD (188 mg, 0.82 mmol, 2.00 equivalentes), 5 ml de tetrahidrofurano, PPh_3 (214 mg, 0.82 mmol, 2.00 equivalentes) y ácido acético (49 mg,

0.82 mmol, 2.00 equivalentes). La solución resultante se agita durante la noche a temperatura ambiente y después se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/PE (1:15). Esto resulta en 76 mg (35%) de 206.1 como un sólido blanco.

Síntesis del compuesto I-85. El compuesto I-85 se prepara a partir de 206.1 de una manera análoga a 2.5. Se aíslan 23.1 mg (34%) de un sólido blanco. EM (ES): *m/z* 475 $(M+H)^+$, 415 $(M+H-CH_3COOH]^+$. RMN ^1H RMN ^1H (300 MHz, CD_3OD): δ 1.40 (t, *J*=7.2, 3H), 2.00 (s, 3H), 2.84 (s, 3H), 4.33-4.40 (m, 4H), 4.72 (t, *J*=5.1, 2H), 6.25 (t, *J*=7.2, 1H), 7.37-7.50 (m, 5H).

Ejemplo 207: Síntesis del ácido 2-[6-(etoxicarbonil)-1-[(2S)-2-hidroxi-2-feniletil]-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acético (I-77) y Ejemplo 208: ácido 2-[6-(etoxicarbonil)-1-[(2R)-2-hidroxi-2-feniletil]-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acético (I-78).



Se purifica I-60 (120 mg, 0.28 mmol,

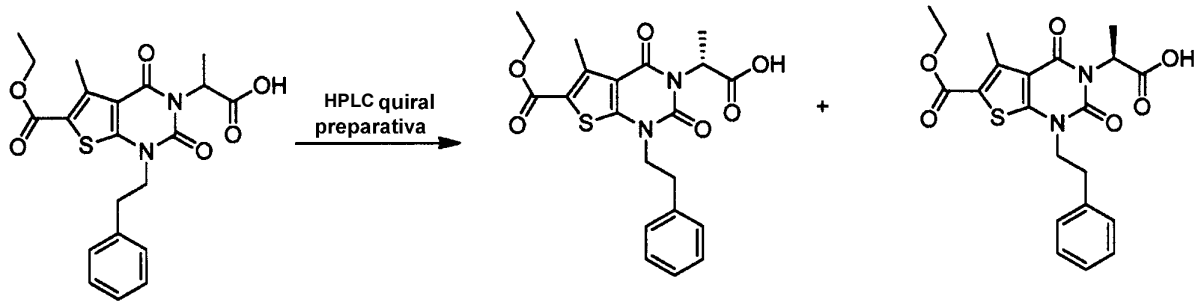
1.00 equivalentes) por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): columna: Chiralpak IC(SFC), 2*25 cm, 5 µm; fase móvil; hexanos y etanol (TFA 0.1%) (se mantiene en etanol 20.0% (TFA 0.1%) en 18 min); detector: UV 220/254 nm. Esto resulta en 24.6 mg (tR = 10.1 min, 21%) de I-77 como un sólido blanco y 15.2 mg (12.5 min, 13%) de I-78 como un sólido blanco.

Datos analíticos para I-77: EM (ES): *m/z* 433 $(M+H)^+$, 496 $(M+Na+CH_3CN)^+$. RMN ^1H (400 MHz, DMSO-d_6): δ 1.32(t, *J*=7.2, 3H), 2.77 (s, 3H), 3.80-3.86 (m, 1H), 4.13-4.18 (m, 1H), 4.29 (c, *J*=6.9, 2H), 4.57 (d, *J*=6.0, 2H), 4.99 (t, *J*=4.8, 1H), 5.90 (d, *J*=4.4, 1H), 7.29-7.44 (m, 5H).

Datos analíticos para I-78: EM (ES): *m/z* 433 $(M+H)^+$, 496 $(M+Na+CH_3CN)^+$. RMN ^1H (400 MHz, DMSO-d_6): δ 1.32 (t, *J*=7.2, 3H), 2.77 (s, 3H), 3.80-3.86 (m, 1H), 4.13-4.18 (m, 1H), 4.29 (c, *J*=6.9, 2H), 4.57 (d, *J*=6.0, 2H), 4.99 (t, *J*=4.8, 1H), 5.90 (d, *J*=4.4, 1H), 7.29-7.44 (m, 5H).

Ejemplo 209: Síntesis de (2R)-2-[6-(etoxicarbonil)-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-76) y Ejemplo 210: Síntesis de (2S)-2-[6-(etoxicarbonil)-5-metil-2,4-dioxo-1-(2-feniletil)-

1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-80).



I-56 **I-76** **I-80**

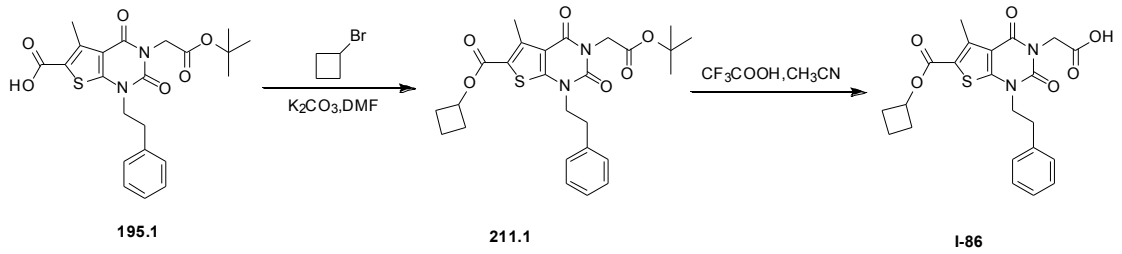
Los enantiómeros I-56 se preparan por *HPLC* quiral bajo las siguientes condiciones (Gilson Gx 281): columna: Chiralpak IA, 2*25 cm, 5 µm; fase móvil: hexanos y etanol (DEA 0.1%) (que se mantiene en etanol 40.0% (DEA 0.1%) en 20 min); detector: UV 220/254 nm. Esto resulta en 20 mg (tR = 5.27 min, 31%) de I-76 como un sólido blanco y 20 mg (tR = 10.4 min, 27%) de I-80 como un sólido blanco.

Datos analíticos para I-76: EM (ES): *m/z* 431 $(M+H)^+$. RMN ^1H ($CDCl_3$, 300 MHz): δ 1.29 (t, *J*=9.6 Hz, 3H), 1.48 (d, *J*=10.0 Hz, 3H), 2.74 (s, 3H), 3.00 (t, *J*=9.6 Hz, 2H), 4.12 (t, *J*=10.0 Hz, 2H), 4.28 (c, *J*=9.6 Hz, 2H), 5.37(c, 1H), 7.18-7.30 (m, 5H), 12.72 (s, 1H).

Datos analíticos para I-80: EM (ES): *m/z* 431 $(M+H)^+$. RMN ^1H ($CDCl_3$, 300 MHz): δ 1.29 (t, *J*=9.6 Hz, 3H), 1.42 (d, *J*=9.6 Hz, 3H), 2.73 (s, 3H), 2.98 (t, *J*=9.6 Hz, 2H), 4.12 (t, *J*=6.8 Hz, 2H), 4.27 (c, 2H), 4.96 (c, 1H), 7.19-7.32 (m, 5H).

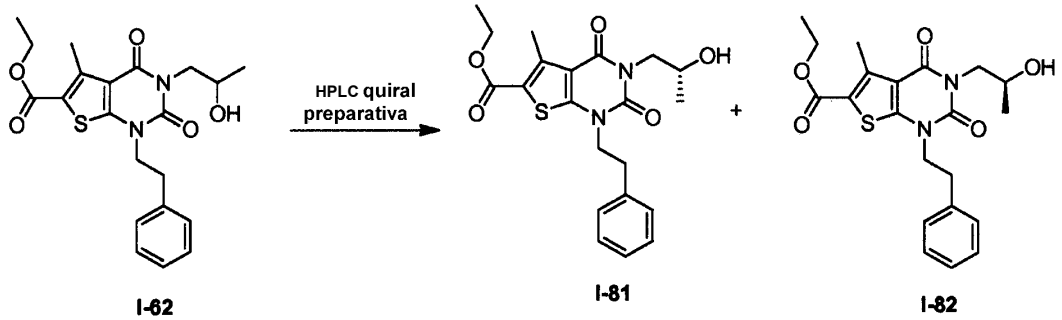
Ejemplo 211: Síntesis del ácido 2-[6-

(ciclobutoxicarbonil)-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acético (I-86).



Se prepara el compuesto I-86 a partir de 195.1 y bromociclobutano de una manera análoga a la síntesis del compuesto I-68 (Ejemplo 195). Se aísla 93 mg (55%) de un sólido amarillo oscuro. EM (ES): *m/z* 443 $(M+H)^+$. RMN ^1H (CD_3OD, 300 MHz): δ 1.69-1.95 (m, 2H), 2.14-2.28 (m, 2H), 2.39-2.48 (m, 2H), 2.80 (s, 3H), 3.08-3.13 (t, 2H), 4.17-4.22 (t, 2H), 4.71 (s, 2H), 5.12-5.22 (m, 1H), 7.22-7.32 (m, 5H).

Ejemplo 212: Síntesis de 3-[(2R)-2-hidroxipropil]-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxilato de etilo (I-81) y Ejemplo 213: Síntesis de 3-[(2S)-2-hidroxipropil]-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxilato de etilo (I-82).



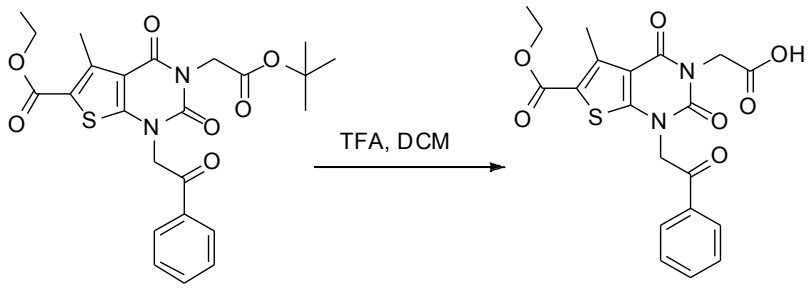
Los enantiómeros de I-62 (250 mg) se separan por

HPLC preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): columna: Chiralpak IB, 2*25 cm, 5 µm; fase móvil: hexanos y etanol (se mantiene el etanol 5.0% en 12 min); detector: UV 220/254 nm. Esto resulta en 100 mg (tR = 15.2 min, 80%) de I-81 como un sólido blanco y 100 mg (tR = 17.6 min, 80%) de I-82 como un sólido blanco.

Datos analíticos para I-81: EM (ES): *m/z* 417 $(M+H)^+$. RMN ^1H (400 MHz, DMSO-d_6): δ 1.03(d, *J*=5.2 Hz, 3H), 1.30 (t, *J*=6.8 Hz, 3H), 2.76 (s, 3H), 3.00 (m, *J*=7.2 Hz, 2H), 3.70 (c, 1H), 3.95 (t, *J*=8.0 Hz, 2H), 4.12 (t, *J*=8.0 Hz, 2H), 4.28 (m, *J*=7.2 Hz, 2H), 4.77 (s, 1H), 7.19-7.32 (m, 5H).

Datos analíticos para I-82: EM (ES): *m/z* 417 $(M+H)^+$. RMN ^1H (DMSO-d_6, 400 MHz): δ 1.03 (d, *J*=5.2 Hz, 3H), 1.30 (t, *J*=6.8 Hz, 3H), 2.76 (s, 3H), 3.00 (t, *J*=7.2 Hz, 2H), 3.70 (c, 1H), 3.95 (t, *J*=8.0 Hz, 2H), 4.12 (t, *J*=8.0 Hz, 2H), 4.28 (c, *J*=7.2 Hz, 2H), 4.77 (s, 1H), 7.19-7.32 (m, 5H).

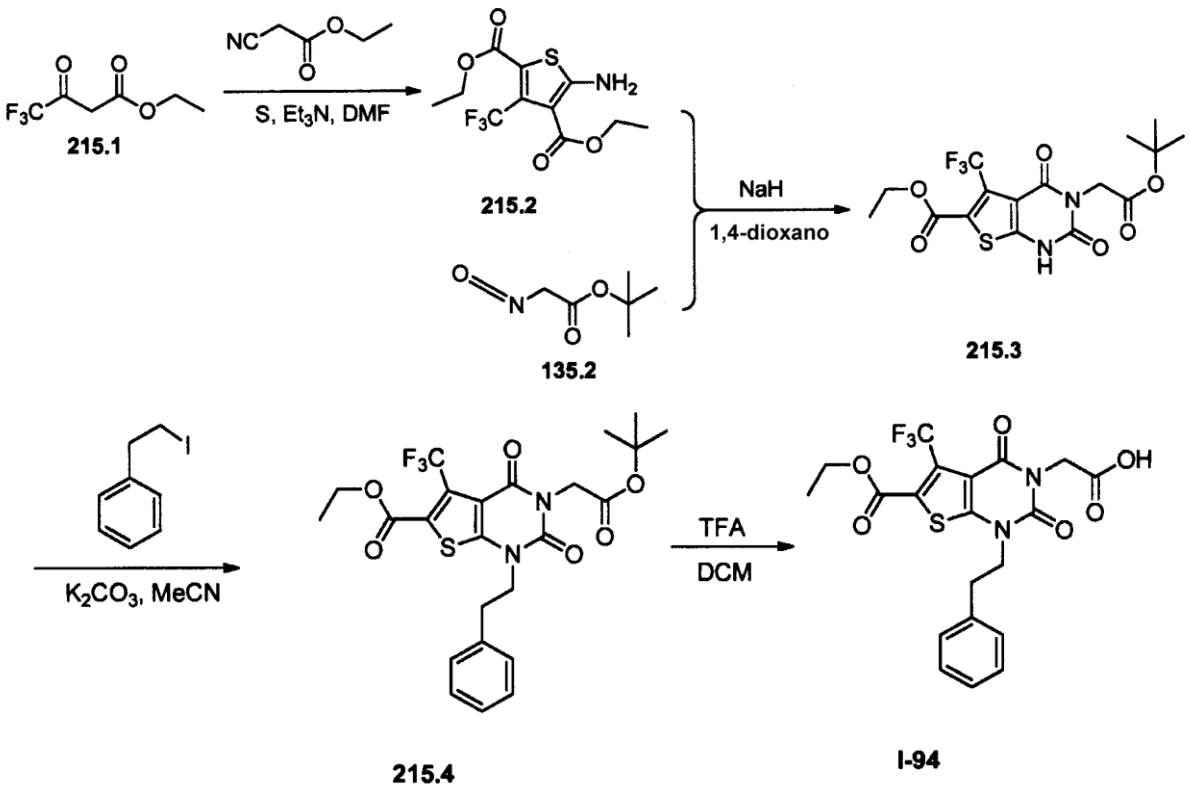
Ejemplo 214: Síntesis del ácido 2-[6-(etoxicarbonil)-5-metil-2,4-dioxo-1-(2-oxo-2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acético (I-73).



203.1 **I-73**

El compuesto I-73 se prepara a partir de 203.1 de una manera análoga a la síntesis de 2.5. Se aíslan 69.2 mg (78%) de un sólido blanco. RMN ^{1}H (400 MHz, DMSO-d_6): δ 1.26 (t, J=7.2, 3H), 2.80 (s, 3H), 4.26 (c, J=7.2, 2H), 4.57 (s, 2H), 5.73 (s, 2H), 7.63 (t, J=7.6, 2H), 7.78 (t, J=7.6, 1H), 8.12 (d, J=7.6, 2H).

Ejemplo 215: Síntesis del ácido 2-[6-(etoxicarbonil)-2,4-dioxo-1-(2-feniletil)-5-(trifluorometil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acético (I-94).



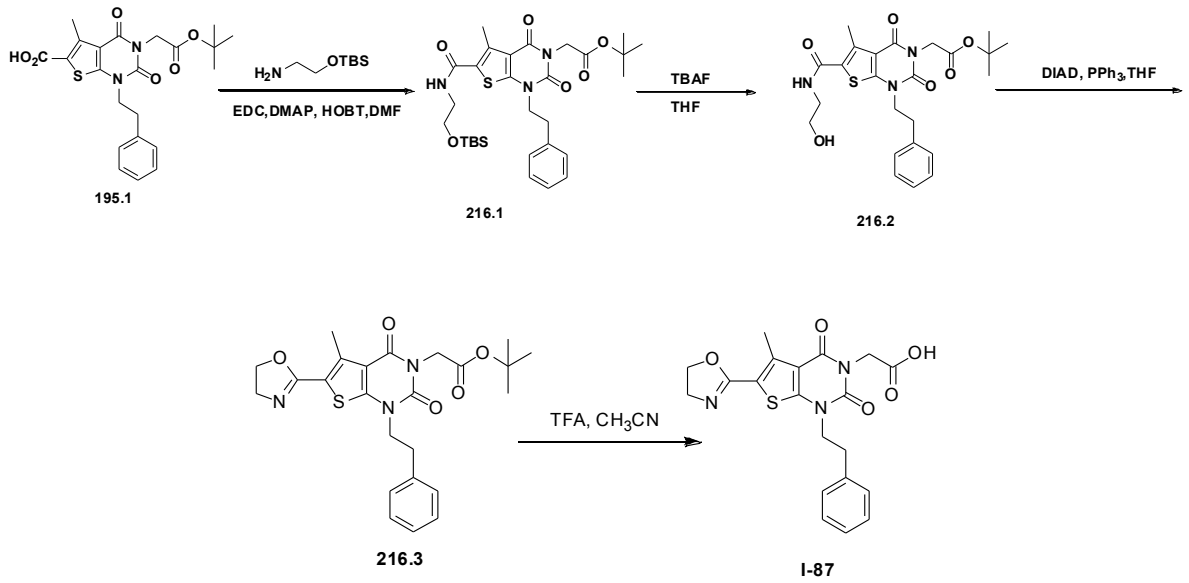
Síntesis del compuesto 215.2. En un matraz de fondo redondo de 3 cuellos de 1 l se coloca S (8.84 g,

276.25 mmol, 1.00 equivalentes), 4,4,4-trifluoro-3-oxobutanoato de etilo (50.8 g, 275.92 mmol, 1.00 equivalente), 300 ml de N,N-dimetilformamida y 2-cianoacetato de etilo (31.2 g, 275.83 mmol, 1.00 equivalente). Esto es seguido por la adición de trietilamina (28 g, 276.71 mmol, 1.00 equivalente) a gotas, con agitación, a 0°C. La solución resultante se agita durante la noche a temperatura ambiente. Se permite que la solución resultante reaccione, con agitación, durante 1 día adicional mientras que la temperatura se mantiene a 40°C en un baño de aceite. La reacción después se suspende por la adición de 500 ml de agua. La solución resultante se extrae con 3 x 500 ml de éter y las capas orgánicas se combinan y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:12). Esto resulta en 5.8 g (7%) de 215.2 como un sólido amarillo.

Síntesis del compuesto I-94. El compuesto I-94 se prepara a partir de 215.2 y 135.2 de una manera análoga a la síntesis del compuesto 136.2. Se aíslan 0.4 g de un sólido blanco con 53% de rendimiento. EM (ES): *m/z* 471 $(M+H)^+$. RMN ^1H (400 MHz, DMSO-d_6): δ 1.30 (t, *J*=6.8, 3H), 3.02(t, *J*=7.2, 2H), 4.17 (t, *J*=7.2, 2H), 4.34 (t, *J*=7.2, 2H), 4.58 (s, 2H), 7.21-7.32 (m, 5H), 13.11 (s, 1H).

Ejemplo 216: Síntesis del ácido 2-[6-(4,5-dihidro-

1,3-oxazol-2-il)-5-metil-2,4-dioxo-1-(2-feniletil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acético (I-87).



Síntesis del compuesto 216.1. El compuesto 216.1 se prepara a partir de 195.1 de una manera análoga al compuesto 136.3. Se aíslan 600 mg (89%) de un sólido blanco.

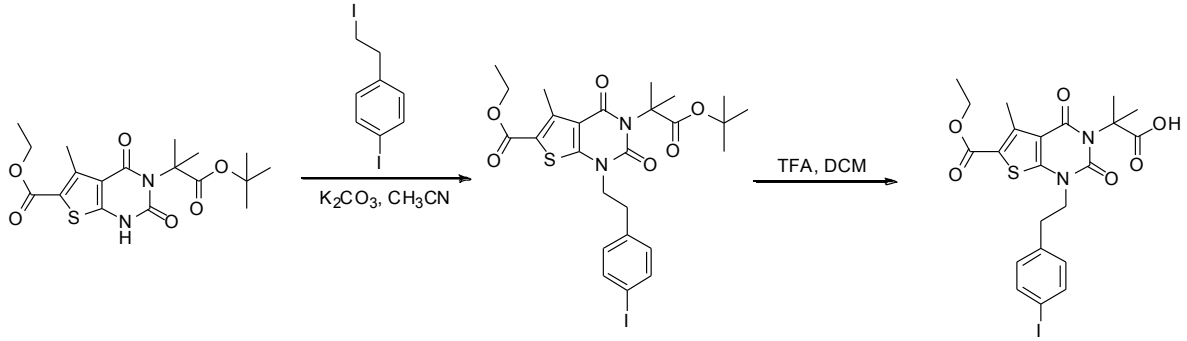
Síntesis del compuesto 216.2. En un matraz de fondo redondo de 50 ml se coloca 216.1 (600 mg, 1.00 mmol, 1.00 equivalentes), 10 ml de oxolano y TBAF (300 mg, 1.15 mmol, 1.15 equivalentes). La solución resultante se agita durante la noche a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/PE (1:5). La purificación proporciona 205 mg (42%) de 216.2 como un sólido blanco.

Síntesis del compuesto 216.3. En un matraz de fondo

redondo de 10 ml se coloca 216.2 (100 mg, 0.21 mmol, 1.00 equivalente), DIAD (94 mg, 0.46 mmol, 1.99 equivalentes), PPh_3 (107 mg, 0.41 mmol, 2.00 equivalentes) y 5 ml de tetrahidrofurano. La solución resultante se agita durante la noche a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:20). La purificación proporciona 70 mg (73%) de 216.3 como un sólido blanco.

Síntesis del compuesto I-87. El compuesto I-87 se prepara a partir de 216.3 de una manera análoga a la síntesis de 2.5. Se aíslan 2.8 mg (9%) de I-87 como un sólido blanco. EM (ES): *m/z* 414 $(M+H)^+$. RMN ^1H (400 MHz, CD_3OD): δ 2.76 (s, 1H), 3.11 (t, *J*=8.0, 2H), 3.99 (t, *J*=9.6, 2H), 4.17 (t, *J*=7.6, 2H), 4.49 (t, *J*=9.6, 2H), 4.62 (s, 2H), 7.22-7.30 (m, 5H).

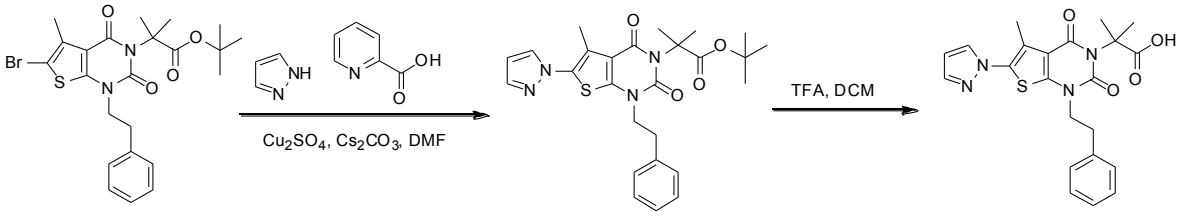
Ejemplo 217: Síntesis del ácido 2-[6-(etoxicarbonil)-1-[2-(4-yodofenil)etil]-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-95).



1.4 217.1 I-95

Síntesis del compuesto I-95. El compuesto I-95 se prepara a partir de 1.4 y 1-yodo-4-(2-yodoetil)benceno de una manera análoga a la síntesis de 136.2. EM (ES): *m/z* 571 $(M+H)^+$, 612 $(M+H+CH_3CN)^+$. RMN ^1H (400 MHz, CD_3CN): δ 1.32 (t, *J*=7.2, 3H), 1.67 (s, 6H), 2.71 (s, 3H), 2.98 (t, *J*=7.2, 2H), 4.05 (t, *J*=7.2, 2H), 4.28 (c, *J*=7.2, 2H), 7.01 (d, *J*=8.4, 2H), 7.62 (d, *J*=8.0, 2H).

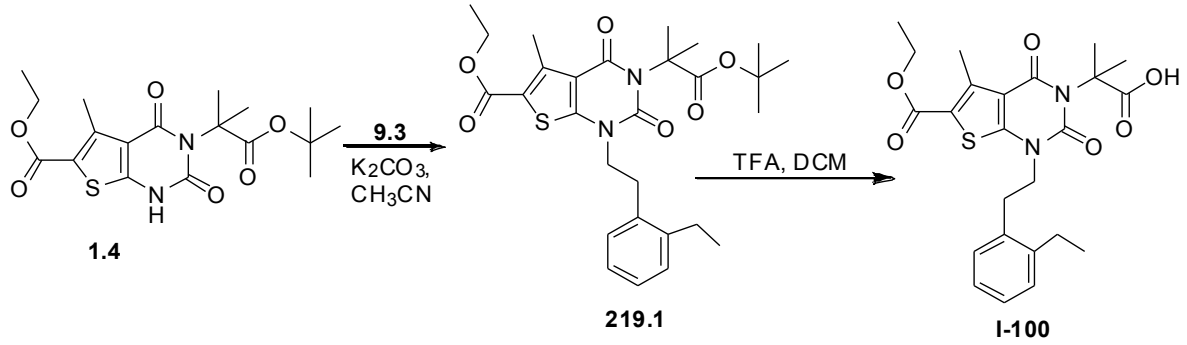
Ejemplo 218: Síntesis del ácido 2-metil-2-[5-metil-2,4-dioxo-1-(2-feniletil)-6-(1H-pirazol-1-il)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]propanoico (I-116).



El compuesto I-116 se prepara a partir de 121.3 y pirazol de una manera análoga al compuesto I-157. Se aíslan 150 mg de un sólido blanco con un rendimiento general de 30%. EM (ES): *m/z* 439 $(M+H)^+$, 480 $(M+H+CH_3CN)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 1.62 (s, 6H), 2.27 (s, 3H), 2.95 (t, *J*=7.2, 2H), 4.00 (t, *J*=7.2, 2H), 6.52 (t, *J*=2.1, 1H), 7.15-7.28 (m, 5H), 7.73 (d, *J*=2.1, 1H), 8.10 (d, *J*=2.4, 1H), 12.40 (s, 1H).

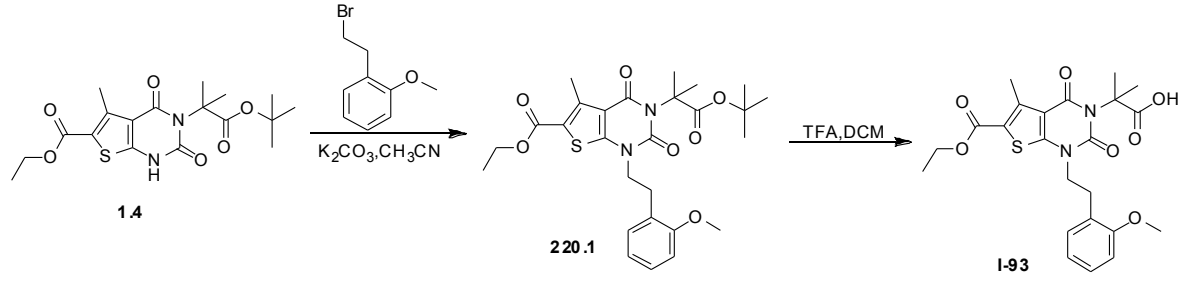
Ejemplo 219: Síntesis del ácido 2-[6-(etoxicarbonil)-1-[2-(2-etilfenil)etil]-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-

100).



El compuesto I-100 se prepara a partir de 1.4 y 9.3 de una manera análoga a la síntesis de 136.2. Se aíslan 0.041 g de un sólido blanco con un rendimiento general de 59% a partir de 1.4. EM (ES): *m/z* 473 $(M+H)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.25 (t, *J*=7.5, 3H), 1.36 (t, *J*=7.5, 3H), 1.25 (s, 6H), 2.76 (c, *J*=7.5, 5H), 3.12 (t, *J*=7.5, 2H), 4.10 (t, *J*=7.5, 2H), 4.32 (c, *J*=7.2, 3H), 7.08-7.20 (m, 4H).

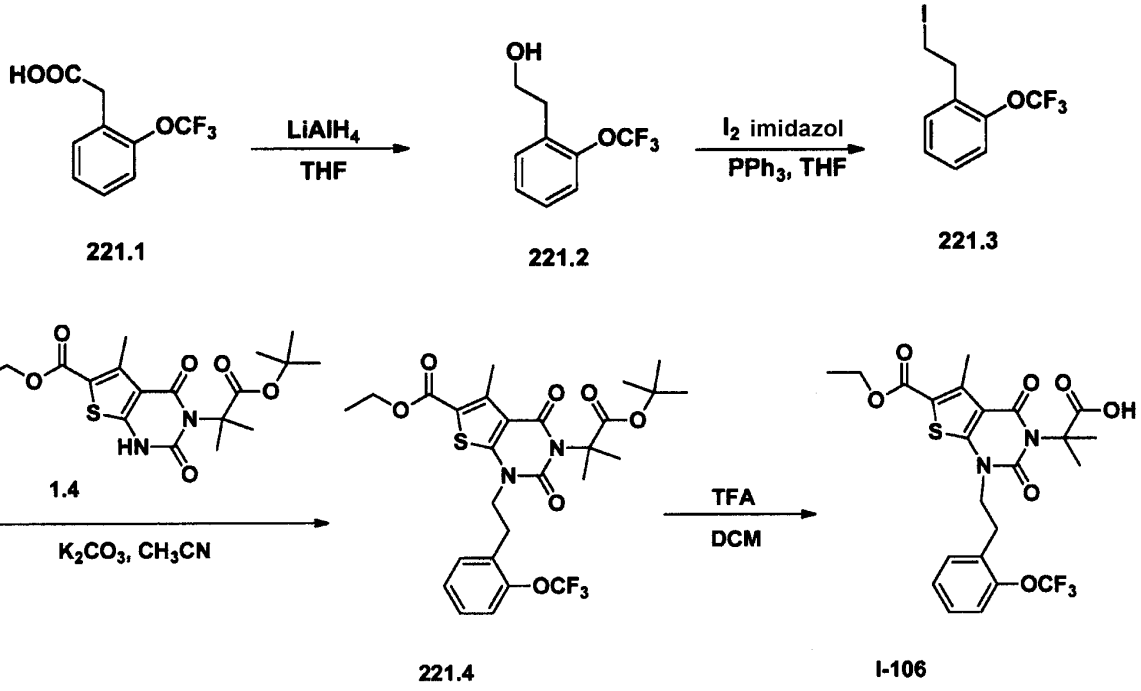
Ejemplo 220: Síntesis del ácido 2-[6-(etoxicarbonil)-1-[2-(2-metoxifenil)etil]-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-93).



El compuesto I-93 se prepara a partir de 1.4 y 1-(2-bromoetoil)-2-metoxibenceno disponible comercialmente de una manera análoga a la síntesis de 136.2. EM (ES): *m/z* 475 $(M+H)^+$. RMN ^1H (DMSO-d_6, 400 MHz): δ 1.29~1.32 (t, 3H), 1.64 (s, 6H), 2.70 (s, 3H), 2.96~2.95 (t, 2H), 3.76 (s, 3H),

4.03~4.07 (t, 2H), 4.25~4.30 (c, 2H), 6.84~6.87 (t, 1H), 6.91~6.93 (d, 1H), 7.12~7.14 (d, 1H), 7.19~7.23 (t, 1H).

Ejemplo 221: Síntesis del ácido 2-[6-(etoxicarbonil)-5-metil-2,4-dioxo-1-[2-[2-(trifluorometoxi)fenil]etil]-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-106).



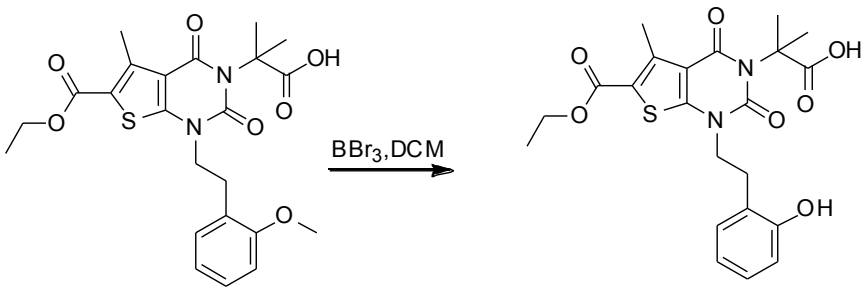
Síntesis del compuesto 221.2. En un matraz de fondo redondo de 100 ml se coloca ácido 2-[2-(trifluorometoxi)fenil]acético (1 g, 4.54 mmol, 1.00 equivalentes), 30 ml de THF y alumano de litio (173 mg, 4.55 mmol, 1.00 equivalentes). La solución resultante se agita durante 2 h a temperatura ambiente. La reacción después se suspende por la adición de 40 ml de NH_4Cl acuoso. La solución resultante se extrae con 3 x 50 ml de acetato de etilo y las

capas orgánicas se combinan y se secan sobre sulfato de sodio anhidro y se concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:20). Esto resulta en 300 mg (32%) de 221.2 como un aceite incoloro.

Síntesis del compuesto 221.3. Se prepara 221.3 a partir de 221.2 de una manera análoga a la síntesis del compuesto 9.3. Se aíslan 300 mg de un aceite incoloro con un rendimiento de 65%.

Síntesis del compuesto I-106. El compuesto I-106 se prepara a partir de 221.3 y 1.4 de una manera análoga a la síntesis de 136.2. Se aíslan 80 mg (rendimiento total, 60%) como un sólido blanco. EM (ES): *m/z* 528.8 $(M+H)^+$, 591.8 $(M+Na+CH_3CN)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ1.26 (t, 3H), 1.56 (s, 6H), 2.67 (s, 3H), 3.05 (t, 2H), 4.04 (t, 2H), 4.26 (c, 2H), 7.24-7.40 (m, 4H).

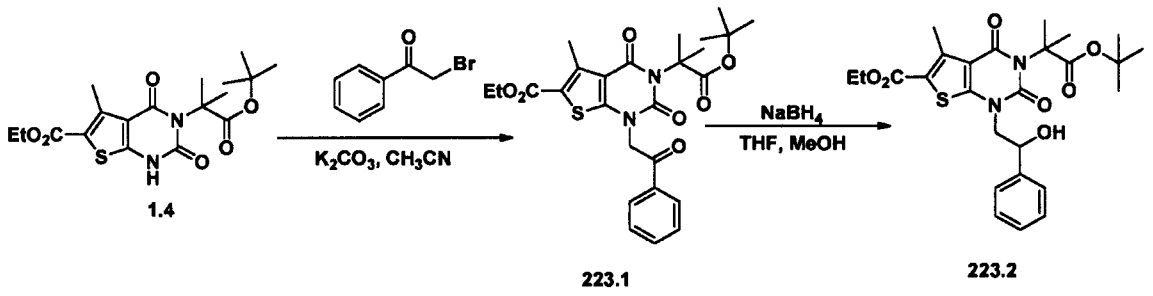
Ejemplo 222: Síntesis del ácido 2-[6-(etoxicarbonil)-1-[2-(2-hidroxifenil)etil]-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-99).

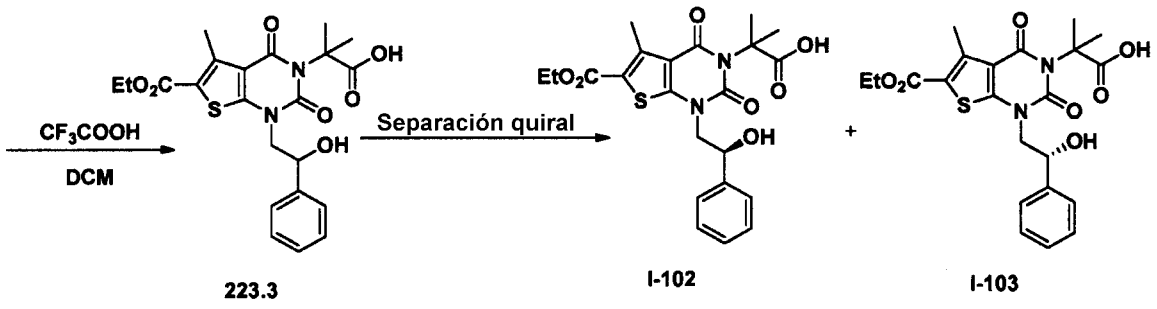


I-93 **I-99**

En un matraz de fondo redondo de 10 ml se coloca I-93 (50 mg, 0.11 mmol, 1.00 equivalentes), 105 mg de BBr_3 y 5 ml de diclorometano. La solución resultante se agita durante la noche a temperatura ambiente. La reacción después se suspende por la adición de 2 ml de agua. La solución resultante se extrae con 3 x 5 ml de acetato de etilo y las capas orgánicas se combinan y concentran bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/hexano (1:2). Esto resulta en 4.6 mg (9%) de I-99 como un aceite incoloro. EM (ES): *m/z* 461 $(M+H)^+$. RMN ^1H (CD_3OD, 300Mz): δ 1.29~1.37 (t, 3H), 1.77 (s, 6H), 2.73 (s, 3H), 3.04~3.09 (t, 2H), 4.13~4.17 (t, 2H), 4.26 ~4.33 (c, 2H), 6.68~6.72 (m, 2H), 6.98~7.03 (m, 2H).

Ejemplo 223: Síntesis del ácido 2-[6-(etoxicarbonil)-1-[(2S)-2-hidroxi-2-feniletil]-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-102) y Ejemplo 224: Síntesis del ácido 2-[6-(etoxicarbonil)-1-[(2S)-2-hidroxi-2-feniletil]-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico





Síntesis del compuesto 223.3. El compuesto 223.3 se prepara a partir de 1.4 y 2-bromo-1-feniletan-1-ona de una manea análoga a la síntesis de I-60 (Ejemplo 203). Se aíslan 140 mg de un sólido blanco con un rendimiento total de 60% a partir de 1.4.

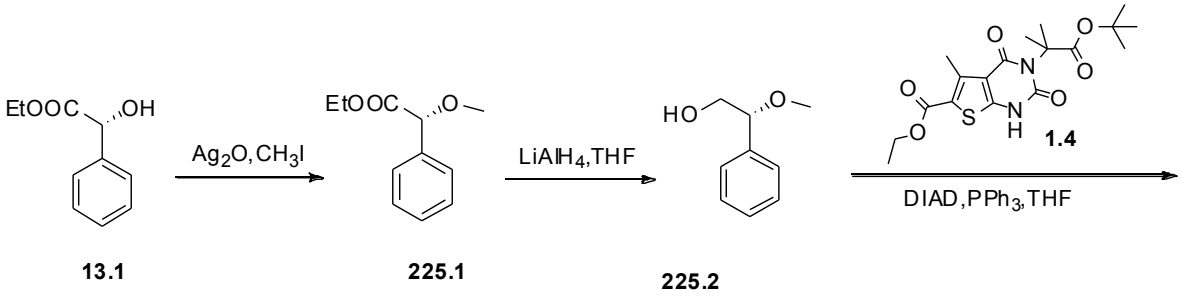
Síntesis de los compuestos I-102 y I-103. Los enantiómeros de 223.3 (140 mg) se aíslan por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): columna: Chiralpak IC(SFC), 2*25 cm, 5 µm; fase móvil: hexanos (TFA 0.1%) y etanol (que se mantiene en etanol 10.0% en 16 min); detector: UV 220/254 nm. Esto resulta en 15.9 mg (11%) de I-102 como un sólido blanco y 15.2 mg (11%) de I-103 como un sólido blanco.

Datos analíticos para I-102: EM (ES): *m/z* 461 $(M+H)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ1.30 (t, 3H), 1.66 (s, 6H), 2.71 (s, 3H), 3.73 (m, 1H), 4.14 (m, 1H), 4.27 (m, 2H), 4.98 (c, 1H), 5.88 (d, 1H), 7.28-7.41 (m, 5H), 12.3 (s,1H).

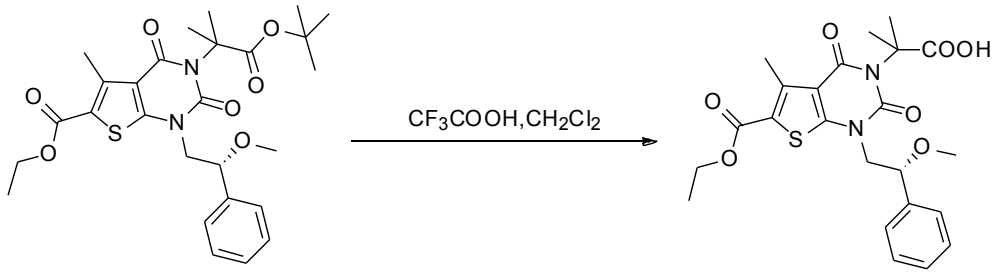
Datos analíticos para I-103: EM (ES): *m/z* 461 $(M+H)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 1.30 (t, 3H), 1.66 (s, 6H), 2.71 (s, 3H), 3.73 (m, 1H), 4.14 (m, 1H), 4.27 (c, 2H),

4.98 (d, 1H), 5.88 (m,1H), 7.28-7.41 (m, 5H), 12.3 (s amplio, 1H).

Ejemplo 225: Síntesis del ácido 2-[6-(etoxicarbonil)-1-[(2R)-2-metoxi-2-feniletil]-5-metil-2,4-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-110).



13.1 225.1 225.2



225.3 I-110

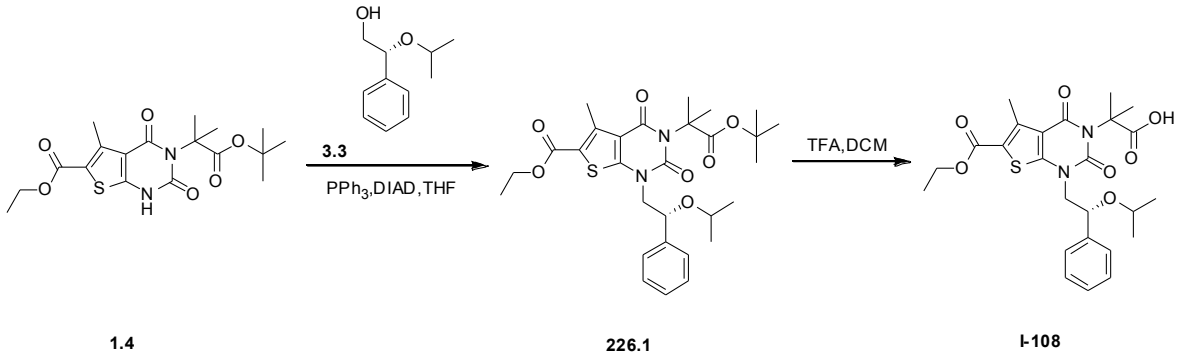
Síntesis del compuesto 225.1. Se prepara 225.1 a partir de 13.1 de una manera análoga a la síntesis de 13.2. Se aíslan 1.26 g (22%) como un aceite incoloro.

Síntesis del compuesto 225.2. En un matraz de fondo redondo de 3 cuellos de 100 ml se colocan 50 ml de tetrahidrofurano y 225.1 (1.26 g, 6.49 mmol, 1.00 equivalentes). Esto es seguido por la adición de $LiAlH_4$ (247 mg, 6.51 mmol, 1.00 equivalentes) en porciones a 0°C. La

solución resultante se agita durante 2 h a 0°C. La reacción después se suspende por la adición de 20 ml de NH_4Cl acuoso. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/hexano (1:5). Esto resulta en 610 mg (62%) de 225.2 como un aceite incoloro.

Síntesis del compuesto I-110. El compuesto I-110 se prepara a partir de 225.2 de una manera análoga a la síntesis de 2.5. Se aíslan 70 mg (78%) de un sólido blanco. EM (ES): *m/z* 475 $(M+H)^+$. RMN ^1H (CD_3OD, 300 MHz): δ 1.34 (m, 3H), 1.75 (s, 6H), 2.74 (s, 3H), 3.27 (s, 3H), 3.92 (m, 1H), 4.10 (m, 1H), 4.28 (m, 2H), 4.66 (m, 1H), 7.37 (m, 5H).

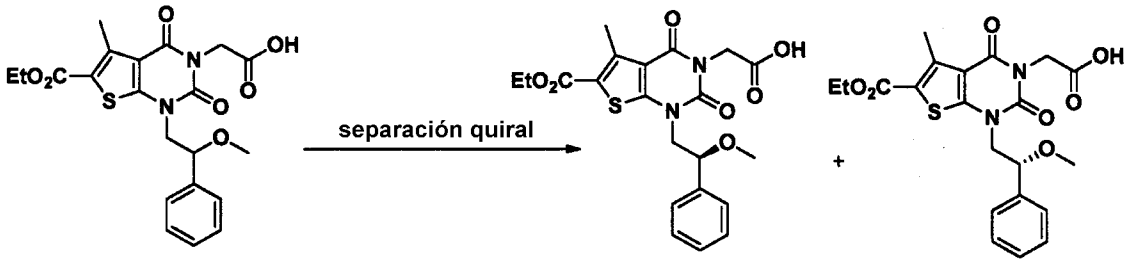
Ejemplo 226: Síntesis del ácido 2-[6-(etoxicarbonil)-5-metil-2,4-dioxo-1-[(2R)-2-fenil-2-(propan-2-iloxi)etil]-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-108).



El compuesto I-108 se prepara a partir de 1.4 y 3.3 de una manera análoga a la síntesis de 2.5. Se aíslan 51.6 mg

(22% general) de un sólido blanco. EM (ES): *m/z* 503 $(M+H)^+$. RMN ^1H ($CDCl_3$, 400 MHz): δ 0.85 (d, 3H), 0.89 (d, 3H), 1.25~1.33 (t, 3H), 1.67~1.71 (d, 6H), 2.73 (s, 3H), 3.41~3.47 (m, 1H), 3.81~3.85 (m, 1H), 4.02~4.11 (m, 1H), 4.27~4.34 (m, 2H), 4.80~4.82 (m, 1H), 7.32~7.37 (m, 1H), 7.41~7.42 (d, 4H), 12.45 (s, 1H).

Ejemplo 227: Síntesis del ácido 2-[6-(etoxicarbonil)-1-[(2S)-2-metoxi-2-feniletil]-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acético (I-104) y Ejemplo 228: Síntesis de 2-[6-(etoxicarbonil)-1-[(2S)-2-metoxi-2-feniletil]-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acético (I-105).



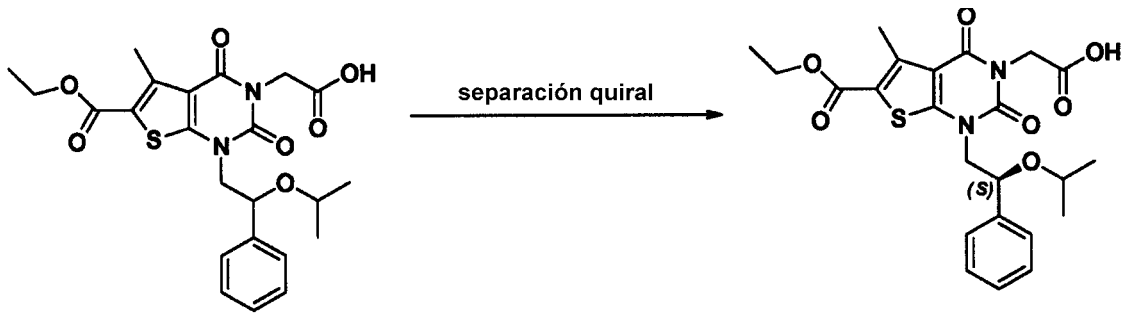
Síntesis de los compuestos I-104 y I-105. Los enantiómeros de I-67 se aíslan por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): columna Chiralpak IC(SFC), 2*25 cm, 5 µm; fase móvil: hexanos (TFA 0.1%) y etanol (que se mantiene en etanol 30% durante 15 min); detector; UV 220/254 nm. Esto resulta en 4.4 mg de I-104 como

un sólido blanco (tR = 11.52 min) y 3.7 mg de I-105 como un sólido blanco (tR = 14.07 min).

Datos analíticos para I-104: EM (ES): *m/z* 446.9 $(M+H)^+$, 509.8 $(M+Na+CH_3CN)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.39 (t, 3H), 2.83 (s, 3H), 3.20 (s, 3H), 4.02 (m, 2H), 4.16 (c, 2H), 4.70 (m, 3H), 7.33-7.46 (m, 5H).

Datos analíticos para I-105: EM (ES): *m/z* 446.9 $(M+H)^+$, 509.8 $(M+Na+CH_3CN)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.39 (t, 3H), 2.83 (s, 3H), 3.21 (s, 3H), 4.02 (m, 2H), 4.16 (c, 2H), 4.70 (m, 3H), 7.33-7.46 (m, 5H).

Ejemplo 229: Síntesis del ácido (S)-2-(6-(etoxicarbonil)-1-(2-isopropoxi-2-feniletil)-5-metil-2,4-dioxo-1,2-dihidrotieno[2,3-d]pirimidin-3(4H)-il)acético (I-96).

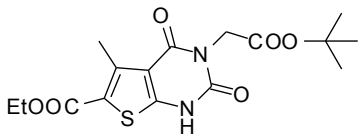


I-89 I-96

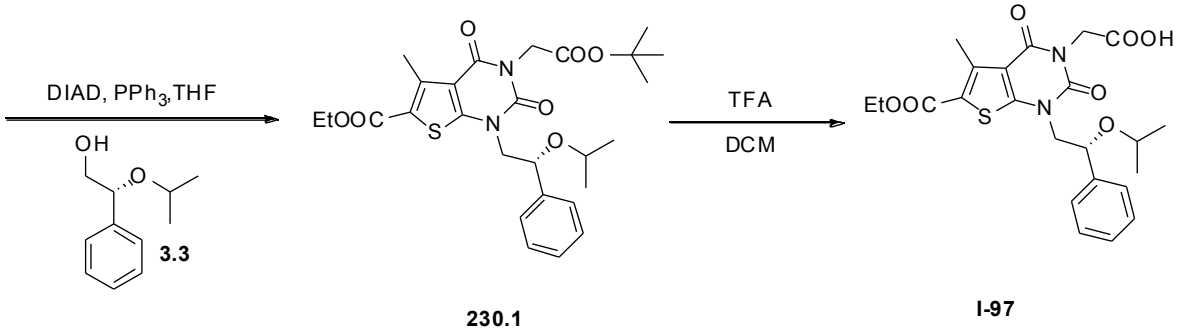
El enantiómero (S) de I-89 se aísla por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): columna: Chiralpak IC(SFC), 2*25 cm, 5 µm; fase móvil: hexanos y etanol (0.1% DEA) (que se mantiene en etanol 10.0%

(DEA 0.1%) en 25 min); detector: UV 220/254 nm. Se obtienen 1.7 mg (tR = 14.9 min, 9%) de producto como un sólido blanco. EM (ES): *m/z* 475 $(M+H)^+$, 497 $(M+Na)^+$, 538 $(M+Na+CH_3CN)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 0.98 (d, 3H), 1.03 (d, 3H), 1.42 (t, 3H), 2.84 (s, 3H), 3.51 (m, 1H), 3.98 (m, 1H), 4.22 (m, 1H), 4.40 (m, 2H), 4.75 (m, 2H), 4.92 (m, 1H), 7.33-7.49 (m, 5H).

Ejemplo 230: Síntesis del ácido (R)-2-(6-(etoxicarbonil)-1-(2-isopropoxi-2-feniletil)-5-metil-2,4-dioxo-1,2-dihidrotieno[2,3-d]pirimidin-3(4H-il)acético (I-97).



135.3



3.3

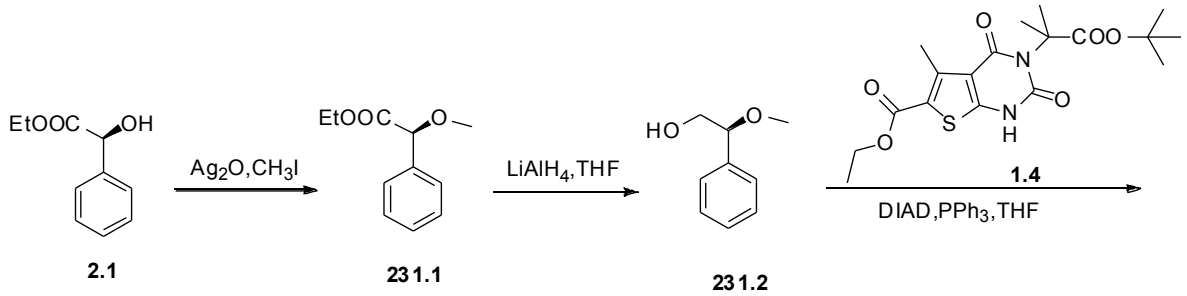
230.1

I-97

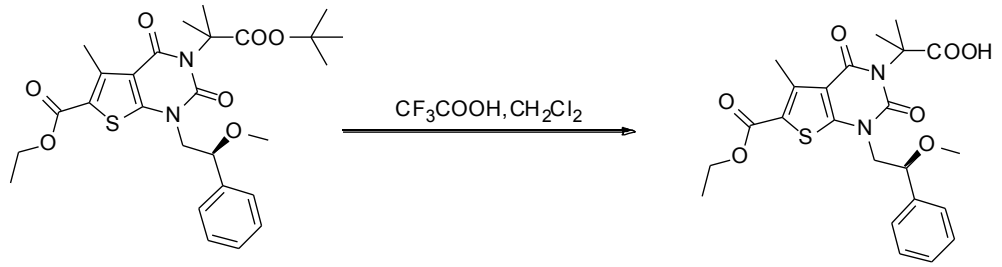
El compuesto I-97 se prepara a partir de 135.3 y 3.3 de una manera análoga a la síntesis del compuesto 2.5. Se aíslan 180 mg de un sólido blanco (tR = 17.8 min) con un rendimiento general de 21%. EM (ES): *m/z* $(M+H)^+$ 475. RMN ^1H (CD_3OD, 300 MHz): δ 0.90(d, *J* = 6.0 Hz, 3H), 0.97(d, *J* = 6.3 Hz, 3H), 1.35 (t, 3H), 2.80 (s, 3H), 3.48 (m, 1H), 3.88 (m, 1H), 4.16 (m,1H), 4.32 (m, 2H), 4.68 (m, 2H), 4.89 (m, 1H),

7.25-7.44 (m, 5H).

Ejemplo 231: Ácido 2-[6-(etoxicarbonil)-1-[(2S)-2-metoxi-2-feniletil]-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-111).



2.1 231.1 231.2

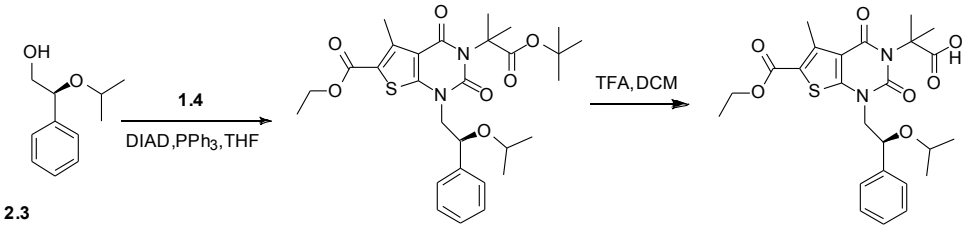


231.3 I-111

El compuesto I-111 se prepara a partir de 2.1 y 1.4 de una manera análoga a la síntesis del compuesto I-110 (Ejemplo 225). Se aíslan 65 mg de un sólido blanco con un rendimiento de 11% a partir de 2.1. EM (ES): *m/z* 475 $(M+H)^+$. RMN ^1H (CD_3OD, 300 MHz): δ 1.34 (t, 3H), 2.00 (s, 6H), 2.74 (s, 3H), 3.18 (s, 3H), 3.93 (m, 1H), 4.10 (m, 1H), 4.28 (c, 2H), 4.65 (m, 1H), 7.34 (m, 5H).

Ejemplo 232: Síntesis del ácido 2-[6-(etoxicarbonil)-5-metil-2,4-dioxo-1-[(2S)-2-fenil-2-(propan-2-iloxi)etil]-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-

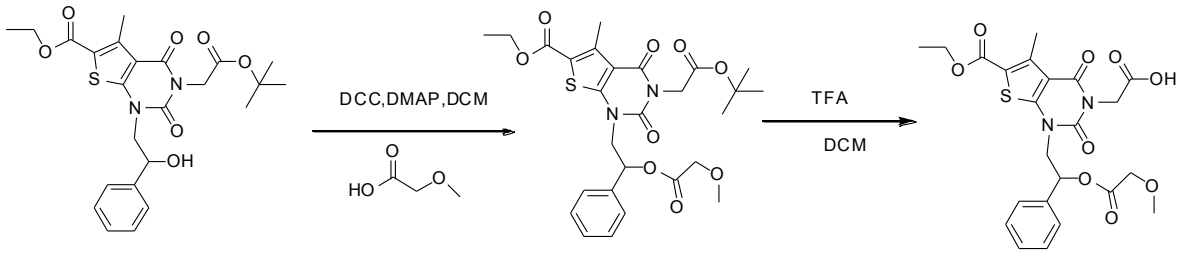
metilpropanoico (I-109).



2.3 232.1 I-109

El compuesto I-109 se prepara a partir de 2.3 y 1.4 de una manera análoga a la síntesis de 2.5. Se aíslan 11.3 mg de un sólido blanco con un rendimiento general de 10% a partir de 1.4. EM (ES): *m/z* 503 $(M+H)^+$. RMN ^1H (CD_3OD, 400 MHz): δ 0.97~1.04 (m, 6H), 1.37~1.41 (t, 3H), 1.79~1.81 (d, 6H), 2.79 (s, 3H), 3.48~3.51 (m, 1H), 3.82~3.87 (m, 1H), 4.14~4.17 (m, 1H), 4.32~4.38 (m, 2H), 4.87~4.92 (m, 1H), 7.31~7.34 (m, 1H), 7.38~7.42 (t, 2H), 7.45~7.47 (d, 2H).

Ejemplo 233: Síntesis del ácido 2-[6-(etoxicarbonil)-1-[2-[(2-metoxiacetil)oxi]-2-feniletil]-5-metil-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]acético (I-101).



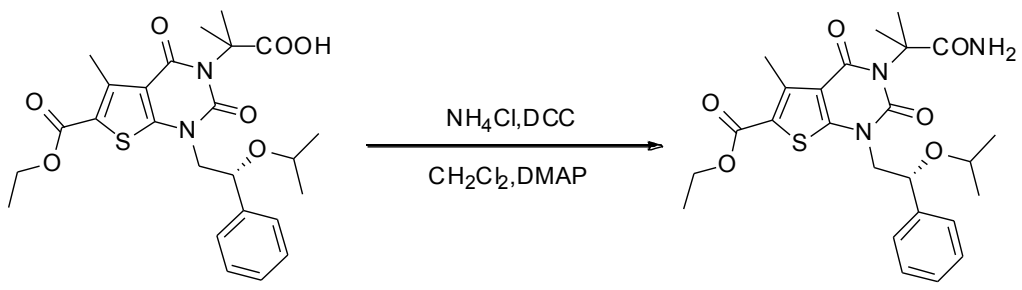
203.2 233.1 I-101

Síntesis del compuesto 233.1. En un matraz de fondo redondo de 50 ml se coloca 203.2 (200 mg, 0.41 mmol, 1.00 equivalentes), DCC (101 mg, 0.49 mmol,

1.20 equivalentes), 4-dimetilaminopiridina (90 mg, 0.74 mmol, 1.80 equivalentes), 10 ml de diclorometano y ácido 2-metoxiacético (73 mg, 0.81 mmol, 1.98 equivalentes). La solución resultante se agita durante la noche a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:10). Esto resulta en 190 mg (85%) de 233.1.

Síntesis del compuesto I-101. El compuesto I-101 se prepara a partir de 233.1 de una manera análoga a la síntesis del compuesto 2.5. Se aíslan 60.4 mg (67%) de un sólido blanco. EM (ES): *m/z* 527 $(M+H)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 1.33 (t, 3H), 2.74 (s, 3H), 3.16 (s, 3H), 3.91 (d, 1H), 4.09 (d, 1H), 4.34 (m, 4H), 4.53 (s, 2H), 6.18 (m, 1H), 7.35-7.44 (m, 5H) 13.05 (s amplio, 1H).

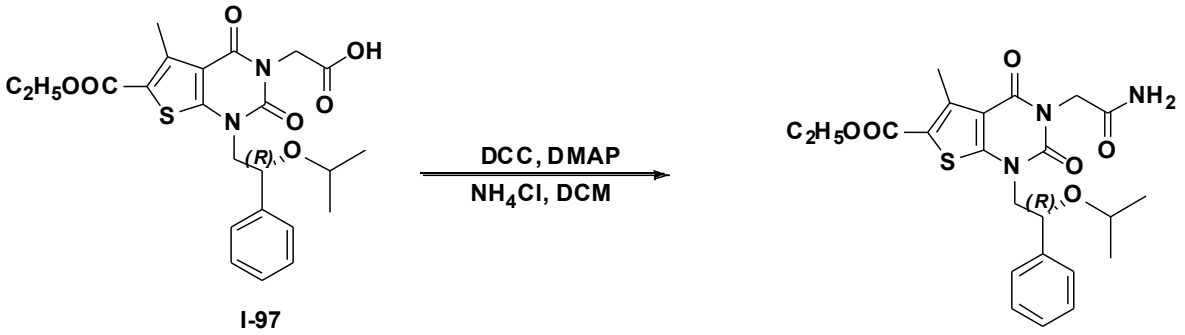
Ejemplo 234: Síntesis de 3-(1-carbamoil-1-metiletil)-5-metil-2,4-dioxo-1-[(2R)-2-fenil-2-(propan-2-iloxi)etil]-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxilato de etilo (I-115).



I-108 **I-115**

El compuesto I-115 se prepara a partir de I-108 (Ejemplo 226) y cloruro de amonio de una manera análoga a la síntesis de I-121 (Ejemplo 4). Se aíslan 0.059 g (42%) de un sólido blanco. EM (ES): *m/z* 524 $(M+Na)^+$. RMN ^1H (DMSO-d_6, 300 MHz): δ 0.90 (m, 6H), 1.26 (t, 3H), 1.63 (d, *J* = 8.1 Hz, 6H), 3.29 (s, 3H), 3.40 (m, 1H), 3.73 (m, 1H), 4.03 (m, 1H), 4.26 (m, 2H), 4.74 (m, 1H), 7.23 (m, 5H).

Ejemplo 235: Síntesis de 3-(carbamoilmetil)-5-metil-2,4-dioxo-1-[(2R)-2-fenil-2-(propan-2-iloxi)etil]-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxilato de etilo (I-112).

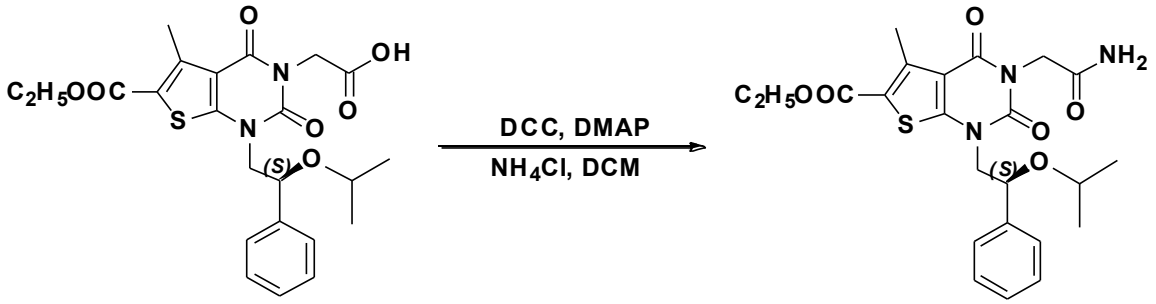


I-97 I-112

El compuesto I-112 se prepara a partir de I-97 (Ejemplo 230) y cloruro de amonio de una manera análoga a la síntesis de I-121 (Ejemplo 4). Se aíslan 53.7 mg (41%) de un sólido blanco. EM (ES): *m/z* 474 $(M+H)^+$. RMN ^1H (300 MHz, CD_3OD): δ 0.97(d, 3H), 0.99 (d, 3H), 1.37 (t, 3H), 2.78 (s, 3H), 3.49 (m, 1H), 3.88 (m, 1H), 4.15 (dd, 1H), 4.32 (c, 2H), 4.65 (s, 2H) , 4.87 (m, 1H), 7.25-7.44 (m, 5H).

Ejemplo 236: Síntesis de 3-(carbamoilmetil)-5-metil-2,4-dioxo-1-[(2S)-2-fenil-2-(propan-2-iloxi)etil]-1H,2H,3H,4H-

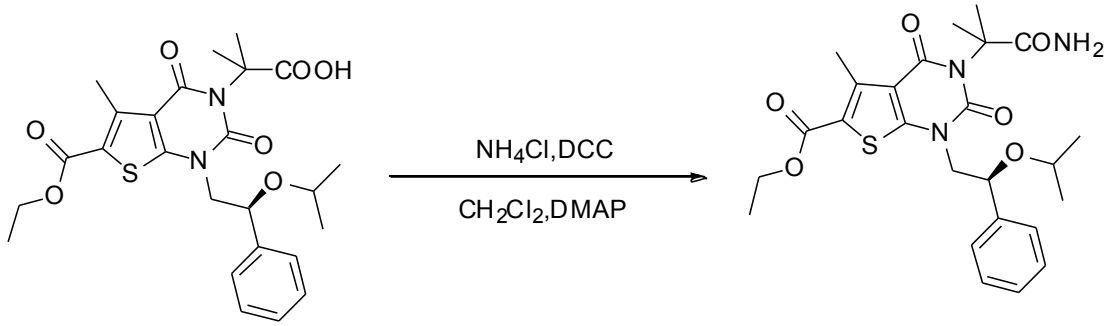
tieno[2,3-d]pirimidin-6-carboxilato de etilo (I-113).



I-96 I-113

El compuesto I-113 se prepara a partir de I-96 (Ejemplo 229) y cloruro de amonio de una manera análoga a la síntesis de I-121 (Ejemplo 4). EM (ES): *m/z* 474 $(M+H)^+$. RMN ^1H (300 MHz, CD_3OD): δ 0.97 (d, 3H), 0.99 (d, 3H), 1.37 (t, 3H), 2.78 (s, 3H), 3.49 (m, 1H), 3.88 (m, 1H), 4.15 (dd, 1H), 4.32 (c, 2H), 4.65 (s, 2H), 4.87 (m,1H), 7.25-7.44 (m, 5H).

Ejemplo 237: Síntesis de 3-(1-carbamoil-1-metiletil)-5-metil-2,4-dioxo-1-[(2S)-2-fenil-2-(propan-2-iloxi)etil]-1H,2H,3H,4H-tieno[2,3-d]pirimidin-6-carboxilato de etilo (I-114).

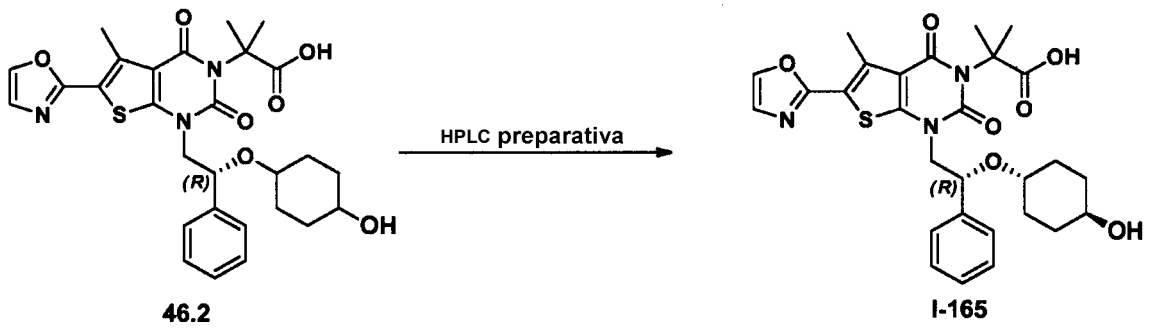


I-109 I-114

El compuesto I-114 se prepara a partir de I-109 (Ejemplo 232) y cloruro de amonio de una manera análoga a la

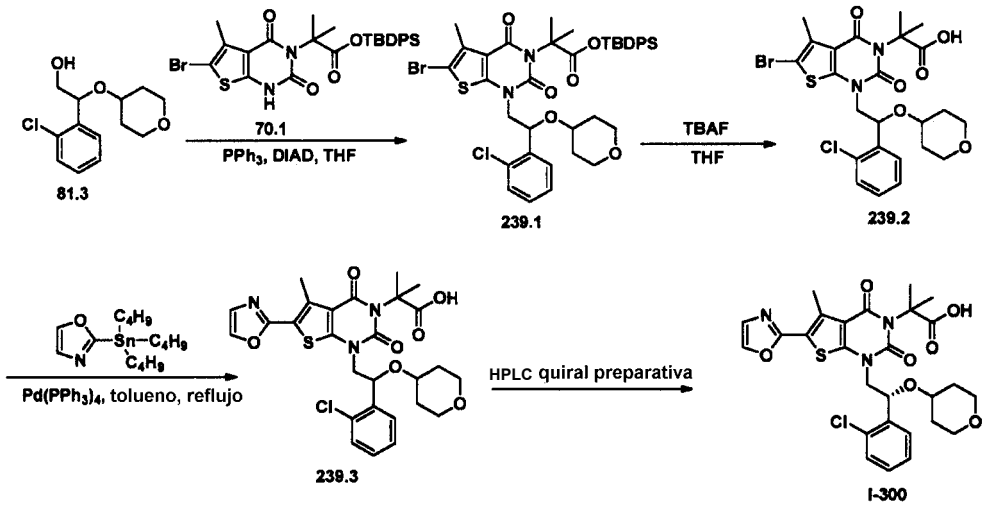
síntesis de I-121 (Ejemplo 4). Se aíslan 0.064 g (64%) de un sólido blanco. EM (ES): *m/z* 524 $(M+H)^+$. RMN ^1H (DMSO-d_6, 300 MHz): δ 0.89 (m, 6H), 1.26 (c, 3H), 1.62 (d, J = 8.7 Hz, 6H), 2.67 (s, 3H), 3.38 (m, 1H), 3.76 (m, 1H), 4.03 (m, 1H), 4.26 (m, 2H), 4.75 (m, 1H), 7.35 (m, 5H).

Ejemplo 238: Síntesis del ácido 2-[1-[(2R)-2-[(4-hidroxiciclohexil)oxi]-2-feniletil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-165).



El enantiómero (R) del compuesto 46.2 (30 mg) se aísla por *HPLC* preparativa bajo las siguientes condiciones (Waters): Columna: Xbridge Shield RP18 OBD 5 µm, 19*150 mm; fase móvil: agua (NH_4HCO_3 50 mM) y CH_3CN (CH_3CN 6.0% hasta 50.0% en 14 min); detector: UV 254/220 nm. Se obtienen 11.1 mg de I-165 (tR = 8.82) como un sólido blanco. EM (ES): *m/z* 554 $(M+H)^+$, 576 $(M+Na)^+$, 617 $(M+Na+CH_3CN)^+$. RMN ^1H (300MHz, CD_3OD): δ 1.29-1.38 (m, 6H), 1.44-1.64 (m, 2H), 1.75 (s, 6H), 2.77 (s, 3H), 3.50 (m, 1H), 3.81 (m, 1H), 4.19 (m, 1H), 4.95 (m, 1H), 7.24-7.45 (m, 6H), 7.94 (s, 1H).

Ejemplo 239: Síntesis del ácido 2-[1-[(2R)-2-(2-clorofenil)-2-(oxan-4-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-300).



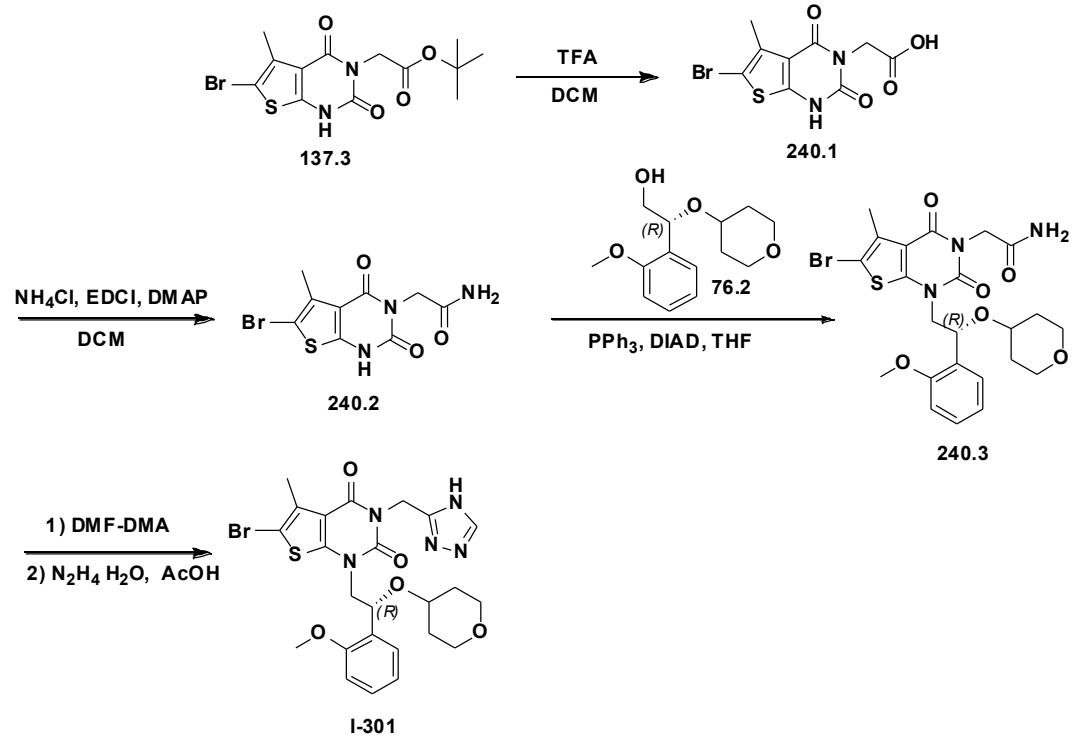
Síntesis del compuesto 239.2. El compuesto 239.2 se prepara a partir de 70.1 y 81.3 de una manera análoga a I-264 (Ejemplo 96). Se aíslan 180 mg de un aceite incoloro con un rendimiento de 36% a partir de 70.1.

Síntesis del compuesto 239.3. El compuesto 239.3 se prepara a partir de 239.2 de una manera análoga a la síntesis de I-120 (Ejemplo 2). Se aíslan 40 mg (23%) de un aceite incoloro.

Síntesis del compuesto I-300. Se purifican 41 mg del producto crudo por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): Columna: Chiralpak IA, 2*25 cm 5 µm; fase móvil: hexanos e IPA (que se mantiene en IPA 20% durante 22 min); detector: UV 220/254 nm. La purificación

proporciona 2.8 mg (7%) del Compuesto I-300 como un sólido blanco. EM (ES): *m/z* 574 $(M+H)^+$. RMN ^1H (300MHz, CD_3OD): δ 8.00 (s, 1H), 7.75 (d, 1H, *J* = 6.0 Hz), 7.45 (m, 2H), 7.35 (d, 1H, *J* = 5.1 Hz), 7.29 (s, 1H), 5.49 (c, 1H, *J* = 5.1Hz), 4.32 (m, 1 H), 3.99 (m, 1H), 3.70 (m, 2 H), 3.50 (m, 1H), 3.40 (m, 2H), 2.83 (s, 3H), 1.82 (s, 3H), 1.80 (s, 3H), 1.75 (m, 2H), 1.52 (m, 2H).

Ejemplo 240: Síntesis de 6-bromo-1-[(2R)-2-(2-metoxifenil)-2-oxan-4-iloxi)etil]-5-metil-3-(4H-1,2,4-triazol-3-ilmetil)-1H,2H,3H,4H-tieno[2,3-d]pirimidin-2,4-diona (I-301).



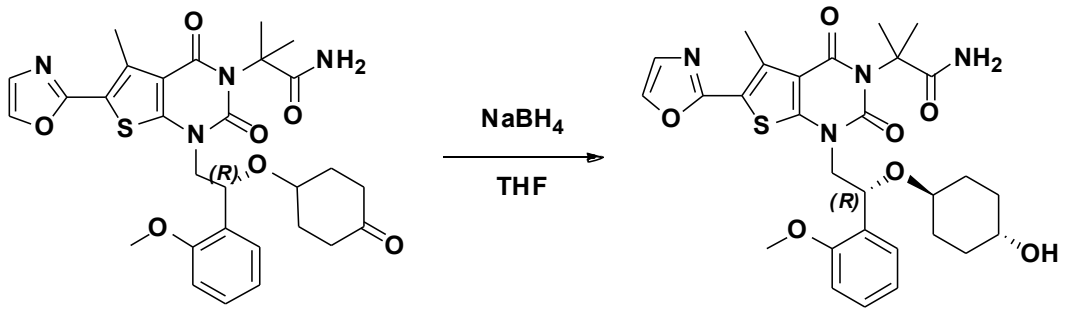
Síntesis del compuesto 240.1. El compuesto 240.1 se prepara a partir de 137.3 de una manera análoga a la síntesis de 136.2 a partir de 136.1. Se aíslan 1.9 g de un sólido

blanco con un rendimiento de 97%.

Síntesis del compuesto 240.3. El compuesto 240.3 se prepara a partir de 240.1 y 76.2 de una manera análoga a la síntesis de I-285 a partir de 141.1 (Ejemplo 141). Se aíslan 106 mg de un sólido blanco con un rendimiento total de 6%.

Síntesis del compuesto I-301. El compuesto I-301 se prepara a partir de 240.3 de una manera análoga a la síntesis de I-289 a partir de I-285 (Ejemplo 145). Se aíslan 40 mg de un sólido blanco con un rendimiento de 43%. EM (ES): *m/z* 576 $(M+H)^+$. RMN ^1H (300MHz, d_6-DMSO): δ 13.81 (1H, s amplio), 8.42 (1H, s), 7.49-7.46 (1H, dd, J_1 = 7.2 Hz, J_2 = 1.5 Hz), 7.31 (1H, m), 7.05-6.98 (2H, m), 5.23-5.16 (3H, m), 4.15-4.09 (1H, m), 3.77-3.75 (4H, m), 3.53-3.48 (2H, m), 3.29-3.24 (2H, m), 2.36 (3H, s), 1.59 (2H, m), 1.28-1.15 (2H, m).

Ejemplo 241: Síntesis de 2-[1-[(2R)-2-[(4-hidroxiciclohexil)oxi]-2-(2-metoxifenil)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanamida (I-302).



129.1 I-302

El compuesto I-302 se prepara a partir de 129.1 de una manera análoga a la síntesis de I-279 a partir de 129.1. El enantiómero deseado se aísla por *HPLC* preparativa bajo las siguientes condiciones (Waters): Columna: HPrepC-012(T) Xbridge Prep Phenyl 5 µm, 19*150 mm; fase móvil: agua (50 mM NH_4HCO_3) y CH_3CN (30.0% CH_3CN hasta 70.0% en 15 min); detector: UV 254/220 nm. Esto resulta en 17.4 mg (3%) de I-302 (9.34 min) como un sólido blanco. EM (ES): *m/z* 605 $(M+Na)^+$. RMN ^1H (300 MHz, DMSO-d_6): δ 1.02-1.08 (m, 4H), 1.21 (m, 1H), 1.59 (m, 4H), 1.66 (d, 6H), 2.74 (s, 3H), 3.17 (m,1H), 3.78 (s, 3H), 3.99 (m, 2H), 4.29 (s, 1H), 5.28 (t, 1H), 6.79-7.28 (m, 4H), 7.30 (m,1H), 7.37 (s,1H), 7.47 (m, 1H), 8.21 (s, 1H).

Ejemplo 242: Síntesis del ácido (S)-2-(1-(2-(2-cianometil)fenil)-2-((tetrahidro-2H-piran-4-il)oxi)etil)-5-metil-6-(oxazol-2-il)-2,4-dioxo-1,2-dihidrotieno[2,3-d]pirimidin-3(4H)-il)-2-metilpropanoico (I-303).

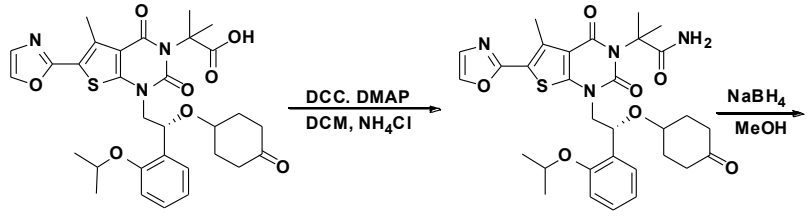


154.7 I-303

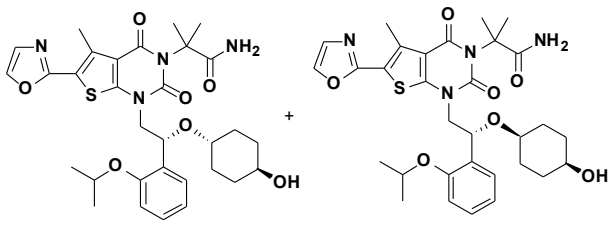
El enantiómero S de 154.7 se aísla por *HPLC* preparativa quiral bajo las siguientes condiciones: columna: CHIRALPK IC-3; fase móvil; hexanos (AcOH 0.1%):IPA = 70:30;

detector: UV 254 nm; tiempo de retención: 23.375 min. Se obtienen 11.4 mg (sólido blanco) del producto deseado. EM (ES): *m/z* 579 $(M+H)^+$, 601 $(M+Na)^+$. RMN ^1H (400 MHz, DMSO-d_6): δ 12.41 (s amplio, 1 H) , 8.26 (s, 1H), 7.63 (d, 1H), 7.49-7.42 (m, 4H), 5.12 (d, 1H), 4.31-4.16 (m, 3H), 3.70 (s, 1H), 3.53 (d, 1H), 3.43-3.32 (m, 2H), 3.25-3.20 (m, 2H), 2.78 (s, 3H), 1.72-1.62 (m, 8H), 1.33-1.21 (m, 2H).

Ejemplo 243: Síntesis de 2-(1-((R)-2-(((1r,4R)-4-hidroxiciclohexil)oxi)-2-(2-isopropoxifenil)etil)-5-metil-6-(oxazol-2-il)-2,4-dioxo-1,2-dihidrotieno[2,3-d]pirimidin-3(4H)-il)-2-metilpropanamida (I-304) y Ejemplo 244: Síntesis de 2-(1-((R)-2-(((1s,4S)-4-hidroxiciclohexil)oxi)-2-(2-isopropoxifenil)etil)-5-metil-6-(oxazol-2-il)-2,4-dioxo-1,2-dihidrotieno[2,3-d]pirimidin-3(4H)-il)-2-metilpropanamida (I-305).



150.7 242.1



I-304 I-305

Síntesis del compuesto 242.1. Se prepara el

compuesto 242.1 a partir de 150.7 de una manera análoga a I-121 (Ejemplo 4). Se aíslan 1.6 g (84%) de un sólido blanco.

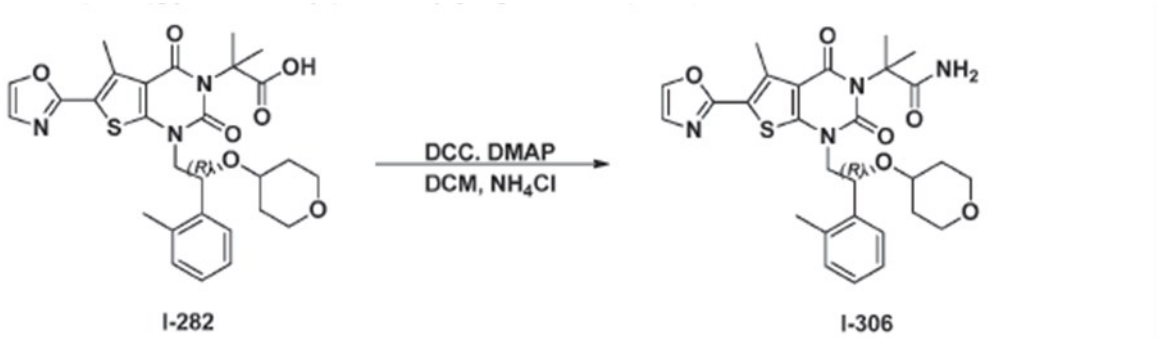
Síntesis de los compuestos I-304 y I-305. En un matraz de fondo redondo de 50 ml se colocan 242.1 (1.6 g, 2.63 mmol, 1.00 equivalentes) y 20 ml de metanol. Esto es seguido por la adición de $NaBH_4$ (208 mg, 5.50 mmol, 2.09 equivalentes) a 0°C. La solución resultante se agita durante la noche a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se purifica por cromatografía en capa delgada revelado con diclorometano/MeOH/HOAc (30:1:0.15). Esto resulta en 86.4 mg (5%) de I-304 como un sólido blanco y 270 mg (17%) de I-305 como un sólido blanco.

Datos analíticos para I-304: EM (ES): *m/z* 633 $(M+Na)^+$. RMN ^1H (400 MHz, CD_3OD): δ 1.15-1.39 (m, 10H), 1.69-1.80 (m, 10H), 2.82 (s, 3H), 3.17 (m, 1H), 3.52 (m, 1H), 3.95 (m, 1H), 4.18 (m, 1H), 4.69 (m, 1H), 5.42 (t, 1H), 6.99 (m, 2H), 7.28 (m, 2H), 7.52 (m, 1H), 8.01 (s, 1H).

Datos analíticos para I-305: EM (ES): *m/z* 633 $(M+Na)^+$. RMN ^1H (400 MHz, CD_3OD): δ 1.31-1.49 (m, 12H), 1.70-1.83 (m, 8H), 2.82 (s, 3H), 3.50 (m, 1H), 4.02-4.22 (m, 2H), 4.69 (m, 1H), 5.43 (t, 1H), 6.99 (m, 2H), 7.28 (m, 2H), 7.55 (m, 1H), 7.98 (s, 1H).

Ejemplo 244: Síntesis de 2-[1-[(2R)-2-[(4-hidroxiciclohexil)oxi]-2-[2-(propan-2-iloxi)fenil]etil]-5-

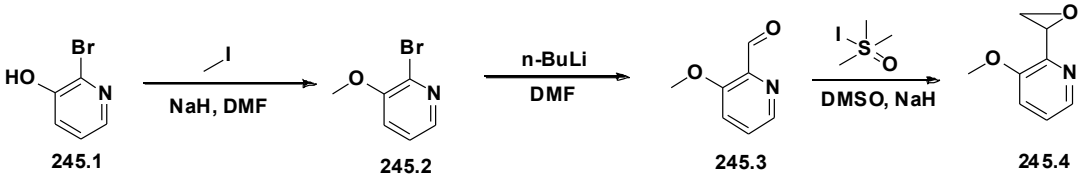
metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanamida (I-306).



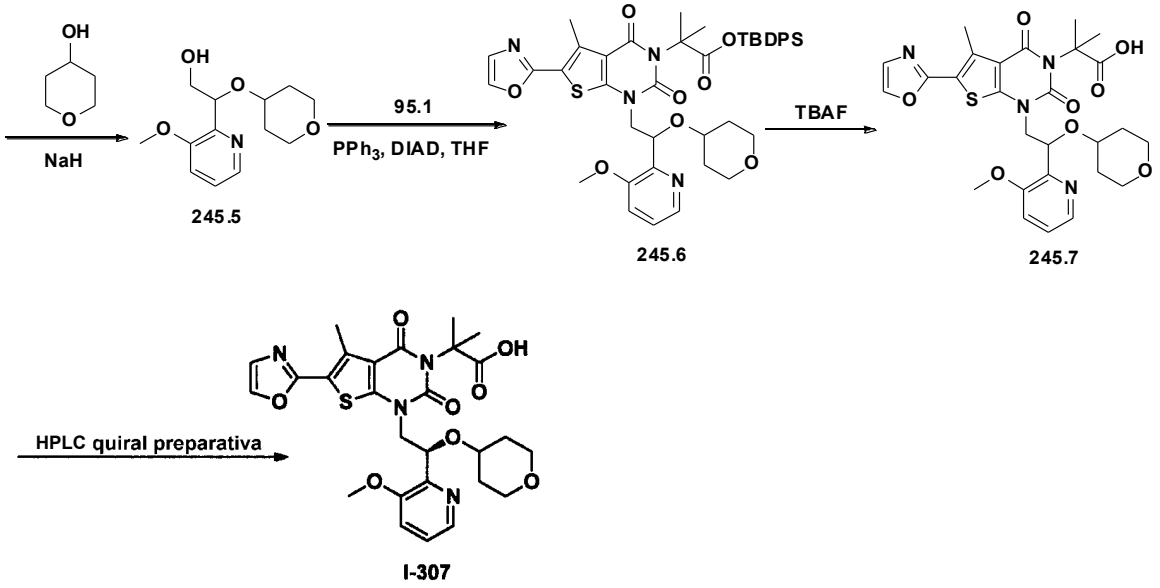
I-282 I-306

El compuesto I-306 se prepara a partir de I-282 de una manera análoga a la síntesis de I-121 (Ejemplo 4). EM (ES): *m/z* 575 $(M+Na)^+$. RMN ^1H (400 MHz, DMSO-d_6): δ 1.12-1.30 (m, 2H), 1.58-1.71 (m, 8H), 2.43-2.51 (s, 3H), 2.75 (s, 3H), 3.19-3.24 (m, 2H), 3.33-3.49 (m, 2H), 3.51-353 (m, 1H), 4.17-4.20 (m, 1H), 5.10-5.13 (m, 1H), 6.80 (s amplio, 1H), 7.20 (s amplio, 1H), 7.21-7.31 (m, 3H) , 7.40 (s, 1H), 7.54 (m, 1H), 8.24 (s, 1H).

Ejemplo 245: Síntesis del ácido 2-[1-[(2R)-2-(3-metoxipiridin-2-il)-2-(oxan-4-iloxi)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-307).



245.1 245.2 245.3 245.4



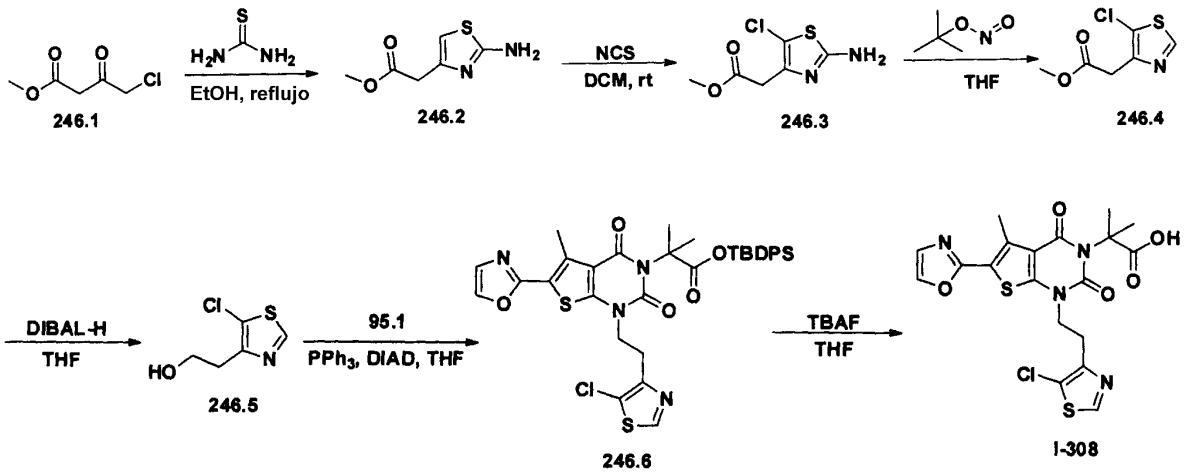
Síntesis del compuesto 245.4. El compuesto 245.4 se prepara a partir de 245.1 de una manera análoga a la síntesis de 149.4 a partir de 149.1. Se aíslan 500 mg de un aceite amarillo con un rendimiento total de 5%.

Síntesis del compuesto 245.5. El compuesto 245.5 se prepara a partir de 245.4 de una manera análoga a la síntesis de 73.2 a partir de 73.1. Se aíslan 200 mg (24%) de un aceite incoloro.

Síntesis del compuesto I-307. El compuesto I-307 se prepara a partir de 245.4 de una manera análoga a la síntesis del compuesto I-265 (Ejemplo 97). Purificación: Se aíslan 20 mg de I-307 por *HPLC* preparativa quiral bajo las siguientes condiciones (Gilson Gx 281): Columna: Chiralpak IC, 2*25 cm, 5 µm; fase móvil: hexanos y EtOH (HAC 0.1%) (que se mantiene en EtOH 30.0% (HAC 0.1%) durante 13 min); detector: UV 254/220

nm. Se aíslan 2.4 mg de I-307 (tiempo de retención, 10.9 min) como un sólido blanco. EM (ES): *m/z* 571 $(M+H)^+$, 593 $(M+Na)^+$. RMN ^1H (300 MHz, CD_3OD): δ 1.33-1.48 (m, 2H), 1.67-1.75 (m, 8H), 2.67 (s, 3H), 3.21 (m, 2H), 3.63-3.70 (m, 6H), 4.32 (m, 1H), 4.57 (m, 1H), 6.20 (m, 1H), 7.11 (m, 1H), 7.29 (d, 2H), 7.82 (s, 1H), 8.09 (m, 1H).

Ejemplo 246: Síntesis del ácido 2-[1-[2-(5-cloro-1,3-tiazol-4-il)etil]-5-metil-6-(1,3-oxazol-2-il)-2,4-dioxo-1H,2H,3H,4H-tieno[2,3-d]pirimidin-3-il]-2-metilpropanoico (I-308).



Síntesis de 246.2. En un matraz de fondo redondo de 3 cuellos de 1000 ml se coloca 4-cloro-3-oxobutanoato de metilo (28 g, 185.97 mmol, 1.00 equivalentes), tiourea (15.2 g, 199.68 mmol, 1.07 equivalentes) y etanol (400 ml, 46.69 equivalentes). La solución resultante se calienta a reflujo durante 4 h. Los sólidos se recolectan por filtración. Se obtienen 20 g (62%) de 246.2 como un sólido amarillo claro.

Síntesis de 246.3. En un matraz de fondo redondo de 3 cuellos de 50 ml se coloca 246.2 (10 g, 58.07 mmol, 1.00 equivalentes) y 40 ml de diclorometano. Esto es seguido por la adición de NCS (7.76 g, 58.11 mmol, 1.00 equivalentes) a gotas con agitación a 0°C. La solución resultante se agita durante la noche a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:5). La purificación proporciona 1 g (crudo) de 246.3 como un sólido amarillo.

Síntesis de 246.4. En un matraz de fondo redondo de 3 cuellos de 100 ml se coloca 246.3 (1 g, 4.84 mmol, 1.00 equivalentes), 40 ml de tetrahidrofurano y nitrito de terbutilo (8.98 g, 87.08 mmol, 18.00 equivalentes). La solución resultante se agita durante 0.5 h a temperatura ambiente. La mezcla resultante se concentra bajo vacío. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:10). La purificación proporciona 200 mg (22%) de 246.4 como un aceite amarillo.

Síntesis de 246.5. En un matraz de fondo redondo de 3 cuellos de 100 ml, purgado y mantenido con una atmósfera inerte de nitrógeno se coloca 246.4 (200 mg, 1.04 mmol, 1.00 equivalentes) y 50 ml de tetrahidrofurano. Esto es seguido por la adición de DIBAL-H (5 ml, 25% en tolueno) a gotas con agitación a −78°C. La solución resultante se agita

durante 0.5 h a −78°C. La reacción después se suspende por la adición de 50 ml de NH_4Cl acuoso. La solución resultante se extrae con 3 x 100 ml de acetato de etilo y las capas orgánicas se combinan. El residuo se aplica sobre una columna de gel de sílice con acetato de etilo/éter de petróleo (1:5). La purificación proporciona 40 mg (23%) de 246.5 como un aceite amarillo.

Síntesis del compuesto I-308. El compuesto I-308 se prepara a partir de 246.5 y 95.1 de una manera análoga a la síntesis del compuesto I-264 (Ejemplo 96). Se aíslan 11.2 mg (14% a partir de 95.1) de I-308 como un sólido blanco. EM (ES): *m/z* 481 $(M+H)^+$. RMN ^1H (400 MHz, DMSO-d_6): δ 1.67 (s, 6H), 2.75 (s, 3H), 3.09-3.13 (t, 2H), 4.14-4.18 (t, 2H), 7.40 (s, 1H), 7.48 (s, 1H), 8.24 (s, 1H).

Los compuestos adicionales de fórmula I se pueden preparar de una manera sustancialmente similar a lo descrito en lo anterior. Los datos de espectroscopía de masas se proporcionan en la Tabla 1, *supra*.

En ciertas modalidades, los compuestos de la presente invención se analizan como inhibidores de ACC utilizando métodos conocidos en el ámbito que incluyen aquellos contenidos en Harwood *et al*. Isozyme-nonselective *N*-Substituted Bipiperidylcarboxamide Acetyl-CoA Carboxylase Inhibitors Reduce Tissue Malonyl-CoA Concentrations, Inhibit Fatty Acid Synthesis, and Increase Fatty Acid Oxidation in

Cultured Cells and in Experimental Animals, J. Biol. Chem., 2003, vol. 278, 37099-37111. En algunas modalidades, los análisis utilizados se seleccionan a partir de análisis de inhibición de enzima ACC *in vitro*, análisis de cultivo de células *in vitro* y análisis de eficacia *in vivo* en animales. En algunas modalidades, los resultados de análisis para compuestos de la presente invención se comparan con resultados obtenidos para inhibidores conocidos de ACC o enzimas relacionadas. En algunas modalidades, el inhibidor de ACC utilizado para comparaciones CP-640186 o sorafeno A.

Los compuestos de la presente invención se evalúan en un análisis de inhibición ACC *in vitro* como se describe por Harwood, *et al*., 2003, la totalidad del cual se incorpora en la presente como referencia.

EJEMPLO 247

Análisis de inhibición de acetil-CoA carboxilasa (ACC) *in vitro*

Un procedimiento ejemplar para el análisis de inhibición de ACC *in vitro*, el cual se puede utilizar para determinar la acción inhibidora de compuestos de la invención hacia ACC1 o ACC2, sigue a continuación. El kit ADP-Glo^{MR} Kinase Assay de Promega es el que se utiliza. El ADP-Glo^{MR} Kinase Assay es un análisis de detección de ADP luminiscente para medir la actividad enzimática al cuantificar la cantidad de ADP producido durante una reacción enzimática. El análisis

se realiza en dos etapas; en primer lugar, después de la reacción de la enzima, se agrega un volumen igual de ADP-Glo^{MR} Reagent para finalizar la reacción y suprimir el ATP remanente. En segundo lugar, se agrega Kinase Detection Reagent para convertir simultáneamente ADP a ATP y permitir que el ATP recién sintetizado sea medido utilizando la reacción de luciferase/luciferina. La luminiscencia se puede correlacionar con las concentraciones de ADP mediante la utilización de una curva de conversión ATP-a-ADP. El procedimiento detallado es el siguiente. Se agregan 50 µl del compuesto que va a ser probado (600 µM en DMSO) a una placa de dilución de 384 pozos. El compuesto se diluye 1:3 en sucesión en DMSO para cada hilera por 11 pozos. Se agregan 0.5 µl de solución de trabajo ACC2 a la placa de análisis Optiplate blanca de 384 pozos. Se agregan 0.5 µl de solución de compuesto diluida en cada columna desde la etapa a la placa de análisis, cada hilera contiene 2 duplicados. Para las últimas dos hileras se agregan 0.5 µl de control negativo (DMSO) en una hilera y 0.5 µl de control positivo (compuesto I-97) en la otra. Las placas se incuban a temperatura ambiente durante 15 minutos. Se agregan a cada pozo para iniciar la reacción 5 µl de solución de trabajo de sustrato. Las concentraciones de reacción finales de ACC2 consisten de: ACC2 5 nM, ATP 20 µM, acetil-CoA 20 µM, $NaHCO_3$ 12 mM, Brij35 0.01%, DTT 2 mM, DMSO 5%, concentraciones del compuesto de prueba: 30 µM, 3.33 µM,

1.11 µM, 0.37 µM, 0.123 µM, 0.0411 µM, 0.0137 µM, 0.00457 µM, 0.00152 µM y 0.00051 µM. Las placas se incuban a temperatura ambiente durante 60 minutos. Se agregan 10 µl de ADP glo reagent. Las placas se incuban a temperatura ambiente durante 40 minutos. Se agregan 20 µl de reactivo de detección de cinasa. Las placas se incuban a temperatura ambiente durante 40 minutos, después se leen en un lector de placas Perkin EnVision 2104 para luminiscencia como unidades de iluminación relativa (RLU, por sus siglas en inglés).

Los datos para cada concentración, así como los controles positivo y negativo se promedian y se calculan a desviación estándar. El porcentaje de inhibición se calcula por la fórmula: 100 x (con promedio de control negativo – compuesto)/(promedio de control negativo – promedio de control positivo). La CI_{50} para cada compuesto se calcula al ajustar los datos con una ecuación de regresión no lineal: Y = inferior + (superior-inferior)/(1+10^((Log CI_{50} – X)*HillSlope)), en donde X es el logaritmo de la concentración del compuesto e Y es el por ciento de inhibición.

Los resultados de los análisis de inhibición *in vitro* de ACC1 y ACC2 se establecen en la Tabla 2. Los números de compuesto corresponden a los números de compuesto en la Tabla 1. Los compuestos que tienen una actividad designada como "AAA" proporciona una $CI_{50} \leq 0.1$ µM; los compuestos que tienen una actividad designada como "AA" proporcionan una CI_{50}

≤ 1 µM; los compuestos que tienen una actividad designada como "A" proporcionan una CI_{50} menor 5 µM; los compuestos que tienen una actividad designada como "B" proporcionan una CI_{50} de 5 a 20 µM; los compuestos que tienen una actividad designada como "C" proporcionan una CI_{50} de 20 a 50 µM; y los compuestos que tienen una actividad designada como "D" proporcionan una CI_{50} ≥ 50 µM. "NA" indica "no analizado". Las curvas de inhibición de enzima para el compuesto I-158 contra ACC1 y ACC2 se muestran en la Figura 1. Las curvas de inhibición de enzima para el compuesto I-181 contra ACC1 y ACC2 se muestran en la figura 6.

TABLA 2

Resultados de los análisis de inhibición de ACC1 y ACC2 *in vitro*.

ID del compuesto	ACC1	ACC2
I-1	A	B
I-2	NA	D
I-3	NA	C
I-4	NA	C
I-5	NA	D
I-6	NA	C
I-7	NA	D
I-8	NA	B
I-9	NA	D
I-10	NA	D
I-11	NA	D

I-12	NA	D
I-13	A	A
I-14	A	A
I-15	NA	D
I-16	NA	D
I-17	NA	D
I-18	NA	D
I-19	A	B
I-20	B	A
I-21	NA	D
I-22	NA	D
I-23	NA	C
I-24	NA	D
I-25	NA	D
I-26	NA	B
I-27	NA	D
I-28	NA	D
I-29	NA	D
I-30	NA	D
I-31	A	A
I-32	A	A
I-33	B	B
I-34	NA	B
I-35	NA	D
I-36	NA	C
I-37	NA	B
I-38	NA	D
I-39	NA	C
I-40	NA	D
I-41	NA	D

I-42	NA	C
I-43	NA	B
I-44	NA	D
I-45	A	A
I-46	A	A
I-47	NA	D
I-48	NA	B
I-49	NA	D
I-50	NA	D
I-51	NA	D
I-52	D	D
I-53	NA	B
I-54	NA	B
I-55	A	A
I-56	NA	A
I-57	NA	D
I-58	NA	D
I-59	NA	D
I-60	A	A
I-61	A	A
I-62	NA	B
I-63	NA	C
I-64	NA	D
I-65	NA	D
I-66	NA	A
I-67	NA	A
I-68	NA	B
I-69	NA	A
I-70	AA	AA
I-71	NA	D

I-72	NA	D
I-73	NA	C
I-74	NA	B
I-75	NA	B
I-76	NA	A
I-77	NA	B
I-78	NA	A
I-79	NA	B
I-80	NA	A
I-81	NA	B
I-82	NA	B
I-83	NA	A
I-84	NA	D
I-85	NA	A
I-86	NA	B
I-87	NA	A
I-88	NA	D
I-89	AA	AA
I-90	NA	C
I-91	NA	B
I-92	NA	A
I-93	AA	AA
I-94	NA	A
I-95	NA	C
I-96	AAA	B
I-97	AAA	AA
I-98	NA	C
I-99	NA	A
I-100	AAA	AA
I-101	NA	B

I-102	NA	B
I-103	NA	AA
I-104	NA	C
I-105	NA	AA
I-106	NA	A
I-107	NA	A
I-108	AAA	AA
I-109	NA	B
I-110	AA	AA
I-111	NA	B
I-112	AAA	AA
I-113	NA	C
I-114	NA	C
I-115	AA	AA
I-116	NA	A
I-117	NA	A
I-118	NA	C
I-119	AAA	AA
I-120	NA	B
I-121	AA	AA
I-122	NA	AA
I-123	AAA	AA
I-124	NA	B
I-125	NA	B
I-126	NA	C
I-127	NA	C
I-128	NA	C
I-129	NA	B
I-130	AAA	AA
I-131	AA	AA

I-132	NA	C
I-133	AAA	AA
I-134	AA	AA
I-135	AAA	AA
I-136	NA	A
I-137	NA	AA
I-138	NA	B
I-139	AA	AA
I-140	AAA	AA
I-141	NA	A
I-142	NA	AA
I-143	AA	AA
I-144	NA	B
I-145	AAA	AA
I-146	NA	AA
I-147	AA	AA
I-148	NA	A
I-149	NA	AA
I-150	NA	B
I-151	NA	AA
I-152	NA	AA
I-153	NA	AA
I-154	NA	AA
I-155	NA	AA
I-156	NA	A
I-157	NA	C
I-158	AAA	AAA
I-159	NA	AA
I-160	AAA	AAA
I-161	NA	A

I-162	AAA	AA
I-163	AA	AA
I-164	AAA	AAA
I-165	AAA	AAA
I-166	NA	AA
I-167	NA	A
I-168	NA	AA
I-169	NA	AAA
I-170	NA	AA
I-171	NA	AA
I-172	NA	AA
I-173	NA	AA
I-174	AAA	AAA
I-175	NA	AA
I-176	NA	A
I-177	AAA	AAA
I-178	NA	A
I-179	AAA	AAA
I-180	AAA	AAA
I-181	AAA	AAA
I-182	NA	C
I-183	NA	AAA
I-184	NA	AA
I-185	NA	AA
I-186	NA	AA
I-227	NA	
I-229	NA	
I-228	NA	
I-249	AAA	AAA
I-230	NA	A

I-235	AAA	AAA
I-236	AAA	AAA
I-231	NA	A
I-234	NA	A
I-246	AAA	AAA
I-243	AAA	AAA
I-233	NA	A
I-257	NA	A
I-277	AAA	AAA
I-278	AAA	AAA
I-254	AAA	AAA
I-258	AAA	AAA
I-244	AAA	AAA
I-245	AAA	AAA
I-256	AAA	AAA
I-237	AAA	AAA
I-238	AAA	AAA
I-239	AAA	AAA
I-242	AAA	AAA
I-255	AAA	AAA
I-263	NA	AA
I-240	NA	AAA
I-241	AAA	AAA
I-286	AAA	AAA
I-251	NA	A
I-261	NA	A
I-262	NA	A
I-285	NA	A
I-259	AAA	AAA
I-290	AAA	AAA

I-287	AAA	AAA
I-247	AAA	AAA
I-270	A	NA
I-267	AAA	AAA
I-260	AAA	AAA
I-275	AAA	NA
I-266	AA	NA
I-265	AA	NA
I-271	AAA	AAA
I-253	AA	NA
I-272	AAA	AAA
I-268	AAA	AAA
I-252	AA	NA
I-248	AA	NA
I-264	AAA	AAA
I-276	AAA	NA
I-274	AAA	AAA
I-269	A	NA
I-273	AAA	NA
I-283	AAA	NA
I-284	AAA	NA
I-288	AAA	AAA
I-289	AAA	AAA
I-291	AAA	AAA
I-279	AAA	AAA
I-282	AAA	AAA
I-296	NA	AAA
I-293	NA	AAA
I-297	AAA	AAA
I-303	AAA	AAA

I-292	AAA	AAA
I-294	AAA	AAA
I-295	AAA	AAA

EJEMPLO 248

Análisis de desplazamiento térmico

Los compuestos de la presente invención se evaluaron en un análisis de desplazamiento térmico utilizando métodos sustancialmente similares a los descritos por Vedadi *et al*., "Chemical screening methods to identify ligands that promote protein stability, protein crystallization, and structure determination." PNAS (2006) vol. 103, 43, 15835-15840, la totalidad de la cual se incorpora en la presente como referencia.

Los resultados del análisis de desplazamiento térmico muestran la capacidad del compuesto I-97 para unirse efectivamente e inducir un cambio conformacional en la proteína que resulta en su mecanismo de inhibición alostérica es resaltado por los datos en la figura 2. La figura 2 muestra los resultados de un análisis de desplazamiento térmico (TSA, por sus siglas en inglés) que compara I-97 y Sorafeno A (CI_{50} = 4 nM) y que ilustra la capacidad del compuesto I-97 para cambiar la estructura terciaria de la proteína objetivo, la que resulta en un cambio en el punto de fusión térmico de más de 14°C.

Los resultados del análisis de desplazamiento

térmico muestran la capacidad del compuesto I-97 para unirse efectivamente e inducir un cambio conformacional sobre la proteína que resulta en su mecanismo de inhibición alostérico que se resalta por los datos en la figura 3. La figura 3 muestra los resultados de un análisis de desplazamiento térmico (TSA) que compara los compuestos I-1, I-158, I-174 y Sorafeno A (CI_{50} = 4 nM), y que ilustra la capacidad de los compuestos I-158 y I-174 para cambiar la estructura terciaria de la proteína objetivo, lo que resulta en un cambio en el punto de fusión térmico equivalente al del Sorafeno A.

EJEMPLO 249

Análisis de incorporación de [^{14}C] acetato

Los compuestos de la presente invención se evaluaron en un análisis de incorporación de acetato [^{14}C]. Un procedimiento ejemplar para el análisis, el cual mide la incorporación de acetato marcado isotópicamente en ácidos grasos, es el siguiente. Se mantienen células HepG2 en matraces T-75 que contienen DMEM suplementado con 1-glutamina 2 mM, penicilina G (100 unidades/ml), estreptomicina 100 µg/ml con FBS 10% y se incuba en un incubador humidificado con CO_2 5% a 37°C. Las células se alimentan cada 2-3 días. En el día 1, las células se siembran en placas de 24 pozos a una densidad de 1.2 x 10^5 células/ml/pozo con el medio de crecimiento. En el día 3 el medio se sustituye con medio fresco que contiene FBS 10%. En el día 4 el medio se sustituye

con 0.5 ml de medio fresco que contiene compuesto de prueba (en DMSO; [DMSO] final de 0.5%) y las células se incuban a 37°C durante 1 hora. A una copia de la placa, se agregan 4 µl de [2-^{14}C] acetato (56 mCi/mmol; 1 mCi/ml; PerkinElmer) y las células se incuban a 37°C, CO_2 5% durante 5 h. A una segunda copia de la placa, se agregan 4 µl de acetato frío y las células se incuban a 37°C, CO_2 5% durante 5 h. Esta placa se utiliza para medición de concentración de proteína. El medio se separa y se coloca en un tubo de centrífuga de 15 ml (BD, Falcon/352096). Las células se enjuagan con 1 ml de PBS, después se aspira y se repiten las etapas de enjuagado y aspiración. Se agrega 0.5 ml de NaOH 0.1 N a cada pozo y se deja reposar a t.a. para disolver la monocapa de células. La suspensión de células remanentes se acumula con medio. Para la placa de determinación de proteína, se retira una alícuota para determinación de proteína (25 µl). Se agregan 1.0 ml de EtOH y 0.17 ml de KOH 50% a tubos que contienen medio y suspensiones celulares. Las células se incuban a 90°C durante 1 h y después se enfrían a temperatura ambiente. Se agregan por tubo 5 ml de éter de petróleo, se agita vigorosamente, se centrifuga a 1000 rpm durante 5 min y 500 µl de la capa de éter de petróleo se transfiere a tubos para lectura Microbeta, después se agregan 2 ml de Aquasol-2 a cada tubo, los tubos se agitan y se realiza la cuenta con un equipo de contador de centelleo líquido Microbeta (Perkin Elmer).

La capa de éter de petróleo remanente se desecha y la fase acuosa se reserva para extracciones del ácido graso. La fase acuosa se acidifica con 1 ml de HCl concentrado, se verifica el pH de uno o dos extractos para asegurarse que el pH está por debajo 1. Se agregan por tubo 5 ml de éter de petróleo, se agita vigorosamente, se centrifuga a 1000 rpm durante 5 min y se transfieren 4 ml de la capa de éter de petróleo a un tubo de vidrio nuevo (10*18 mm). Se agregan por tubo 5 ml de éter de petróleo, se agita vigorosamente, se centrifuga a 1000 rpm durante 5 min y se transfieren 5 ml de la capa de éter de petróleo al tubo de vidrio y se repite nuevamente la extracción. Los extractos de éter de petróleo se acumulan y evaporan a sequedad durante la noche. En el día 5 el residuo de las fracciones de éter de petróleo se resuspende en 120 µl de cloroformo-hexano (1:1) que contiene 200 µg del ácido linoleico como un portador. Una cantidad de 5 µl de esto se coloca en puntos sobre láminas de gel de sílice y las placas se revelan utilizando heptano-dietiléter-ácido acético (90:30:1) como eluyente. La banda del ácido graso se visualiza con vapor de yodo y las bandas correspondientes se recortan en frascos de centelleo. Se agregan 2 ml de Aquasol-2 a cada frasco y los frascos se agitan y se realiza determinación de cuenta con un contador de centelleo.

Los resultados del análisis de incorporación de [^{14}C] acetato se muestran en la figura 4 y en la figura 7. La

figura 4 ilustra la capacidad de los compuestos I-158 y I-174 para inhibir la incorporación de acetato marcado isotópicamente en ácidos grasos con una CI_{50} de menos de 100 nM. Otro inhibidor, CP-640186 (en una concentración única de 3 µM) se muestra para comparación. La figura 7 ilustra la capacidad del compuesto I-181 para inhibir la incorporación de acetato marcado isotópicamente en ácidos grasos en células Hep-G2.

EJEMPLO 250

Se evaluaron compuestos de la presente invención en un análisis de actividad antimicótico. A continuación se presenta un procedimiento ejemplar para el análisis, el cual mide la susceptibilidad de diversas especies de *Candida* a compuestos antimicóticos. Los compuestos que se van a analizar (que incluyen fluconazol y anfotericina B) se disuelven en DMSO para obtener una solución que tiene una concentración de 1 mg/ml. Estas soluciones concentradas se filtran por esterilización utilizando un filtro con jeringa de nylon de 0.22 µm, después se diluyen en agua estéril para obtener una concentración final de 128 µg/ml.

Todas las especies se hacen crecer a partir de un concentrado congelado al sembrar en placa directamente sobre agar Sabouraud Dextrosa recién preparado (BD, Difco) y se incuban durante la noche con aire ambiente a 35°C durante 24 h. Se prepara una suspensión directa en RPMI 1640 + MOPS

(Lonza, Biowhittaker) al tomar las columnas individuales de los cultivos durante la noche utilizando isopos estériles remojados en solución salina estéril. La concentración de la suspensión se determina utilizando curvas estándar predeterminadas. Estas suspensiones después se reducen por dilución a 5 x 10^3 UFC/ml para obtener una concentración final de 2.5 x 10^3 UFC/ml una vez agregada a la placa de microtitulación según las líneas de guía de CLSI (M27-A3, Vol. 28 No. 14).

Se prepararon placas de exposición MIC de microtitulación en caldo siguiendo las líneas de guía CLSI (M27-A3, Vol. 28, No. 14). Las líneas CLSI originales se enfocan en la lectura de MIC de *Candida* después de 48 h de incubación. Dado que una lectura después de solo 24 h proporciona una clara ventaja para el cuidado del paciente, se han establecido límites QC para todos los fármacos a 24 h. Lo que se ha hdicho es que no hay puntos de ruptura de intersección conocidos para anfotericina B a las 24 h y que los puntos de ruptura interpretativos de fuconazol actuales se basan en una lectura de 48 h. Los puntos de ruptura MIC para los compuestos de prueba Pharmaron se registraron a las 48 h y para sorafeno al punto de tiempo de 24 h se agregó. Todas las determinaciones de MIC se obtiene al comparar visualmente el crecimiento encontrado en pozos expuestos a antibiótico con las del control de crecimiento. El primer pozo encontrado en

el esquema de dilución mostró que no hay crecimiento (o hay inhibición completa) y se registró como la MIC.

Los resultados del análisis de actividad antimicótica se muestran en la Tabla 3. La Tabla 3 ilustra que los compuestos I-158, I-159, I-174, I-235, I-236 e I-246 tienen actividad antimicótica con MIC en un intervalo bajo de µg/ml.

TABLA 3: RESULTADOS DE ANÁLISIS DE ACTIVIDAD ANTIMICÓTICA

	MIC (µg/ml; 3 duplicados)											
especie de *Candida*	Amph. B	Fluc.	I-158	I-174	I-181	I-235	I-236	I-246	I-159	I-160	I-162	I-165
C. albicans	0.5	1	2	2	>64	8	8	4	8	>64	>64	>64
ATCC 90028	0.5	1	2	2	>64	8	8	4	8	>64	>64	>64
	1	2	2	2	>64	8	8	4	8	>64	>64	>64
C. parapsilosis	1	2	8	8	>64	8	2	4	>64	>64	>64	>64
	1	2	8	8	>64	8	2	4	>64	>64	>64	>64
ATCC 22019	1	4	8	8	>64	8	2	4	>64	>64	>64	>64
C. krusei	1	32	2	2	>64	8	8	16	16	>64	>64	>64
ATCC 6258	1	32	2	2	>64	8	4	16	16	>64	>64	>64
	1	2	2	2	>64	8	4	16	32	>64	>64	>64

EJEMPLO 251

Los compuestos de la invención también se analizaron en un análisis de viabilidad de células cancerosas como se describe en Beckers *et al*. "Chemical Inhibition of Acetyl-CoA Carboxylase Induces Growth Arrest and Cytotoxicity Selectively in Cancer Cells" Cancer Res. (2007) 67, 8180-8187. Un procedimiento ejemplar para el análisis, el cual mide el porcentaje de células cancerosas después de la administración

de compuestos inhibidores si se presenta a continuación.

Células LNCaP (línea de células de cáncer de próstata) sembradas en placas a 4 x 10^5 por placa de 6 cm se incubaron a 37°C y al siguiente día se les trató con concentraciones en aumento de compuestos inhibidores y se incubaron. Las células viables y los porcentajes de células muertas se contaron y calcularon cada día durante 5 días, desde el día 0 utilizando tinción con azul de tripan.

Los resultados de los análisis de viabilidad de células cancerosas se muestran en la figura 5, el cual muestra la capacidad del compuesto I-158 para inhibir completamente el crecimiento de población de células a una concentración de 5 µM.

EJEMPLO 252

Los compuestos de la presente invención también se analizaron en un estudio de síntesis del ácido graso *in vivo* como se describe en Harwood *et al*. "Isozyme-nonselective N-Substituted Bipiperidylcarboxamide Acetyl-CoA Carboxylase Inhibitors Reduce Tissue Malonyl-CoA Concentrations, Inhibit Fatty Acid Synthesis, and Increase Fatty Acid Oxidation in Cultured Cells and in Experimental Animals" Journal of Biological Chemistry (2008) 278, 37099-37111. Un procedimiento ejemplar para el análisis, el cual mide la cantidad de acetato [$^{C}_{1-4}$] radioactivo incorporado en tejido de hígado de rata sigue a continuación.

A los animales se les administró con alimento y agua *ad libitum* y fueron tratados oralmente con un volumen de 1.0 ml/200 g de peso corporal (rata) con ya sea una solución acuosa que contiene metilcelulosa 0.5% (vehículo) o una solución acuosa que contiene metilcelulosa 0.5% más el compuesto de prueba. Una a cuatro horas después de la administración del compuesto a los animales recibieron una inyección intraperitoneal de [C^{14}]-acetato 0.5 ml (64 µCi/ml; 56 µCi/ml). Una hora después de la administración del acetato radiomarcado se mató a los animales por asfixia con CO_2 y dos piezas de hígado de 0.75 g se extrajeron y se saponificaron a 70°C durante 120 minutos en 1.5 ml de NaOH 2.5 M. Después de la saponificación se agregó 2.5 ml de etanol absoluto a cada muestra y las soluciones se mezclaron y se permitió que reposaran durante la noche. Después se agregó a cada muestra 4.8 ml de éter de petróleo y las mezclas se agitaron primero vigorosamente durante 2 minutos y después se centrifugaron a 1000 x g en una centrífuga Sorvall de mesa durante 5 minutos. Las capas de éter de petróleo resultante, las cuales contienen lípidos no saponificables se removieron y desecharon. La capa acuosa remanente se acidificó a pH < 2 por la adición de HCl 12M y se extraen dos veces con 4.8 ml de éter de petróleo. Las fracciones orgánicas acumuladas se transfirieron a frascos de centelleo líquido, se secaron bajo nitrógeno, se disolvieron en 7 ml de fluido de centelleo líquido Aquasol y se determinó

la radioactividad utilizando un contador de centelleo líquido Beckman 6500. Los resultados se registraron como desintegraciones por minuto (DPM) por miligramo de tejido.

Los resultados del estudio de síntesis del ácidos grasos *in vivo* se muestra en la figura 8 y en la figura 16 lo cual muestra que la DE_{50} de cada compuesto I-181 e I-278 es menor de 0.3 mg/kg de peso corporal.

EJEMPLO 253

Los compuestos de la presente invención también se analizaron en un análisis de medición de cociente respiratorio, como se describe por Harwood *et al*. "Isozyme-nonselective N-Substituted Bipiperidylcarboxamide Acetyl-CoA Carboxylase Inhibitors Reduce Tissue Malonyl-CoA Concentrations, Inhibit Fatty Acid Synthesis, and Increase Fatty Acid Oxidation in Cultured Cells and in Experimental Animals" Journal of Biological Chemistry (2008) 278, 37099-37111. Sigue a continuación un procedimiento ejemplar para el análisis, el cual mide la relación de producción de dióxido de carbono respecto a consumo de oxígeno. en ratas.

Ratas macho Sprague-Dawley (350-400 g) albergadas bajo condiciones de laboratorio estándar se les alimentó con alimento convencional, se sometieron a ayuno o se sometieron a ayuno y se les realimentó con una dieta alta en sacarosa durante 2 días antes de la experimentación y fueron retiradas de sus jaulas de origen, se pesaron y colocaron en cámaras

selladas (43" (109.2cm) 43" 10 cm) de un calorímetro (una rata por cámara). Las cámaras se colocaron en monitores de actividad. El calorímetro se calibró antes de cada uso, la velocidad de flujo de aire se ajustó a 1.6 litros/min y los tiempos de ajuste y de muestreo del sistema se establecieron en 60 y 15 s, respectivamente. El consumo de oxígeno de línea basal, la producción de CO_2 y la actividad ambulatoria se midieron cada 10 min hasta durante 3 h antes del tratamiento. Después de recolectar los datos de línea de base, se abrieron las cámaras y se les suministró a las ratas un bolo oral de 1.0 ml ya sea de una solución de metilcelulosa 0.5% acuosa (control de vehículo) o una solución de metilcelulosa 0.5% acuosa que contiene el compuesto de prueba y se les regresó a las cámaras Oxyma. Se realizaron mediciones cada 30 min durante 3-6 h adicionales después de dosificación. Los controles de vehículo alimentados se les utilizó para determinar los efectos producidos por administración de vehículo y por deriva en la medición de RQ durante el curso de la experimentación (si la hay). Controles tratados con vehículo, sometidos a ayuno durante la noche se utilizaron para determinar la reducción RQ potencial máxima. Los resultados se gravitan como su valor RQ absoluto (± SEM) con respecto al tiempo.

Los resultados del estudio de síntesis del ácido graso *in vivo* se muestran en la figura 9 y en la figura 10, la

cual muestra que el compuesto I-181 disminuye RQ en aproximadamente 80-90% de su valor de línea de base, y muestra disminuciones dependientes de la dosis en RQ ante el tratamiento con I-181.

EJEMPLO 254

Los compuestos de la presente invención también se analizaron en un análisis de muerte de células con yoduro de propidio (PI) en base en el procedimiento descrito por van Engeland *et al*. "A novel assay to measure loss to plasma membrane asymmetry during apoptosis of adherent cells in culture" Cytometry (1996) 24 (2), 131-139. A continuación se muestra un procedimiento ejemplar para el análisis el cual mide el número de células mitóticas intactas después de la aplicación del fármaco.

Se sembraron células de carcinoma hepatocelular (tal como HepG2 o Hep3B) en una placa de 24 pozos a una densidad de 1.106/ml 0.5 ml de medio de cultivo y se incubaron durante 3 horas para permitir tiempo para que las células se adhieran. Las células se tratan con compuestos experimentales, doxorrubicina 1 µM (1,2) o vehículo (DMSO) control durante 120 horas después del tratamiento: a. Primer sobrenadante de cultivo removido en un tubo de polipropileno de 2 ml y colocado en hielo; b. pozos lavados con 0.5 ml de PBS, que transfieren el volumen de lavado a un tubo 2 ml que contiene sobrenadante de cultivo (células flotantes). Se mantienen las

células en hielo. Se cosechan al agregar en los pozos 200 µl de accutase durante 5 min. Se inactiva con 300 µl de medio. Se pipetea hacia arriba y hacia abajo y las células tripsinizadas transferidas desde el pozo a un tubo de 2 ml con las células flotantes (volumen total: 1.5 ml). Se mantiene a las células en hielo. Las células se centrifugan 0.6 rfc durante 10 min a 4°. Se aspira el medio. Se resuspenden en 500 µl de medio al someter a remolino en pulsos de aproximadamente 15 s. Se mantiene a las células en hielo.

Para la cuenta de células: se agregan 20 µl de células a una placa después de someter a remolino en pulsos durante 15 s. Se mantienen en una placa sobre hielo. Después se agregan 20 µl de azul de tripan justo antes del conteo. Las células contadas con un contador de células biorad TC10. Las células se centrifugan 0.6 rfc durante 10 min a 4 grados. Se aspira el medio cuidadosamente. Se resuspende en 500 µl de amortiguador de unión de anexina 1X por remolino. Se transfiere la suspensión celular a un tubo FACS de 5 ml y después se agregan 5 µl de yoduro de propidio. Se mezcla cuidadosamente a las células y se incuban durante 15 min a t.a. en la oscuridad.

Para el análisis citométrico de flujo, se utilizan muestras no teñidas/no tratadas en cada punto del tiempo como control negativo y se utilizan muestras tratadas con doxorrubicina en cada punto de tiempo como un control

positivo. Se utiliza el citómetro de flujo FACScan, y se analizan los histogramas FL2-A con el programa FlowJo. Los resultados de un análisis de muerte celular por PI se muestran en la figura 14.

EJEMPLO 255

Los compuestos de la presente invención también se analizaron por estudios de obesidad inducida con una dieta alta en grasas (DIO). A continuación se presenta un protocolo representativo para el análisis.

Los compuestos de la presente invención están adaptados fácilmente a uso clínico como agentes contra la obesidad, agentes sensibilizantes a insulina, agentes que invierten hiperinsulinemia y agentes que revierten esteatosis hepática. Esta actividad se puede determinar al establecer la cantidad de compuesto de prueba que reduce el peso corporal y el porcentaje de grasa corporal, reduce los niveles de insulina en plasma, establece un límite al ascenso y/o acelera la reducción en los niveles plasmáticas de insulina y glucosa en respuesta a una exposición oral a glucosa y reduce el contenido lipídico hepático en relación a un vehículo control sin el compuesto de prueba en mamíferos. Se alimentaron ratas Sprague-Dawley ya sea con alimento para ratas o una dieta alta en sacarosa (por ejemplo, la dieta de roedor AIN76A; Research diets Inc. catálogo #10001) o una dieta alta en grasa (por ejemplo las Research diets Inc. catálogo #12451) durante 3 a 8

semanas antes y durante la administración del compuesto de prueba.

El potencial contra la obesidad, sensibilizante a insulina, de inversión de hiperinsulinemia y el potencial de inversión de estatosis hepática de los compuestos de la presente invención se demostró por evaluación de modificaciones en una diversidad de parámetros de metabolismo de lípidos y carbohidratos utilizando métodos basados en procedimientos estándar conocidos por aquellos expertos en el ámbito. Por ejemplo, después de un período de 3 a 8 semanas de alimentación libre ya sea con alimento para ratas, una dieta alta en grasa o una dieta alta en sacarosa. Los animales que continuaron recibiendo la dieta fueron tratados durante 1 a 8 semanas con el compuesto de prueba administrado ya sea por sonda oral en agua o solución salina o con agua o solución salina que contiene metilcelulosa 0.5% utilizando un régimen de dosificación Q.D., B.I.D o T.I.D. En diversos momentos durante el estudio y al momento de sacrificio (por asfixia con CO_2) se recolectó sangre ya sea de la vena de la cola de una rata no anestesiada o de la vena cava de animales en sacrificio en heparina o tubos que contienen EDTA para separación centrífuga para preparar plasma. Los niveles de plasma de los parámetros del metabolismo de lípidos y carbohidratos conocidos por los expertos en el ámbito para ser alterados coincidentes con las acciones contra la obesidad,

sensibilizantes a insulina, de inversión de hiperinsulinemia y de inversión de esteatosis hepática, que incluyen pero que no se limitan a colesterol y triglicéridos, glucosa, insulina, leptina, adiponectina, cuerpos cetónicos, ácidos grasos libres y glicerol se miden utilizando métodos conocidos por los expertos en el ámbito.

El potencial antiobesidad de compuestos de la presente invención también se puede demostrar al evaluar su potencial para producir una reducción en el peso corporal, una reducción en el porcentaje de grasa corporal (medido, por ejemplo, por análisis de absorptiometría de rayos x de energía doble (DEXA)) y una reducción en los niveles de leptina plasmáticos. El potencial contra la obesidad y de inversión de esteatosis hepática de los compuestos de la presente invención también se demostró al evaluar su potencial para reducir la concentración de triglicéridos en el hígado, utilizando procedimientos de extracción y cuantificación conocidos por los expertos en el ámbito. El potencial de sensibilización a insulina y reversión de hiperinsulinemia de los compuestos de la presente invención también se puede demostrar al evaluar su potencial para limitar el incremento y/o acelerar la reducción en los niveles plasmáticos de insulina y glucosa en respuesta a una exposición de glucosa oral utilizando procedimientos conocidos por aquellos expertos en el ámbito.

El potencial contra la obesidad, sensibilizante a

insulina, de inversión de hiperinsulinemia e inversión de esteatosis hepática de los compuestos de la presente invención se ejemplifica mediante acciones del compuesto de ejemplo I-181. Cuando el compuesto I-181 se administra una vez al día por sonda oral en metilcelulosa 0.5% en solución salina a dosis de 0, 3, 10 y 30 mg/kg a ratas Sprague Dawley que han consumido una dieta alta en grasas durante 4 semanas antes del inicio de la dosificación y que continúan consumiendo la misma dieta alta en grasas durante las 2 semanas de la administración del compuesto de prueba, el compuesto I-181 produce una reducción dependiente de la dosis en el peso corporal total en relación a animales control tratados con vehículo sin reducción concomitante en el consumo de alimento. Los resultados de la reducción en las mediciones de peso corporal total después del tratamiento con una dieta alta en grasa en ratas alimentadas con DIO con el compuesto I-181 se muestra en la figura 11. El grado de reducción de peso corporal es paralelo a los niveles de fármaco en plasma medido al final del estudio. Los niveles de leptina en plasma, los cuales se sabe son un indicador de la masa grasa corporal total y los cuales se encuentran incrementados por administración de una dieta alta en grasas, se reduce por todas las dosis del compuesto I-181 evaluadas indicando que la reducción en el peso corporal es el resultado de una reducción en la grasa corporal. Los niveles de leptina en plasma para

animales que reciben la dieta comercial estándar (controles magros) también se evaluaron para determinar el grado de normalización de parámetros producida por el compuesto I-181. Los niveles de insulina en plasma, los cuales se incrementaron por una dieta alta en grasa se redujeron a niveles control casi magros en la totalidad de las tres dosis del compuesto I-181 sin reducción concomitante en los niveles de glucosa en plasma, lo que indica una mejora en la sensibilidad a insulina después del tratamiento con el compuesto I-181. Los resultados de la reducción en las mediciones de insulina en plasma después del tratamiento de ratas DIO alimentadas con una dieta alta en grasa con el compuesto I-181 se muestran en la figura 12. Los triglicéridos hepáticos, los cuales estaban elevados con la dieta alta en grasa, se redujeron de una manera dependiente de la dosis después del tratamiento con el compuesto I-181 y se normalizaron a los niveles control magros por la dosis más alta evaluada. Los resultados de la reducción en los triglicéridos hepáticos y las mediciones de colesterol después del tratamiento en ratas DIO alimentadas con una dieta alta en grasa con el compuesto I-181 se muestran en la figura 13. El tratamiento con el compuesto I-181 no incrementan ya sea el peso hepático o los marcadores de la función hepática, ALT y AST. En estudios en donde se administró el compuesto I-181 una vez al día por sonda oral en metilcelulosa 0.5% en solución salina a dosis de 0, 3, 10 y 30 mg/kg a ratas

Sprague-Dawley que han consumido una dieta alta en sacarosa durante 4 semanas antes del inicio de la dosificación y que continúan consumiendo la misma dieta alta en sacarosa durante las dos semanas de la administración del compuesto de prueba, el compuesto I-181 produjo una reducción, dependiente de la dosis, en los niveles plasmáticos de colesterol y triglicéridos. Los resultados de los estudios de obesidad inducida por la dieta miden el efecto del compuesto I-181 sobre colesterol y triglicéridos en plasma se muestran en la Tabla 4 más adelante. Los datos muestran la media de valores para n = 14 animales por grupo ± SEM.

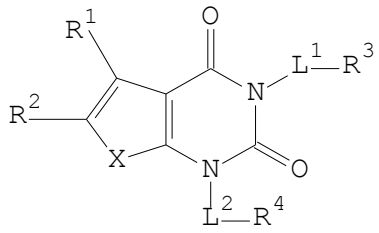
TABLA 4. COLESTEROL EN PLASMA Y DISMINUCIÓN DE TRIGLICÉRIDOS EN RATAS DIO ALIMENTADAS CON UNA DIETA ALTA EN SACAROSA DESPUÉS DEL TRATAMIENTO CON I-181

Dosis I-181	Colesterol en plasma* (mg/dl)			Triglicéridos en plasma* (mg/dl)		
	Antes de la extracción de sangre	Día 7	Día 14	Antes de la extracción de sangre	Día 7	Día 14
0 mg/kg	100 ± 3	106 ± 3	110 ± 6	170 ± 11	226 ± 16	195 ± 15
3 mg/kg	96 ± 2	94 ± 3	96 ± 3	144 ± 12	154 ± 15	171 ± 16
10 mg/kg	96 ± 3	82 ± 3	87 ± 3	183 ± 18	139 ± 10	165 ± 15
30 mg/kg	99 ± 3	78 ± 3	78 ± 2	166 ± 13	116 ± 9	118 ± 14
Controles alimentados con comida comercial	109 ± 2	107 ± 3	107 ± 3	61 ± 5	69 ± 5	67 ± 5

Aunque se han descrito numerosas modalidades de esta invención, será evidente que nuestros ejemplos básicos se pueden alterar para proporcionar otras modalidades que utilicen los compuestos y métodos de esta invención. Por lo tanto, se apreciará que el alcance de esta invención se va a definir por las reivindicaciones anexas en vez de por las modalidades específicas que han sido representadas a modo de ejemplo

REIVINDICACIONES

1. Un compuesto de fórmula I:



I

o una sal farmacéuticamente aceptable del mismo, caracterizado porque:

X es -O-, -S- o -NR-;

R^1 es hidrógeno o un grupo alifático de 1 a 4 átomos de carbono, opcionalmente sustituido con uno o más de halógeno, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o $-SO_2R$;

R^2 es halógeno, -R, -OR, -SR, $-N(R)_2$, -N(R)C(O)R, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, -N(R)C(O)OR, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o $-SO_2R$ o Hy, en donde Hy se selecciona de un anillo heterocíclico de 4 a 8 miembros saturado o parcialmente insaturado monocíclico que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o

azufre, o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

o R^1 y R^2 se toman juntos para formar un anillo, opcionalmente sustituido de 4 a 7 miembros parcialmente insaturado carbociclo- o heterociclo-, benzo- o de 5 a 6 miembros heteroarilo-fusionado;

cada R es independientemente hidrógeno, o un grupo opcionalmente sustituido que se selecciona de un grupo alifático de 1 a 6 átomos de carbono, un anillo de 3 a 8 miembros saturado o parcialmente insaturado monocíclico carbocíclico, fenilo, un anillo carbocíclico aromático bicíclico de 8 a 10 miembros; un anillo heterocíclico monocíclico de 4 a 8 miembros saturado o parcialmente insaturado que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre o un anillo heteroaromático bíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

cada uno de L^1 y L^2 es independientemente un enlace covalente o una cadena de hidrocarburo divalente lineal o ramificada de 1 a 6 miembros opcionalmente sustituida; o un grupo ciclopropilenilo, ciclobutilenilo u oxetanilo;

R^3 es hidrógeno, halógeno, -CN, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-C(O)N(R)S(O)_2R$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, $-SO_2R$, $-B(OH)_2$ o un anillo opcionalmente sustituido que se selecciona de fenilo o un heteroarilo de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre; y

R^4 es hidrógeno o un anillo opcionalmente sustituido que se selecciona de un anillo carbocíclico saturado o parcialmente insaturado monocíclico de 3 a 8 miembros, un anillo heterocíclico saturado o parcialmente insaturado monocíclico de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, fenilo, un anillo arilo bicíclico de 8 a 10 miembros, un anillo heteroarilo monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, o un anillo heteroarilo bicíclico de 8 a 10 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

y en donde, si L^2 es un enlace covalente, entonces R^4 no es hidrógeno; y

en donde el grupo $-L^2-R^4$ no es alquilo cuando R^2 es alquilo no sustituido; y

en donde el grupo $-L^1-R^3$ tomados juntos no es

alquilo no sustituido.

2. El compuesto de conformidad con la reivindicación 1, caracterizado porque X es –S-.

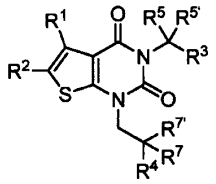
3. El compuesto de conformidad con la reivindicación 2, caracterizado porque R^2 es metilo o trifluorometilo.

4. El compuesto de conformidad con la reivindicación 3, caracterizado porque R^2 es halógeno, -C(O)OR, $-C(O)N(R)_2$, u oxazolilo.

5. El compuesto de conformidad con la reivindicación 3, caracterizado porque R^1 y R^2 se toman juntos para formar un anillo carboxílico parcialmente insaturado de 5 a 6 miembros.

6. El compuesto de conformidad con la reivindicación 3, caracterizado porque R^3 es tetrazolilo, $-C(O)OR$, $-C(O)N(R)_2$, u –OR.

7. Un compuesto de fórmula II:



II

o una sal farmacéuticamente aceptable del mismo, caracterizado porque:

R^1 es hidrógeno o un grupo alifático de 1 a 4 átomos de carbono, opcionalmente sustituido con uno o más de

halógeno, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, $-C(O)R$, $-C(O)OR$, $-OC(O)R$, $-S(O)R$ o $-SO_2R$;

R^2 es halógeno, -R, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, $-C(O)R$, $-C(O)OR$, $-OC(O)R$, $-S(O)R$ o $-SO_2R$ o Hy, en donde Hy se selecciona de un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre; o R^1 y R^2 se toman juntos para formar un anillo opcionalmente sustituido, de 4 a 7 miembros parcialmente insaturado carbociclo- o heterociclo-, benzo- o de 5 a 6 miembros heteroarilo-fusionado;

cada R es independientemente hidrógeno, o un grupo opcionalmente sustituido que se selecciona de un grupo alifático de 1 a 6 átomos de carbono, un anillo carbocíclico monocíclico saturado o parcialmente insaturado de 3 a 8 miembros, fenilo, un anillo carbocíclico aromático bicíclico de 8 a 10 miembros; un anillo heterocíclico monocíclico

saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

R^3 es hidrógeno, halógeno, -CN, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, $-C(O)R$, $-C(O)OR$, $-OC(O)R$, $-S(O)R$, $-SO_2R$, $-B(OH)_2$ o un anillo opcionalmente sustituido que se selecciona de fenilo o un heteroarilo de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

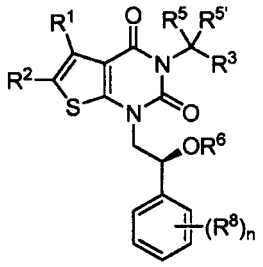
R^4 es un anillo fenilo o naftilo opcionalmente sustituido;

cada uno de R^5 y $R^{5'}$ es independientemente -R, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, $-C(O)R$, $-C(O)OR$, $-OC(O)R$, $-S(O)R$ o $-SO_2R$; o R^5 y $R^{5'}$ se toman juntos para formar un grupo ciclopropilenilo, ciclobutilenilo u oxetanilo; y

Cada uno de R^7 y $R^{7'}$ es independientemente hidrógeno, -R, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$,

$-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, $-C(O)R$, $-C(O)OR$, $-OC(O)R$, $-S(O)R$ o $-SO_2R$; o R^7 y $R^{7'}$ se toman juntos para formar un anillo carbocíclico monocíclico saturado o parcialmente insaturado de 3 a 8 miembros, o un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre.

8. Un compuesto de fórmula III:



III

o una sal farmacéuticamente aceptable del mismo, caracterizado porque:

R^1 es hidrógeno o un grupo alifático de 1 a 4 átomos de carbono, opcionalmente sustituido con uno o más de halógeno, $-OR$, $-SR$, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, $-C(O)R$, $-C(O)OR$, $-OC(O)R$, $-S(O)R$ o $-SO_2R$;

R^2 es halógeno, $-R$, $-OR$, $-SR$, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, $-C(O)R$, $-C(O)OR$, $-OC(O)R$, $-S(O)R$ o $-SO_2R$, o Hy, en donde Hy se selecciona de un anillo heterocíclico monocíclico saturado o parcialmente

insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre; o R^1 y R^2 se toman juntos para formar un anillo, opcionalmente sustituido, de 4 a 7 miembros parcialmente insaturado, carbociclo- o heterociclo-, benzo- o heteroarilo-fusionado de 5 a 6 miembros;

cada R es independientemente hidrógeno, o un grupo opcionalmente sustituido que se selecciona de un grupo alifático de 1 a 6 átomos de carbono, un anillo carbocíclico monocíclico saturado o parcialmente insaturado de 3 a 8 miembros, fenilo, un anillo carbocíclico aromático bicíclico de 8 a 10 miembros; un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, o un anillo heteroaromático bicíclico de 8 a 10 miembros que

tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

R^3 es hidrógeno, halógeno, -CN, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R, $-SO_2R$, $-B(OH)_2$ o un anillo opcionalmente sustituido que se selecciona de fenilo o un heteroarilo de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

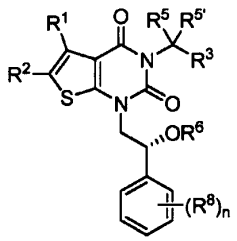
cada uno de R^5 y $R^{5'}$ es independientemente -R, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o $-SO_2R$; o R^5 y $R^{5'}$ se toman juntos para formar un grupo ciclopropilenilo, ciclobutilenilo u oxetanilo;

R^6 es -R, $-C(O)N(R)_2$ o -C(O)R;

cada R^8 se selecciona independientemente de halógeno, -R, -OR, -SR, $-N(R)_2$ o deuterio; y

n es 0 a 5.

9. Un compuesto de fórmula IV:



IV

o una sal farmacéuticamente aceptable del mismo, caracterizado porque:

R^1 es hidrógeno o un grupo alifático de 1 a 4 átomos de carbono, opcionalmente sustituido con uno o más de halógeno, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2RN(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o $-SO_2R$;

R^2 es halógeno, -R, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, -C(O)R, -C(O)OR, -OC(O)R, -S(O)R o $-SO_2R$; o Hy, en donde Hy se selecciona de un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, o un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre; o R^1 y R^2 se toman juntos para formar un anillo, opcionalmente sustituido, de 4 a 7 miembros parcialmente insaturado, carbociclo- o heterociclo-, benzo- o heteroarilo-fusionado de 5 a 6 miembros;

cada R es independientemente hidrógeno, o un grupo opcionalmente sustituido que se selecciona de un grupo

alifático de 1 a 6 átomos de carbono, un anillo carbocíclico monocíclico saturado o parcialmente insaturado de 3 a 8 miembros, fenilo, un anillo carbocíclico aromático bicíclico de 8 a 10 miembros; un anillo heterocíclico monocíclico saturado o parcialmente insaturado de 4 a 8 miembros que tiene 1 a 2 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre, un anillo heteroaromático monocíclico de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre o un anillo heteroaromático bicíclico de 8 a 10 miembros que tiene 1 a 5 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

R^3 es hidrógeno, halógeno, -CN, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $SO_2N(R_2)$, $-C(O)R$, $-C(O)OR$, $-OC(O)R$, $-S(O)R$, $-SO_2R$, $-B(OH)_2$ o un anillo opcionalmente sustituido que se selecciona de fenilo o un heteroarilo de 5 a 6 miembros que tiene 1 a 4 heteroátomos que se seleccionan independientemente de nitrógeno, oxígeno o azufre;

cada uno de R^5 y $R^{5'}$ es independientemente -R, -OR, -SR, $-N(R)_2$, $-N(R)C(O)R$, $-C(O)N(R)_2$, $-N(R)C(O)N(R)_2$, $-N(R)C(O)OR$, $-OC(O)N(R)_2$, $-N(R)SO_2R$, $-SO_2N(R)_2$, $-C(O)R$, $-C(O)OR$, $-OC(O)R$, $-S(O)R$ o $-SO_2R$; o R^5 y $R^{5'}$ se toman juntos para formar un grupo ciclopropilenilo, ciclobutilenilo u oxetanilo;

R^6 es -R, $-C(O)N(R)_2$ o -C(O)R;

cada R^8 se selecciona independientemente de halógeno, -R, -OR, -SR, $-N(R)_2$ o deuterio; y

n es 0 a 5.

10. Una composición caracterizada porque comprende un compuesto de conformidad con la reivindicación 1, y un portador, adyuvante o vehículo farmacéuticamente aceptable.

11. Un método para inhibir ACC en un paciente en necesidad del mismo, caracterizado porque comprende administrar al paciente la composición de conformidad con la reivindicación 10.

12. Un método para inhibir ACC en una muestra biológica, caracterizado porque comprende poner en contacto la muestra biológica con el compuesto de conformidad con la reivindicación 1.

13. Un método para tratar un trastorno metabólico en un paciente en necesidad del mismo, caracterizado porque comprende administrar al paciente la composición de conformidad con la reivindicación 10.

14. El método de conformidad con la reivindicación 13, caracterizado porque el trastorno metabólico es obesidad.

15. El método de conformidad con la reivindicación 13, caracterizado porque el trastorno metabólico es dislipidemia o hiperlipidemia.

16. El método de conformidad con la reivindicación 14, caracterizado porque la obesidad es un síntoma del síndrome de Prader-Willi, síndrome de Bardet-Biedl, síndrome de Cohen o síndrome MOMO.

17. El método de conformidad con la reivindicación 14, caracterizado porque la obesidad es un efecto secundario de la administración de otro medicamento, que incluye pero que no se limita a insulina, sulfunilureas, tiazolidinadionas, antipsicóticos, antidepresivos, estereoides, anticonvulsivantes (que incluyen fenitoina y valproato), pizotifeno, o anticonceptivos hormonales.

18. Un método para tratar cáncer u otro trastorno proliferativo en un paciente en necesidad del mismo, caracterizado porque comprende administrar al paciente la composición de conformidad con la reivindicación 10.

19. Un método para tratar una infección micótica, parasitaria o bacteriana en un paciente en necesidad del mismo, caracterizado porque comprende administrar al paciente la composición de conformidad con la reivindicación 10.

20. Un método para inhibir ACC en una planta, caracterizado porque comprende poner en contacto la planta con el compuesto de conformidad conla reivindicación 1.

RESUMEN DE LA *INVENCION*

La presente invención proporciona compuestos, específicamente derivados de tienopirimidina útiles como inhibidores de acetil CoA carboxilasa (ACC), composiciones farmacéuticas de los mismos y métodos de uso de los mismos para tratar trastornos mediados por ACC tales como obesidad, dislipidemia, hiperlipidemia, infecciones micóticas, parasitarias o bacterianas en un sujeto. La invención proporciona además un método para inhibir ACC en una planta que comprende poner en contacto a la planta con el compuesto inhibidor.

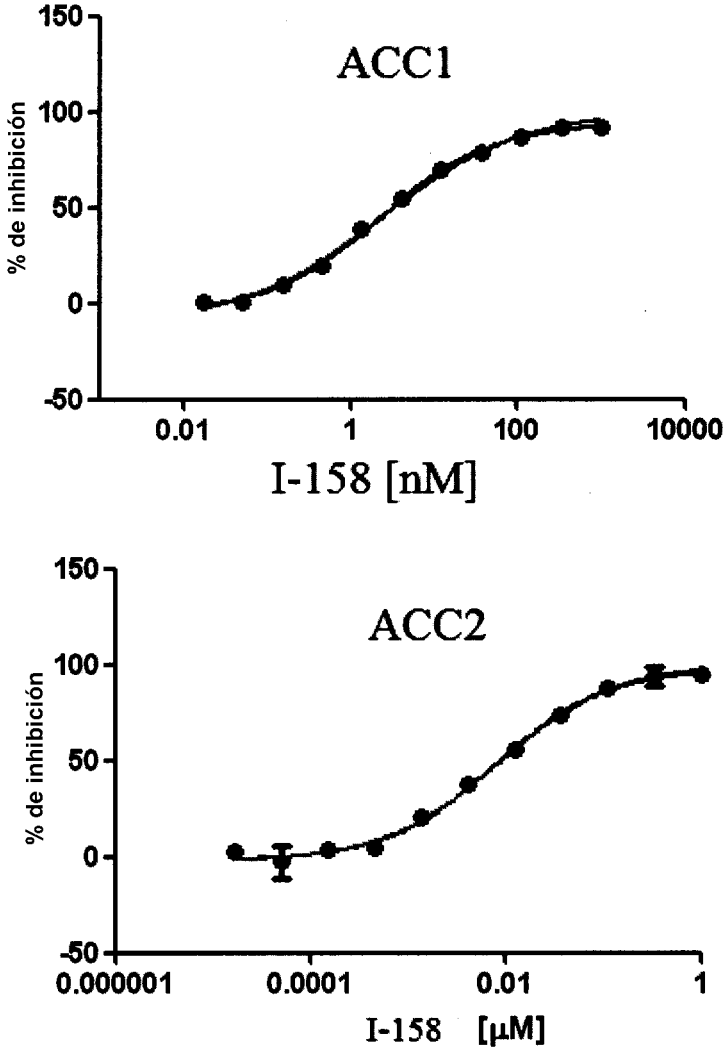

ACC1
% de inhibición
150
100
50
0
-50
0.01
1
100
10000
I-158 [nM]
ACC2
% de inhibición
150
100
50
0
-50
0.000001
0.0001
0.01
1
I-158 [µM]

Figura 1

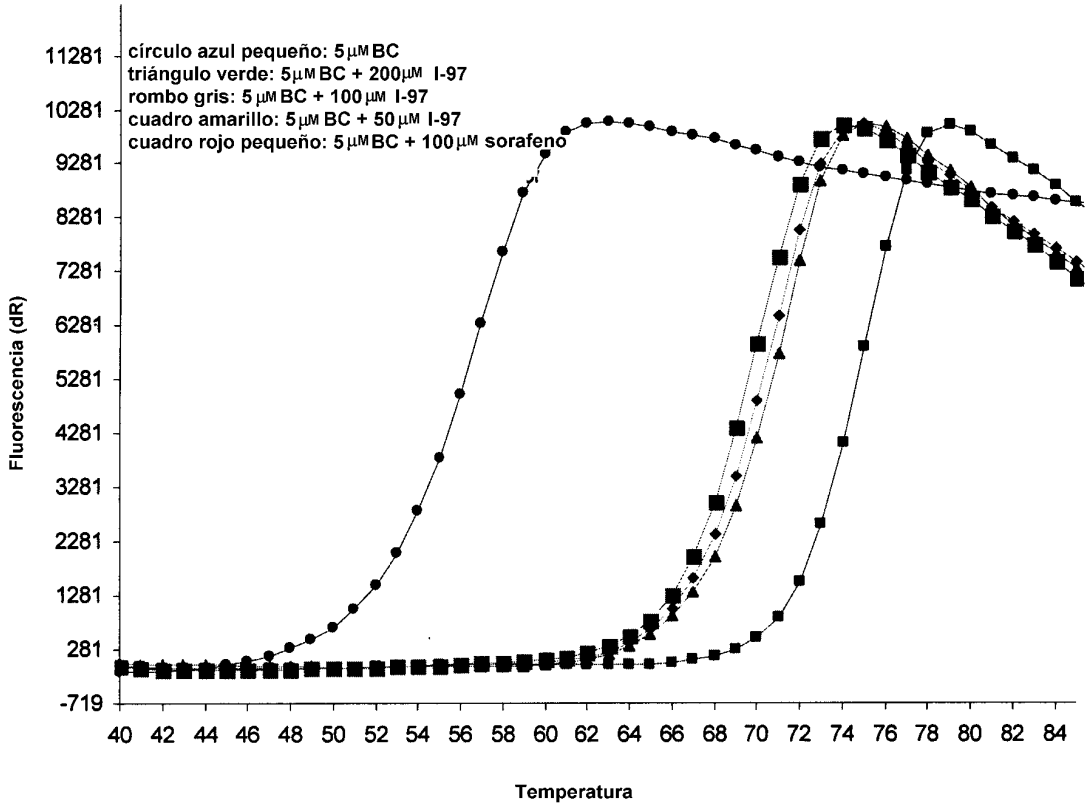

círculo azul pequeño: 5 µM BC
triángulo verde: 5µM BC + 200µM I-97
rombo gris: 5 µM BC + 100 µM I-97
cuadro amarillo: 5 µM BC + 50 µM I-97
cuadro rojo pequeño: 5 µM BC + 100 µM sorafeno
Fluorescencia (dR)
11281
10281
9281
8281
7281
6281
5281
4281
3281
2281
1281
281
-719
40 42 44 46 48 50 52 54 56 58 60 62 64 66 68 70 72 74 76 78 80 82 84
Temperatura

Figura 2

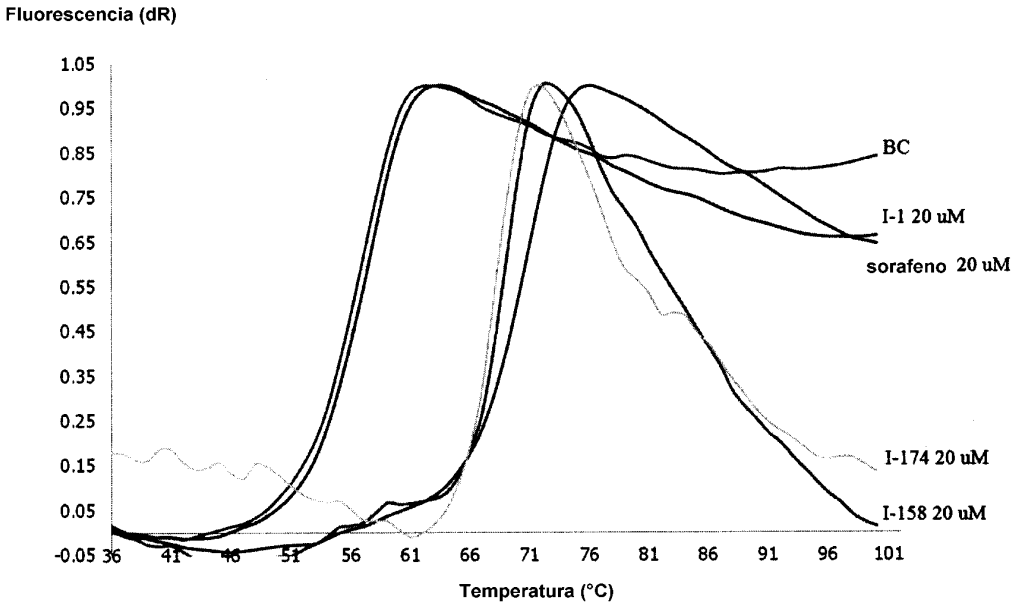
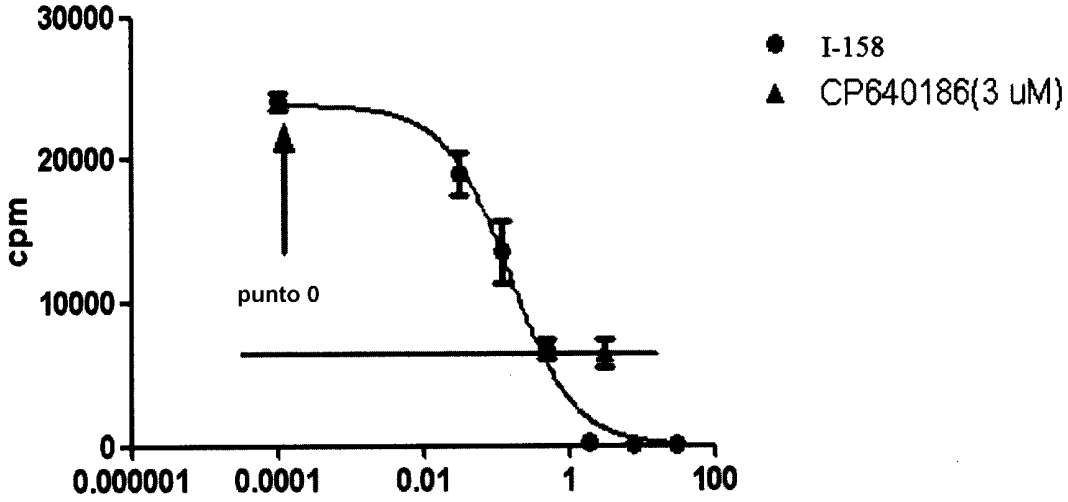
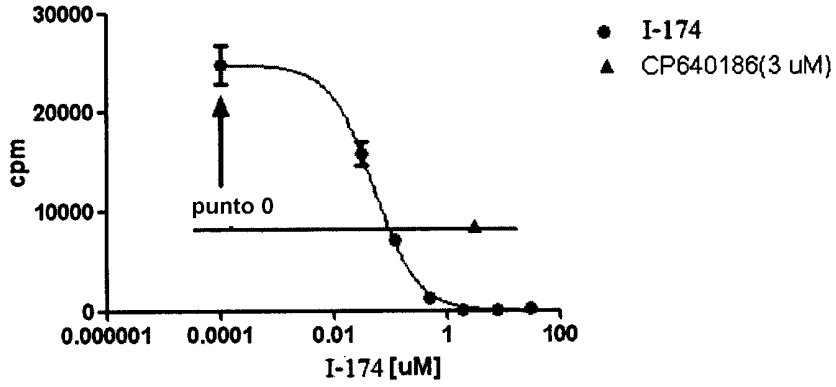

Fluorescencia (dR)
1.05
0.95
0.85
0.75
0.65
0.55
0.45
0.35
0.25
0.15
0.05
-0.05
36
41
46
51
56
61
66
71
76
81
86
91
96
101
Temperatura (°C)
BC
I-1 20 uM
sorafeno 20 uM
I-174 20 uM
I-158 20 uM

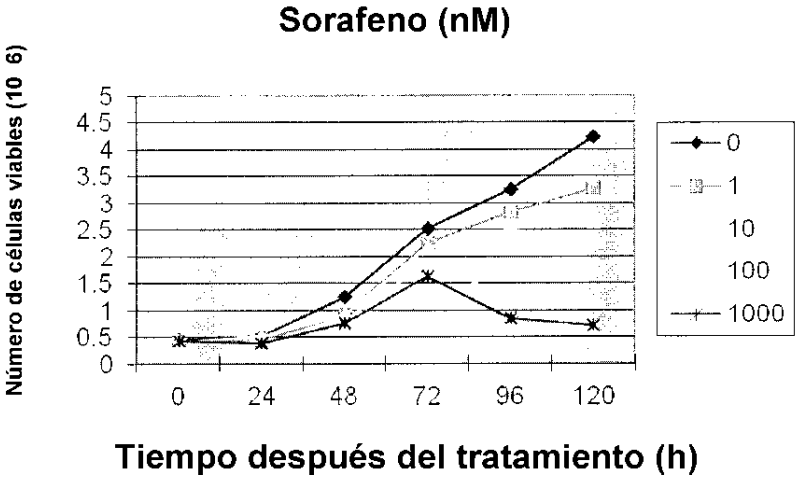
Figura 3





Inferior	= 0.0	Pendiente HI	-1.138
Arriba	24797	CI_{50}	0.04978

Figura 4


Sorafeno (nM)
Número de células viables (10 6)
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0
24
48
72
96
120
0
1
10
100
1000
Tiempo después del tratamiento (h)

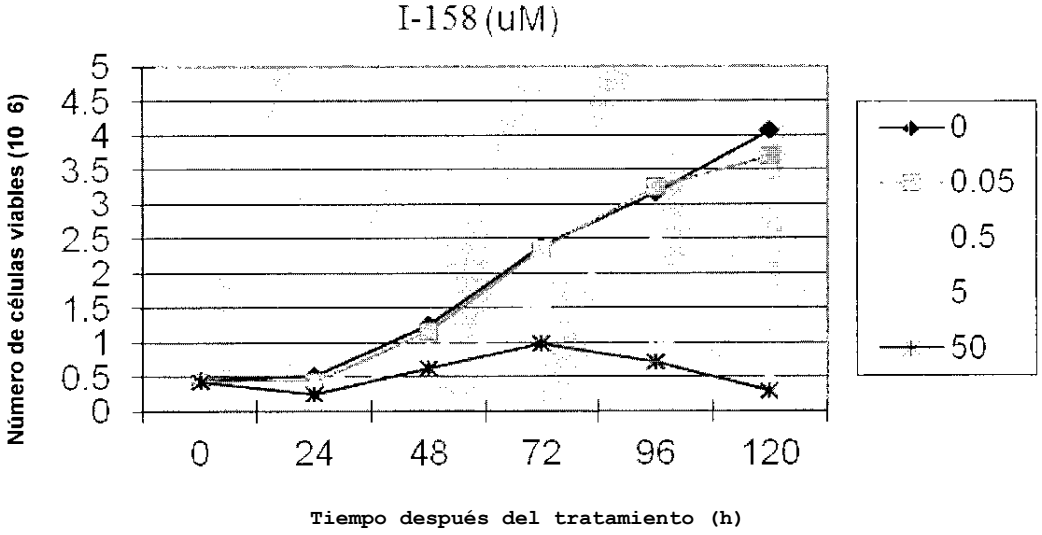
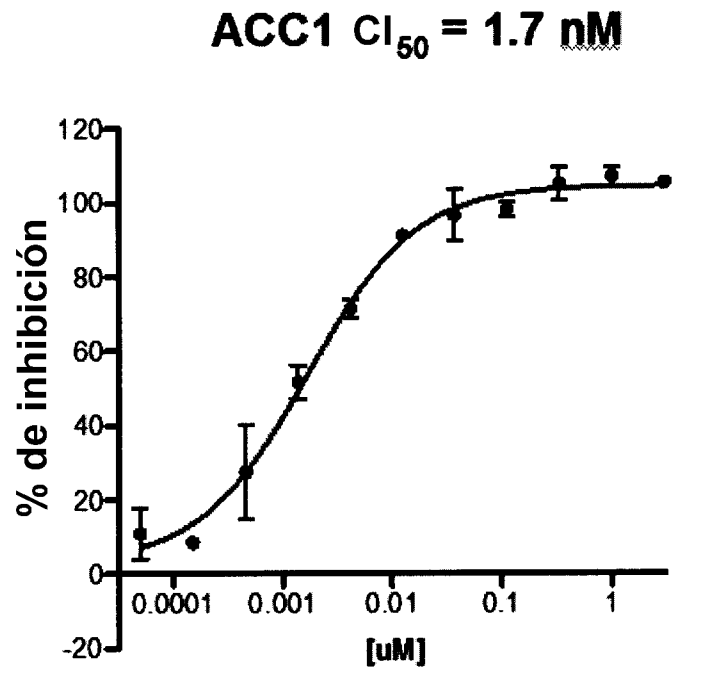

I-158 (uM)
Número de células viables (10 6)
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0
24
48
72
96
120
0
0.05
0.5
5
50
Tiempo después del tratamiento (h)

Figura 5


ACC1 CI50 = 1.7 nM
% de inhibición
120
100
80
60
40
20
0
-20
0.0001
0.001
0.01
0.1
1
[uM]

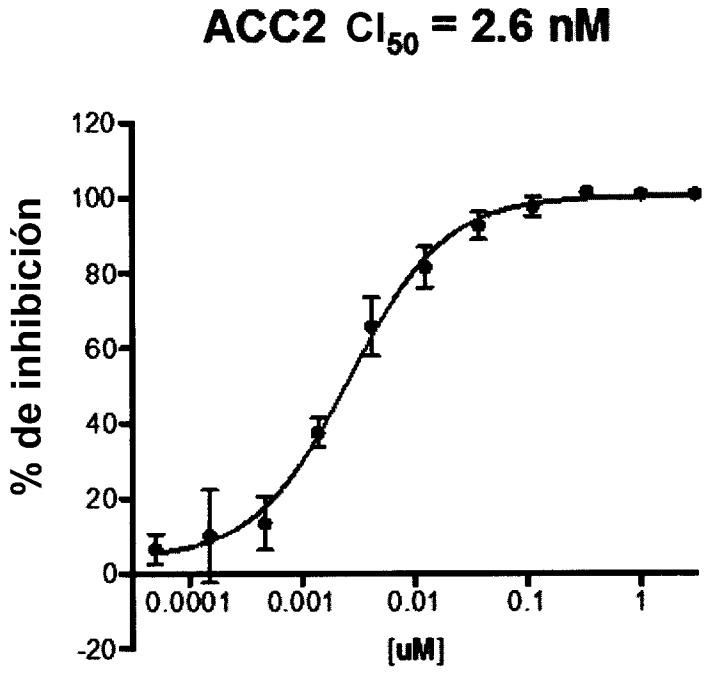

ACC2 CI50 = 2.6 nM
% de inhibición
120
100
80
60
40
20
0
-20
0.0001
0.001
0.01
0.1
1
[uM]

Figura 6

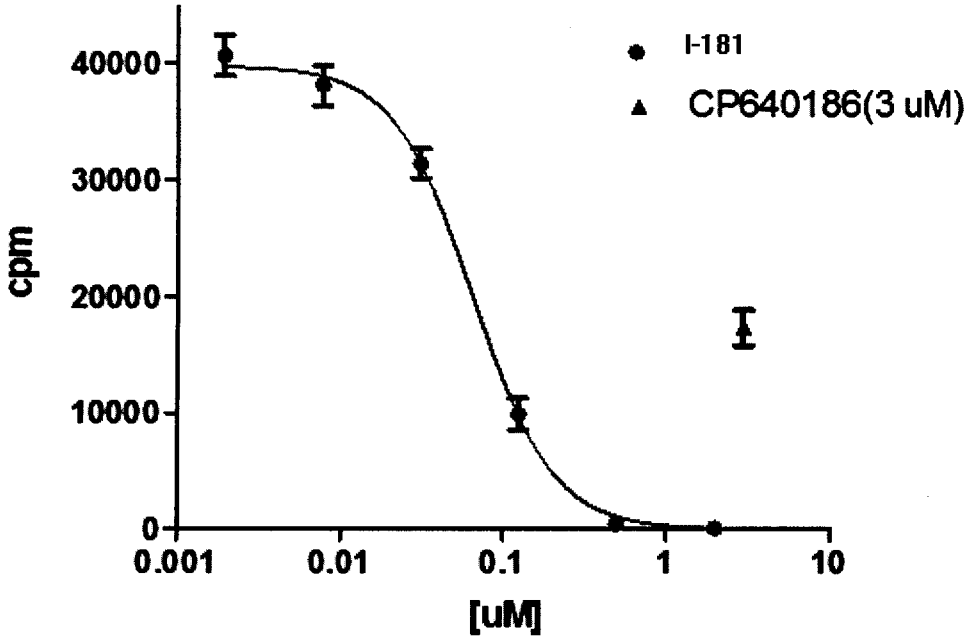
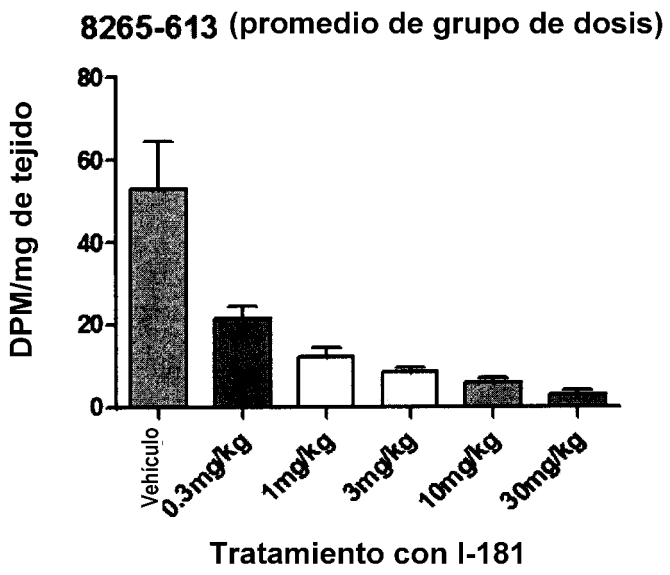

I-181
CP640186(3 uM)
40000
30000
20000
10000
0
cpm
0.001
0.01
0.1
1
10
[uM]

Figura 7



8265-613: Efecto de dosis variable de I-181

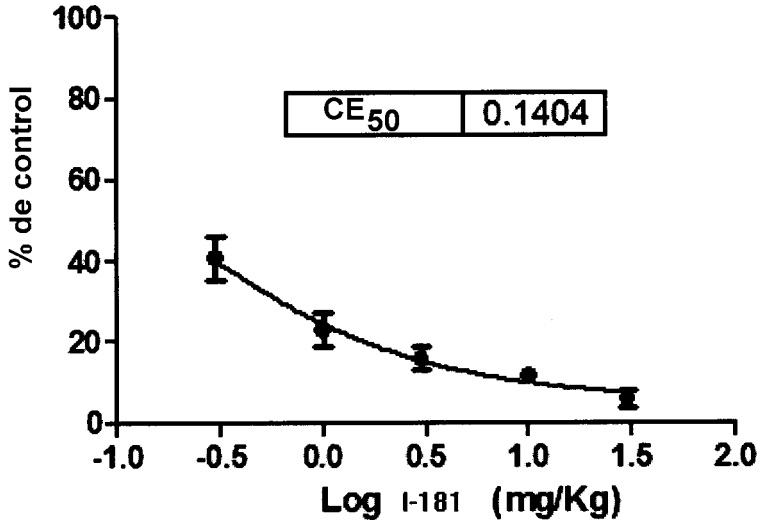


Figura 8

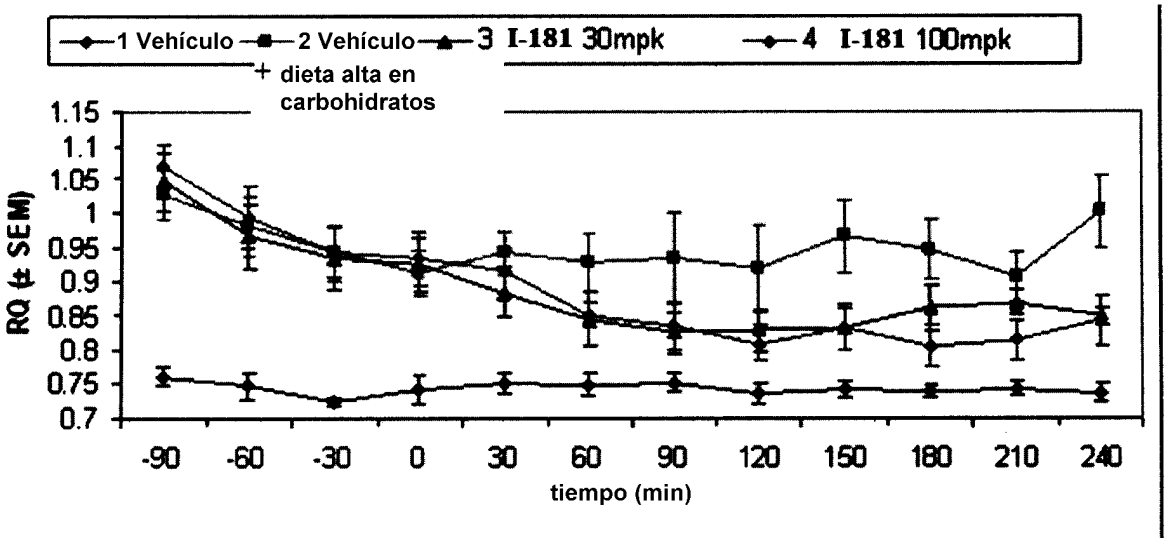

Datos RQ
1 Vehículo
2 Vehículo + dieta alta en carbohidratos
3 I-181 30mpk
4 I-181 100mpk
RQ (± SEM)
1.15
1.1
1.05
1
0.95
0.9
0.85
0.8
0.75
0.7
-90
-60
-30
0
30
60
90
120
150
180
210
240
tiempo (min)

Figura 9

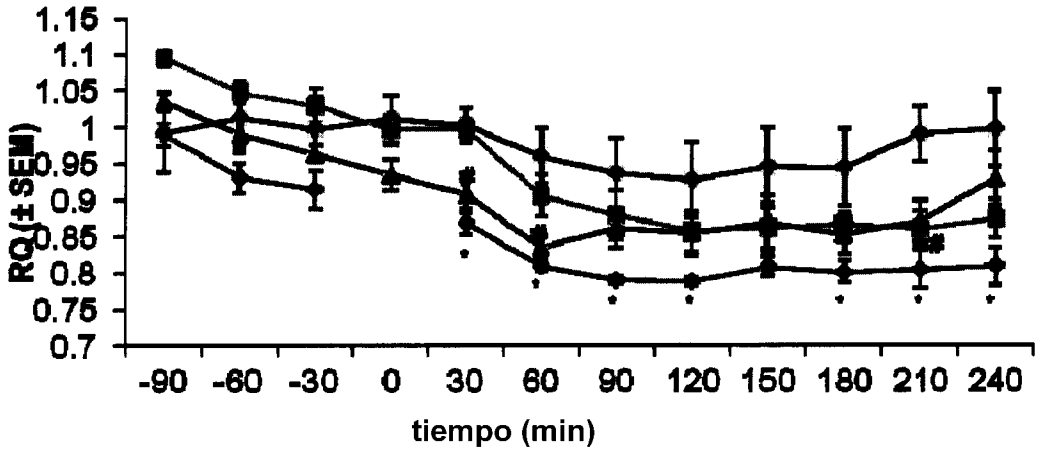

1.15
1.1
1.05
1
0.95
0.9
0.85
0.8
0.75
0.7
RQ(± SEM)
-90 -60 -30 0 30 60 90 120 150 180 210 240
tiempo (min)

Figura 10

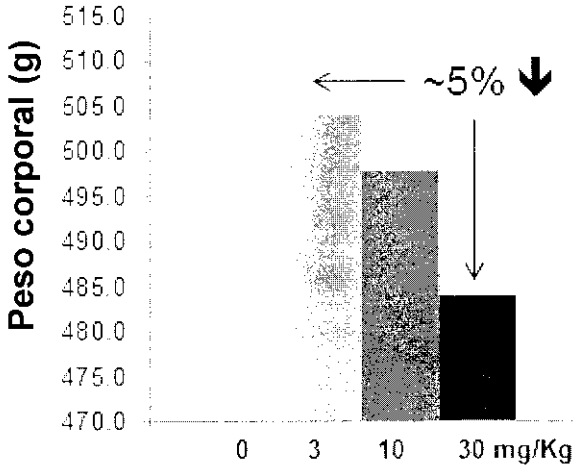

Peso corporal (g)
515.0
510.0
505.0
500.0
495.0
490.0
485.0
480.0
475.0
470.0
~5%
0
3
10
30 mg/Kg

Figura 11

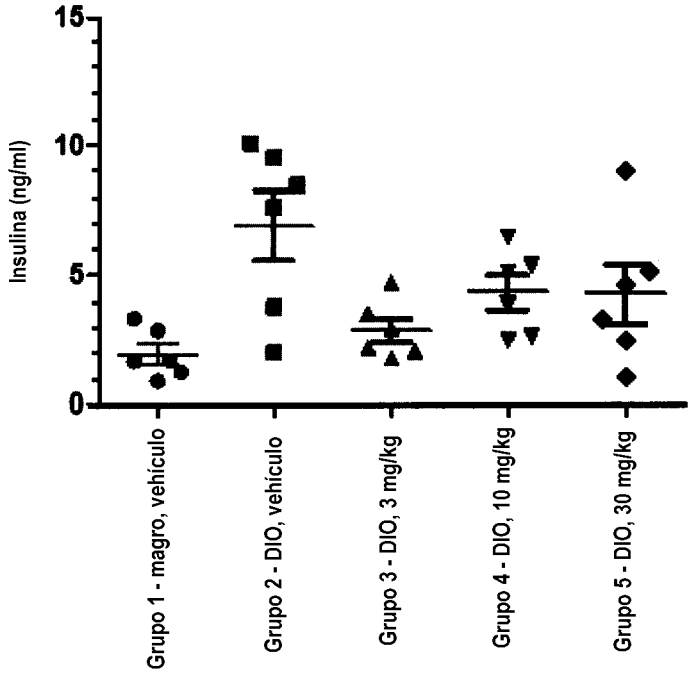

15
10
5
0
Insulina (ng/ml)
Grupo 1 - magro, vehículo
Grupo 2 - DIO, vehículo
Grupo 3 - DIO, 3 mg/kg
Grupo 4 - DIO, 10 mg/kg
Grupo 5 - DIO, 30 mg/kg

Figura 12

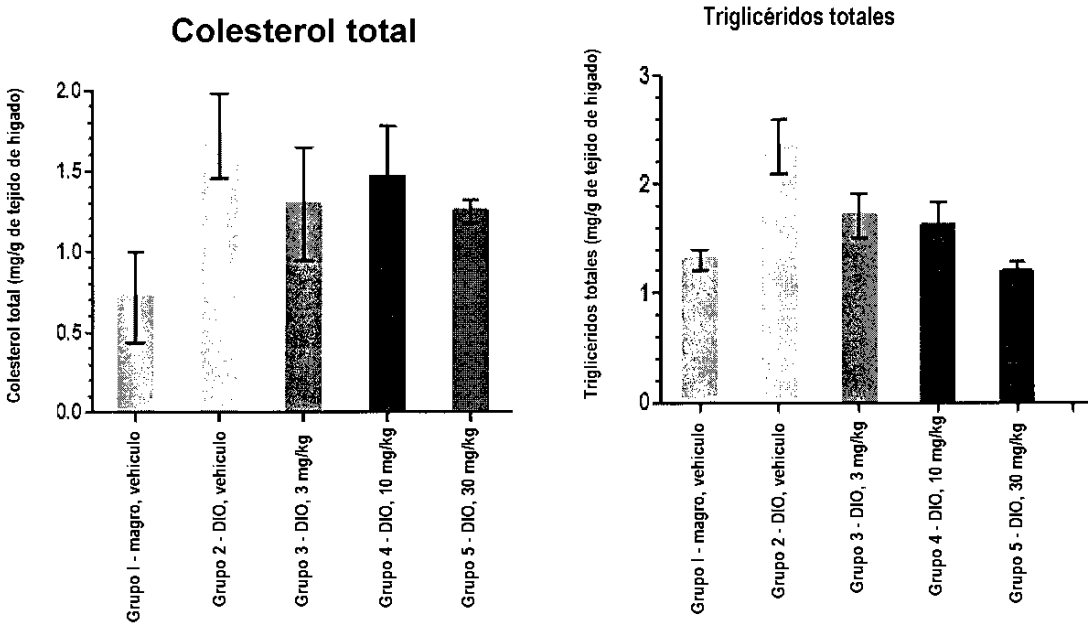

Colesterol total
Colesterol total (mg/g de tejido de higado)
2.0
1.5
1.0
0.5
0.0
Grupo I - magro, vehiculo
Grupo 2 - DIO, vehiculo
Grupo 3 - DIO, 3 mg/kg
Grupo 4 - DIO, 10 mg/kg
Grupo 5 - DIO, 30 mg/kg
Triglicéridos totales
Triglicéridos totales (mg/g de tejido de higado)
3
2
1
0
Grupo I - magro, vehiculo
Grupo 2 - DIO, vehiculo
Grupo 3 - DIO, 3 mg/kg
Grupo 4 - DIO, 10 mg/kg
Grupo 5 - DIO, 30 mg/kg

Figura 13

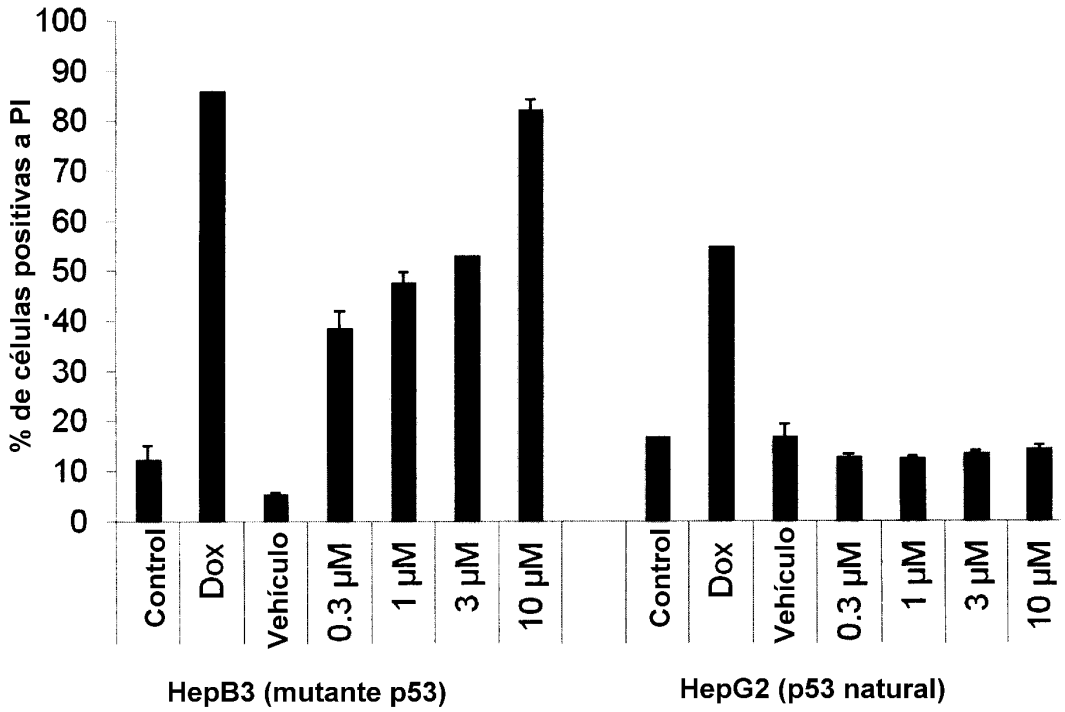

% de células positivas a PI
100
90
80
70
60
50
40
30
20
10
0
Control
Dox
Vehículo
0.3 µM
1 µM
3 µM
10 µM
Control
Dox
Vehículo
0.3 µM
1 µM
3 µM
10 µM
HepB3 (mutante p53)
HepG2 (p53 natural)

Figura 14

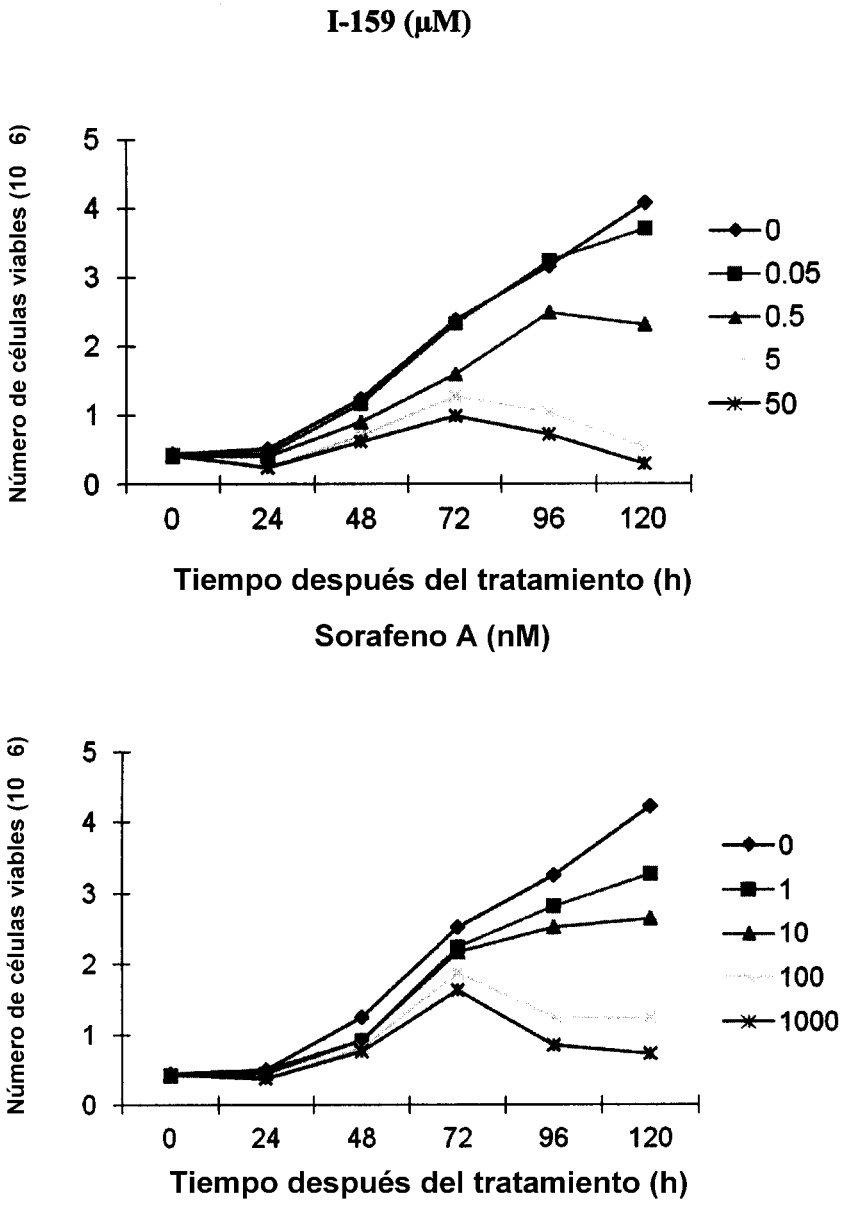

I-159 (µM)
Número de células viables (10 6)
5
4
3
2
1
0
0
24
48
72
96
120
Tiempo después del tratamiento (h)
0
0.05
0.5
5
50
Sorafeno A (nM)
Número de células viables (10 6)
5
4
3
2
1
0
0
24
48
72
96
120
Tiempo después del tratamiento (h)
0
1
10
100
1000

Figura 15

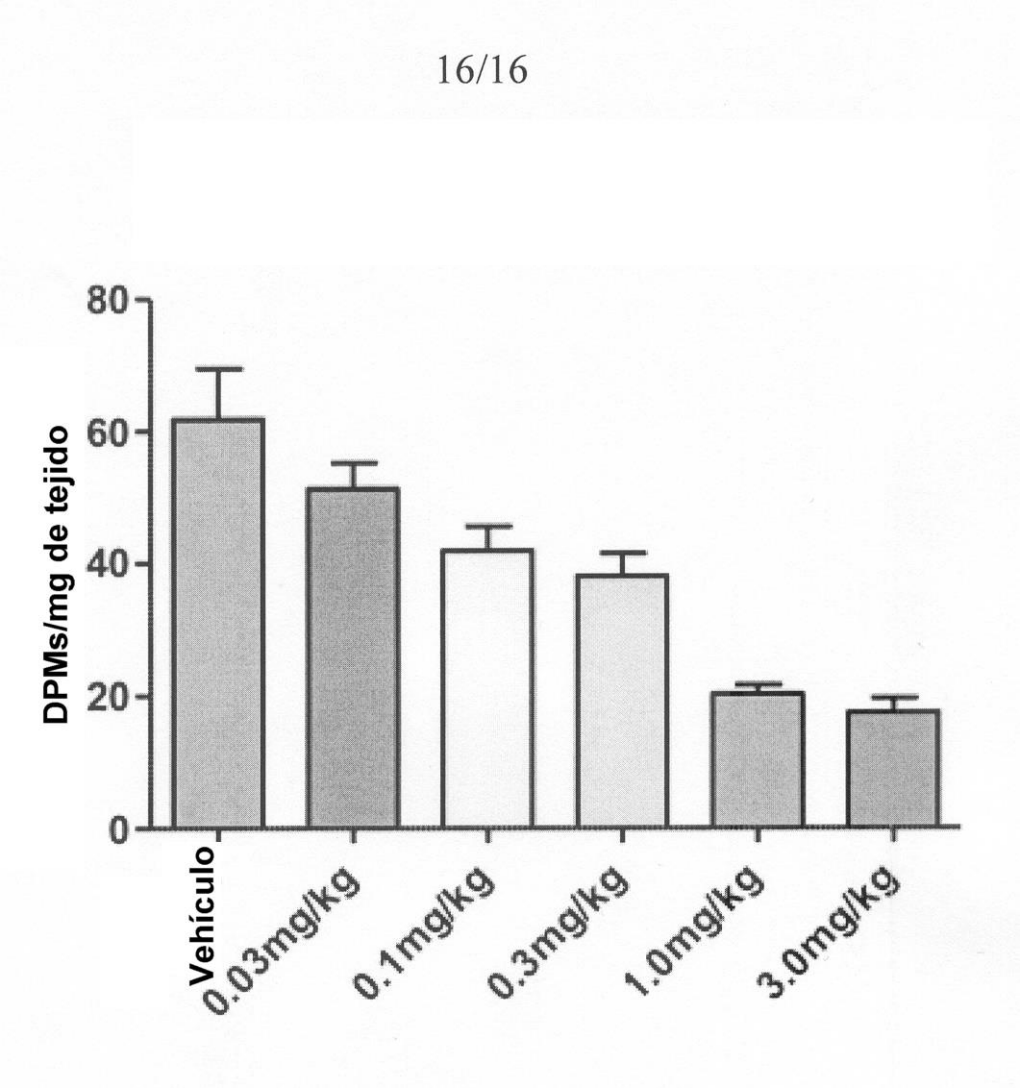

DPMs/mg de tejido
80
60
40
20
0
Vehículo
0.03mg/kg
0.1mg/kg
0.3mg/kg
1.0mg/kg
3.0mg/kg

Figura 16