CSA295318

PE 47361/09

OPS

Industria y Comercio

SUPERINTENDENCIA

Organización y
Digitalización CSA Ltda

Delegatura de Propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

09-47361

21. **EXPEDIENTE No.**

54. **TÍTULO** INHIBIDORES DEL VIRUS DE LA HEPATITIS C

51. **CLASIFICACIÓN INTERNACIONAL**

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

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C.C. 79.143.366 de Usaquén

22. **BOGOTÁ, D. C.,**

(FORMA P-10)

PETIT

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-047361- -00000-0000
Fecha: 2009-05-11 15:36:01 Dep: 2020 NUECREACION
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 826

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Industria y Comercio
SUPERINTENDENCIA

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL

(1) SOLICITUD DE :

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

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Cual

Número

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Nacionalidad o Domicilio: Estados Unidos de América

(5) PCT (85)

Solicitud Internacional No. PCT/US2007/084012 Fecha 08.11.2007

Publicación Internacional No. WO/2008/060927 Fecha 22.05.2008

(6) Título (54) INHIBIDORES DEL VIRUS DE LA HEPATITIS C

(7) Clasificación Internacional (51) C07D 401/12; A61K 31/4709; A61P 31/14; C07D 401/14; C07D 417/14 ; C07K 5/00

(8) Prioridad SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	09.11.2006	60/865,034
US	05.11.2007	11/934,840

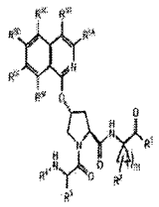
(9) Comprobante de pago No. 09-18514; 09-18408; 09-2341; 08-100364; 08-100365. **Fecha** MAR 6/09; MAR 6/09; ENE 13/09; DIC 26/08; DIC 26/08.

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

(10) **ANEXOS**

- [X] Comprobante de pago de la tasa de presentación de la solicitud
- [X] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- [X] Poderes, si fuere el caso (ver radicado No. 08.129.339 poder General de Bristol-Myers Squibb Company)
- [ ] Documento de cesión del inventor al solicitante o a su causante
- [ ] Declaraciones
- [X] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [X] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [ ] De ser el caso, certificado de depósito del material biológico
- [X] Arte final 12 x 12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros: Extractos

(11) **FIGURA CARATERISTICA**



(12) Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDOÑEZ

FIRMA:

C.C. 79.143.366 de Usaquén T.P. 20.281

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

09927 3

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 May 2008 (22.05.2008)

PCT

(10) International Publication Number
WO 2008/060927 A2

(51) International Patent Classification:
C07D 401/12 (2006.01) *C07K 5/00* (2006.01)
C07D 401/14 (2006.01) *A61K 31/4709* (2006.01)
C07D 417/14 (2006.01) *A61P 31/14* (2006.01)

(21) International Application Number:
PCT/US2007/084012

(22) International Filing Date:
8 November 2007 (08.11.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/865,034 9 November 2006 (09.11.2006) US
11/934,840 5 November 2007 (05.11.2007) US

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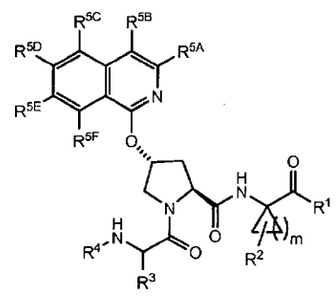
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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH,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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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

(54) Title: HEPATITIS C VIRUS INHIBITORS



(I)

(57) Abstract: Hepatitis C virus inhibitors having the general formula, (I) are disclosed. Compositions comprising the compounds and methods for using the compounds to inhibit HCV are also disclosed.

WO 2008/060927 A2

HEPATITIS C VIRUS INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial Number 60/865,034 filed November 9, 2006.

The present disclosure is generally directed to antiviral compounds, and more specifically directed to compounds which inhibit the function of the NS3 protease (also referred to herein as "serine protease") encoded by Hepatitis C virus (HCV), compositions comprising such compounds, and methods for inhibiting the function of the NS3 protease.

HCV is a major human pathogen, infecting an estimated 170 million persons worldwide - roughly five times the number infected by human immunodeficiency virus type 1. A substantial fraction of these HCV infected individuals develop serious progressive liver disease, including cirrhosis and hepatocellular carcinoma.

Presently, the most effective HCV therapy employs a combination of alpha-interferon and ribavirin, leading to sustained efficacy in 40% of patients. Recent clinical results demonstrate that pegylated alpha-interferon is superior to unmodified alpha-interferon as monotherapy. However, even with experimental therapeutic regimens involving combinations of pegylated alpha-interferon and ribavirin, a substantial fraction of patients do not have a sustained reduction in viral load. Thus, there is a clear and unmet need to develop effective therapeutics for treatment of HCV infection.

HCV is a positive-stranded RNA virus. Based on a comparison of the deduced amino acid sequence and the extensive similarity in the 5' untranslated region, HCV has been classified as a separate genus in the Flaviviridae family. All members of the Flaviviridae family have enveloped virions that contain a positive stranded RNA genome encoding all known virus-specific proteins *via* translation of a single, uninterrupted, open reading frame.

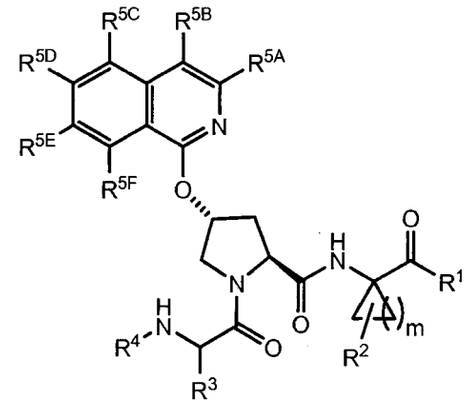
Considerable heterogeneity is found within the nucleotide and encoded amino acid sequence throughout the HCV genome. Six major genotypes have been characterized, and more than 50 subtypes have been described. The major genotypes of HCV differ in their distribution worldwide, and the clinical significance of the genetic heterogeneity of HCV remains elusive despite numerous studies of the

possible effect of genotypes on pathogenesis and therapy.

The single strand HCV RNA genome is approximately 9500 nucleotides in length and has a single open reading frame (ORF) encoding a single large polyprotein of about 3000 amino acids. In infected cells, this polyprotein is cleaved at multiple sites by cellular and viral proteases to produce the structural and non- structural (NS) proteins. In the case of HCV, the generation of mature non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) is effected by two viral proteases. The first one cleaves at the NS2-NS3 junction; the second one is a serine protease contained within the *N*-terminal region of NS3 and mediates all the subsequent cleavages downstream of NS3, both in cis, at the NS3-NS4A cleavage site, and in trans, for the remaining NS4A- NS4B, NS4B-NS5A, NS5A-NS5B sites. The NS4A protein appears to serve multiple functions, acting as a co-factor for the NS3 protease and possibly assisting in the membrane localization of NS3 and other viral replicase components. The complex formation of the NS3 protein with NS4A is essential for efficient polyprotein processing, enhancing the proteolytic cleavage at all of the sites. The NS3 protein also exhibits nucleoside triphosphatase and RNA helicase activities. NS5B is a RNA-dependent RNA polymerase that is involved in the replication of HCV.

The present disclosure provides peptide compounds that can inhibit the functioning of the NS3 protease, e.g., in combination with the NS4A protease. Further, the present disclosure describes the administration of combination therapy to a patient whereby a compound in accordance with the present disclosure, which is effective to inhibit the HCV NS3 protease, can be administered with one or two additional compounds having anti-HCV activity.

In a first aspect the present disclosure provides a compound of formula (I)



(I),

or a pharmaceutically acceptable salt thereof, wherein

m is 1, 2, or 3;

R^1 is selected from hydroxy and $-NHSO_2R^6$; wherein R^6 is selected from alkyl, aryl, cycloalkyl, (cycloalkyl)alkyl, heterocyclyl, and $-NR^aR^b$, wherein the alkyl, the cycloalkyl and the cycloalkyl part of the (cycloalkyl)alkyl are optionally substituted with one, two, or three substituents selected from alkenyl, alkoxy, alkoxyalkyl, alkyl, arylalkyl, arylcarbonyl, cyano, cycloalkenyl, (cycloalkyl)alkyl, halo, haloalkoxy, haloalkyl, and (NR^eR^f)carbonyl;

R^2 is selected from hydrogen, alkenyl, alkyl, and cycloalkyl, wherein the alkenyl, alkyl, and cycloalkyl are optionally substituted with halo;

R^3 is selected from alkenyl, alkoxyalkyl, alkoxycarbonylalkyl, alkyl, arylalkyl, carboxyalkyl, cyanoalkyl, cycloalkyl, (cycloalkyl)alkyl, haloalkoxy, haloalkyl, (heterocyclyl)alkyl, hydroxyalkyl, (NR^cR^d)alkyl, and (NR^eR^f)carbonylalkyl;

R^4 is selected from phenyl and a five- or six-membered partially or fully unsaturated ring optionally containing one, two, three, or four heteroatoms selected from nitrogen, oxygen, and sulfur; wherein each of the rings is optionally substituted with one, two, three, or four substitutents independently selected from alkoxy, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfanyl, carboxy, cyano, cycloalkyl, cycloalkyloxy, halo, haloalkyl, haloalkoxy, $-NR^cR^d$, (NR^eR^f)carbonyl, (NR^eR^f)sulfonyl, and oxo; provided that when R^4 is a six-membered substituted ring all substituents on the ring other than fluoro must be in the meta and/or para positions relative to the ring's point of attachment to the parent molecular moiety;

R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^{5E} and R^{5F} are each independently selected from hydrogen, alkoxy, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, carboxy, cyano, cyanoalkyl, cycloalkyl, halo, haloalkyl, haloalkoxy, heterocyclyl, hydroxy, hydroxyalkyl, nitro,–NR^cR^d, (NR^cR^d)alkyl, (NR^cR^d)alkoxy, (NR^eR^f)carbonyl, and (NR^eR^f)sulfonyl; or

two adjacent R^5 groups, together with the carbon atoms to which they are attached, form a four- to seven-membered partially - or fully-unsaturated ring optionally containing one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the ring is optionally substituted with one, two, or three groups independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, and haloalkyl;

R^a and R^b are independently selected from hydrogen, alkoxy, alkyl, aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, heterocyclyl, and heterocyclylalkyl; or R^a and R^b together with the nitrogen atom to which they are attached form a four to seven-membered monocyclic heterocyclic ring;

R^c and R^d are independently selected from hydrogen, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, arylalkyl, and haloalkyl; and

R^e and R^f are independently selected from hydrogen, alkyl, aryl, arylalkyl, and heterocyclyl; wherein the aryl, the aryl part of the arylalkyl, and the heterocyclyl are optionally substituted with one or two substituents independently selected from alkoxy, alkyl, and halo.

In a first embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1 is $–NHSO_2R^6$.

In a second embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein

m is 1 or 2;

R^1 is $–NHSO_2R^6$; wherein R^6 is selected from alkyl, aryl, cycloalkyl, (cycloalkyl)alkyl, heterocyclyl, and $–NR^aR^b$, wherein the alkyl, the cycloalkyl and the cycloalkyl part of the (cycloalkyl)alkyl are optionally substituted with one, two, or three substituents selected from alkenyl, alkoxy, alkoxyalkyl, alkyl, arylalkyl, arylcarbonyl, cyano, cycloalkenyl, (cycloalkyl)alkyl, halo, haloalkoxy, haloalkyl, and (NR^eR^f)carbonyl;

R^2 is selected from alkenyl, alkyl, and cycloalkyl, wherein the alkenyl, alkyl, and cycloalkyl are optionally substituted with halo;

R^3 is selected from alkenyl and alkyl;

R^4 is selected from phenyl and a five- or six-membered partially or fully unsaturated ring optionally containing one, two, three, or four heteroatoms selected from nitrogen, oxygen, and sulfur; wherein each of the rings is optionally substituted with one, two, three, or four substitutents independently selected from alkoxy, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfanyl, carboxy, cyano, cycloalkyl, cycloalkyloxy, halo, haloalkyl, haloalkoxy, $-NR^cR^d$, (NR^eR^f)carbonyl, (NR^eR^f)sulfonyl, and oxo; provided that when R^4 is a six-membered substituted ring all substituents on the ring other than fluoro must be in the meta and/or para positions relative to the ring's point of attachment to the parent molecular moiety;

R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^{5E} and R^{5F} are each independently selected from hydrogen, alkoxy, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, carboxy, cyano, cyanoalkyl, cycloalkyl, halo, haloalkyl, haloalkoxy, heterocyclyl, hydroxy, hydroxyalkyl, nitro,$-NR^cR^d$, (NR^cR^d)alkyl, (NR^cR^d)alkoxy, (NR^eR^f)carbonyl, and (NR^eR^f)sulfonyl; or

two adjacent R^5 groups, together with the carbon atoms to which they are attached, form a four- to seven-membered partially - or fully-unsaturated ring optionally containing one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the ring is optionally substituted with one, two, or three groups independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, and haloalkyl;

R^a and R^b are independently selected from hydrogen, alkoxy, alkyl, aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, heterocyclyl, and heterocyclylalkyl; or R^a and R^b together with the nitrogen atom to which they are attached form a four- to seven-membered monocyclic heterocyclic ring;

R^c and R^d are independently selected from hydrogen, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, arylalkyl, and haloalkyl; and

R^e and R^f are independently selected from hydrogen, alkyl, aryl, arylalkyl, and heterocyclyl; wherein the aryl, the aryl part of the arylalkyl, and the heterocyclyl are optionally substituted with one or two substituents independently selected from alkoxy, alkyl, and halo.

In a third embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from unsubstituted cycloalkyl and $-NR^aR^b$.

In a fourth embodiment of the first aspect the present disclosure provides a compound formula (I), or a pharmaceutically acceptable salt thereof, wherein

m is 1;

R^1 is $-NHSO_2R^6$; wherein R^6 is unsubstituted cycloalkyl;

R^2 is alkenyl;

R^3 is selected from alkenyl and alkyl;

R^4 is selected from phenyl and a five- or six-membered partially or fully unsaturated ring optionally containing one, two, three, or four heteroatoms selected from nitrogen, oxygen, and sulfur; wherein each of the rings is optionally substituted with one, two, or three substitutents independently selected from alkoxy, alkoxycarbonyl, alkyl, alkylcarbonyl, carboxy, cyano, cycloalkyl, cycloalkyloxy, halo, haloalkyl, haloalkoxy, $-NR^cR^d$, (NR^eR^f)carbonyl, (NR^eR^f)sulfonyl, and oxo; provided that when R^4 is a six-membered substituted ring all substituents on the ring other than fluoro must be in the meta and/or para positions relative to the ring's point of attachment to the parent molecular moiety;

R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^{5E} and R^{5F} are each independently selected from hydrogen, alkoxy, aryl, and $-NR^cR^d$; or

two adjacent R^5 groups, together with the carbon atoms to which they are attached, form a six-membered partially- or fully-unsaturated ring optionally containing one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the ring is optionally substituted with one, two, or three groups independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, and haloalkyl;

R^c and R^d are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, and arylalkyl; and

R^e and R^f are independently selected from hydrogen, alkyl, aryl, and arylalkyl.

In a fifth embodiment of the first aspect the present disclosure provides a compound formula (I), or a pharmaceutically acceptable salt thereof, wherein

m is 1;

R^1 is $-NHSO_2R^6$; wherein R^6 is unsubstituted cycloalkyl;

R^2 is alkenyl;

R^3 is selected from alkenyl and alkyl;

R^4 is phenyl optionally substituted with one, two, or three substitutents independently selected from alkoxy, alkoxycarbonyl, alkyl, alkylcarbonyl, carboxy, cyano, cycloalkyl, cycloalkyloxy, halo, haloalkyl, haloalkoxy, $-NR^cR^d$, (NR^cR^f)carbonyl, (NR^eR^f)sulfonyl, and oxo; provided that all substituents on the ring other than fluoro must be in the meta and/or para positions relative to the ring's point of attachment to the parent molecular moiety;

R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^{5E} and R^{5F} are each independently selected from hydrogen, alkoxy, aryl, and $-NR^cR^d$; or

two adjacent R^5 groups, together with the carbon atoms to which they are attached, form a six-membered partially- or fully-unsaturated ring optionally containing one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the ring is optionally substituted with one, two, or three groups independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, and haloalkyl;

R^c and R^d are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, and arylalkyl; and

R^e and R^f are independently selected from hydrogen, alkyl, aryl, and arylalkyl.

In a sixth embodiment of the first aspect the present disclosure provides a compound formula (I), or a pharmaceutically acceptable salt thereof,
wherein

m is 1;

R^1 is $-NHSO_2R^6$; wherein R^6 is unsubstituted cycloalkyl;

R^2 is alkenyl;

R^3 is selected from alkenyl and alkyl;

R^4 is a six-membered fully unsaturated ring containing one nitrogen atom; wherein the ring is optionally substituted with one, two, or three substitutents independently selected from alkoxy, alkoxycarbonyl, alkyl, alkylcarbonyl, carboxy, cyano, cycloalkyl, cycloalkyloxy, halo, haloalkyl, haloalkoxy, $-NR^cR^d$, (NR^eR^f)carbonyl, (NR^eR^f)sulfonyl, and oxo; provided that all substituents on the ring

other than fluoro must be in the meta and/or para positions relative to the ring's point of attachment to the parent molecular moiety;

R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^{5E} and R^{5F} are each independently selected from hydrogen, alkoxy, aryl, and $-NR^cR^d$; or

two adjacent R^5 groups, together with the carbon atoms to which they are attached, form a six-membered partially- or fully-unsaturated ring optionally containing one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the ring is optionally substituted with one, two, or three groups independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, and haloalkyl;

R^c and R^d are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, and arylalkyl; and

R^e and R^f are independently selected from hydrogen, alkyl, aryl, and arylalkyl.

In a second aspect the present disclosure provides a composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In a first embodiment of the second aspect the composition further comprises at least one additional compound having anti-HCV activity. In a second embodiment of the second aspect at least one of the additional compounds is an interferon or a ribavirin. In a third embodiment of the second aspect the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

In a fourth embodiment of the second aspect the present disclosure provides a composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable carrier, and at least one additional compound having anti-HCV activity; wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

In a fifth embodiment of the second aspect the present disclosure provides a composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable carrier, and at least one additional compound having anti-HCV activity; wherein at least one of the additional

compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

In a third aspect the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof. In a first embodiment of the third aspect the method further comprises administering at least one additional compound having anti-HCV activity prior to, after, or simultaneously with the compound of formula (I), or a pharmaceutically acceptable salt thereof. In a second embodiment of the third aspect at least one of the additional compounds is an interferon or a ribavirin. In a fourth embodiment of the third aspect the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

In a fifth embodiment of the third aspect the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and at least one additional compound having anti-HCV activity prior to, after, or simultaneously with the compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

In a sixth embodiment of the third aspect the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and at least one additional compound having anti-HCV activity prior to, after, or simultaneously with the compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and

IMPDH for the treatment of an HCV infection.

In a fourth aspect the present disclosure provides a composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, one, two, three, four, or five additional compounds having anti-HCV activity, and a pharmaceutically acceptable carrier. In a first embodiment of the fourth aspect the compsition comprises three or four additional compounds having anti-HCV activity. In a second embodiment of the fourth aspect the composition comprises one or two additional compounds having anti-HCV activity.

In a fifth aspect the present disclosure provides a method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof and one, two, three, four, or five additional compounds having anti-HCV activity prior to, after, or simultaneously with the compound of formula (I), or a pharmaceutically acceptable salt thereof. In a first embodiment of the first aspect the method comprises administering three or four additional compounds having anti-HCV activity. In a second embodiment of the first aspect the method comprises administering one or two additional compounds having anti-HCV activity.

Other aspects of the present disclosure may include suitable combinations of embodiments disclosed herein.

Yet other aspects and embodiments may be found in the description provided herein.

The description of the present disclosure herein should be construed in congruity with the laws and principals of chemical bonding. In some instances it may be necessary to remove a hydrogen atom in order accommodate a substitutent at any given location.

It should be understood that the compounds encompassed by the present disclosure are those that are suitably stable for use as pharmaceutical agent.

It is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. For example, when n is 2, each of the two R^5 groups may be the same or different.

All patents, patent applications, and literature references cited in the specification are herein incorporated by reference in their entirety. In the case of inconsistencies, the present disclosure, including definitions, will prevail.

As used in the present specification, the following terms have the meanings indicated:

As used herein, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise.

Unless stated otherwise, all aryl, cycloalkyl, and heterocyclyl groups of the present disclosure may be substituted as described in each of their respective definitions. For example, the aryl part of an arylalkyl group may be substituted as described in the definition of the term 'aryl'.

In some instances, the number of carbon atoms in any particular group is denoted before the recitation of the group. For example, the term "C_{1-2} alkyl" denotes an alkyl group containing one or two carbon atoms. Where these designations exist they supercede all other definitions contained herein.

As used herein, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise.

The term "alkenyl," as used herein, refers to a straight or branched chain group of two to six carbon atoms containing at least one carbon-carbon double bond.

The term "alkoxy," as used herein, refers to an alkyl group attached to the parent molecular moiety through an oxygen atom.

The term "alkoxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkoxy groups.

The term "alkoxycarbonyl," as used herein, refers to an alkoxy group attached to the parent molecular moiety through a carbonyl group.

The term "alkoxycarbonylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three alkoxycarbonyl groups.

The term "alkyl," as used herein, refers to a group derived from a straight or branched chain saturated hydrocarbon containing from one to ten carbon atoms.

The term "alkylcarbonyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a carbonyl group.

The term "alkylsulfanyl," as used herein, refers to an alkyl group attached to the parent molecular moiety through a sulfur atom.

The term "aryl," as used herein, refers to a phenyl group, or a bicyclic fused ring system wherein one or both of the rings is a phenyl group. Bicyclic fused ring systems consist of a phenyl group fused to a four- to six-membered aromatic or non-

aromatic carbocyclic ring. The aryl groups of the present disclosure can be attached to the parent molecular moiety through any substitutable carbon atom in the group. Representative examples of aryl groups include, but are not limited to, indanyl, indenyl, naphthyl, phenyl, and tetrahydronaphthyl. The aryl groups of the present disclosure can be optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkoxycarbonyl, alkyl, alkylcarbonyl, carboxy, cycloalkyl, cycloalkyloxy, cyano, halo, haloalkoxy, haloalkyl, nitro, -NR^cR^d, (NR^cR^d)carbonyl, and oxo.

The term "arylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three aryl groups.

The term "arylcarbonyl," as used herein, refers to an aryl group attached to the parent molecular moiety through a carbonyl group.

The term "carbonyl," as used herein, refers to –C(O)-.

The term "carboxy," as used herein, refers to $–CO_2H$.

The term "carboxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three carboxy groups.

The term "cyano," as used herein, refers to –CN.

The term "cyanoalkyl," as used herein, refers to an alkyl group substituted with one, two, or three cyano groups.

The term "cycloalkenyl," as used herein, refers to a non-aromatic, partially unsaturated monocyclic, bicyclic, or tricyclic ring system having three to fourteen carbon atoms and zero heteroatoms. Representative examples of cycloalkenyl groups include, but are not limited to, cyclohexenyl, octahydronaphthalenyl, and norbornylenyl.

The term "cycloalkyl," as used herein, refers to a saturated monocyclic or bicyclic hydrocarbon ring system having three to ten carbon atoms and zero heteroatoms. Representative examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, and cyclopentyl.

The term "(cycloalkyl)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three cycloalkyl groups.

The term "cycloalkyloxy," as used herein, refers to a cycloalkyl group attached to the parent molecular moiety through an oxygen atom.

The terms "halo" and "halogen," as used herein, refer to F, Cl, Br, and I.

The term "haloalkoxy," as used herein, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

The term "haloalkyl," as used herein, refers to an alkyl group substituted with one, two, three, or four halogen atoms.

The term "heterocyclyl," as used herein, refers to a five-, six-, or seven-membered ring containing one, two, or three heteroatoms independently selected from nitrogen, oxygen, and sulfur. The five-membered ring has zero to two double bonds and the six- and seven-membered rings have zero to three double bonds. The term "heterocyclyl" also includes bicyclic groups in which the heterocyclyl ring is fused to a four- to six-membered aromatic or non-aromatic carbocyclic ring or another monocyclic heterocyclyl group. The heterocyclyl groups of the present disclosure can be attached to the parent molecular moiety through a carbon atom or a nitrogen atom in the group. Examples of heterocyclyl groups include, but are not limited to, benzothienyl, furyl, imidazolyl, indolinyl, indolyl, isothiazolyl, isoxazolyl, morpholinyl, oxazolyl, piperazinyl, piperidinyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrrolopyridinyl, pyrrolyl, thiazolyl, thienyl, and thiomorpholinyl. The heterocyclyl groups of the present disclosure can be optionally substituted with one, two, three, four, or five substituents independently selected from alkoxy, alkoxycarbonyl, alkyl, alkylcarbonyl, carboxy, cycloalkyl, cycloalkyloxy, cyano, halo, haloalkoxy, haloalkyl, nitro, $-NR^cR^d$, (NR^cR^d)carbonyl, and oxo.

The term "heterocyclylalkyl," as used herein, refers to an alkyl group substituted with one, two, or three heterocyclyl groups.

The term "hydroxy," as used herein, refers to –OH.

The term "hydroxyalkyl," as used herein, refers to an alkyl group substituted with one, two, or three hydroxy groups.

The term "nitro," as used herein, refers to $–NO_2$.

The term "$-NR^aR^b$," as used herein, refers to two groups, R^a and R^b, which are attached to the parent molecular moiety through a nitrogen atom. R^a and R^b are independently selected from hydrogen, alkoxy, alkyl, aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, heterocyclyl, and heterocyclylalkyl; or R^a and R^b together with the nitrogen atom to which they are attached form a five or six-membered monocyclic heterocyclic ring.

The term "$-NR^cR^d$," as used herein, refers to two groups, R^c and R^d, which are

attached to the parent molecular moiety through a nitrogen atom. R^c and R^d are independently selected from hydrogen, alkoxycarbonyl, alkyl, and alkylcarbonyl.

The term "(NR^cR^d)alkoxy," as used herein, refers to an (NR^cR^d)alkyl group attached to the parent molecular moiety through an oxygen atom.

The term "(NR^cR^d)alkyl," as used herein, refers to an alkyl group substituted with one, two, or three $-NR^cR^d$ groups.

The term (NR^cR^d)carbonyl," as used herein, refers to an $-NR^cR^d$ group attached to the parent molecular moiety through a carbonyl group.

The term "$-NR^eR^f$," as used herein, refers to two groups, R^e and R^f, which are attached to the parent molecular moiety through a nitrogen atom. R^e and R^f are independently selected from hydrogen, alkyl, aryl, and arylalkyl.

The term "(NR^eR^f)carbonyl," as used herein, refers to an $-NR^eR^f$ group attached to the parent molecular moiety through a carbonyl group.

The term "(NR^eR^f)carbonylalkyl," as used herein, refers to an (NR^eR^f)carbonyl group attached to the parent molecular moiety through an alkyl group.

The term "(NR^eR^f)sulfonyl," as used herein, refers to an $-NR^eR^f$ group attached to the parent molecular moiety through a sulfonyl group.

The term "oxo," as used herein, refers to =O.

The term "sulfonyl," as used herein, refers to $-SO_2-$.

The term "prodrug," as used herein, represents compounds which are rapidly transformed *in vivo* to the parent compounds by hydrolysis in blood. Prodrugs of the present disclosure include esters of hydroxy groups on the parent molecule, esters of carboxy groups on the parent molecule, and amides of the amines on the parent molecule.

The compounds of the present disclosure can exist as pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds of the present disclosure which are water or oil-soluble or dispersible, which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio, and are effective for their intended use The salts can be prepared during the final isolation and purification of the

compounds or separately by reacting a suitable basic functionality with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate; digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylproprionate, picrate, pivalate, propionate, succinate, tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate, and undecanoate. Examples of acids which can be employed to form pharmaceutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric.

Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting an acidic group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of pharmaceutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, *N,N*-dimethylaniline, *N*-methylpiperidine, *N*-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, *N,N*-dibenzylphenethylamine, and *N,N'*-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

As used herein, the term "anti-HCV activity" means the compound is effective to treat the HCV virus.

The term "compounds of the disclosure", and equivalent expressions, are meant to embrace compounds of formula (I), and pharmaceutically acceptable enantiomers, diastereomers, and salts thereof. Similarly, references to intermediates, are meant to embrace their salts where the context so permits.

The term "patient" includes both human and other mammals.

The term "pharmaceutical composition" means a composition comprising a compound of the disclosure in combination with at least one additional pharmaceutical carrier, i.e., adjuvant, excipient or vehicle, such as diluents, preserving agents, fillers, flow regulating agents, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents, perfuming agents, antibacterial agents, antifungal agents, lubricating agents and dispensing agents, depending on the nature of the mode of administration and dosage forms. Ingredients listed in Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing Company, Easton, PA (1999) for example, may be used.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable risk/benefit ratio.

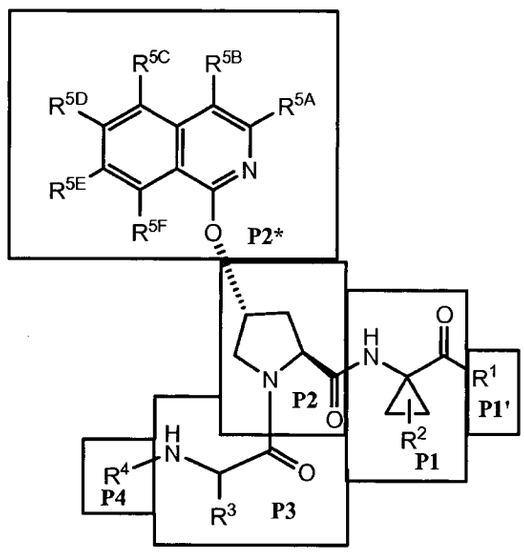
The term "therapeutically effective amount" means the total amount of each active component that is sufficient to show a meaningful patient benefit, e.g., a sustained reduction in viral load. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

The terms "treat" and "treating" refers to: (i) preventing a disease, disorder or condition from occurring in a patient which may be predisposed to the disease, disorder and/or condition but has not yet been diagnosed as having it; (ii) inhibiting the disease, disorder or condition, i.e., arresting its development; and/or (iii) relieving the disease, disorder or condition, i.e., causing regression of the disease, disorder and/or condition.

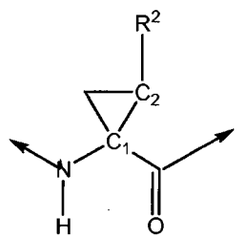
Where used in naming compounds of the present disclosure, the designations P1', P1, P2, P2*, P3, and P4, as used herein, map the relative positions of the amino acid residues of a protease inhibitor binding relative to the binding of the natural peptide cleavage substrate. Cleavage occurs in the natural substrate between P1 and P1' where the nonprime positions designate amino acids starting from the C-terminus end of the peptide natural cleavage site extending towards the *N*-terminus; whereas,

the prime positions emanate from the *N*-terminus end of the cleavage site designation and extend toward the C-terminus. For example, P1' refers to the first position away from the right hand end of the C-terminus of the cleavage site (i.e. *N*-terminus first position); whereas P1 starts the numbering from the left hand side of the C-terminus cleavage site, P2: second position from the C-terminus, etc.). (see Berger A. & Schechter I., Transactions of the Royal Society London series (1970), B257, 249-264].

The following figure shows the designations for the compounds of the present disclosure.

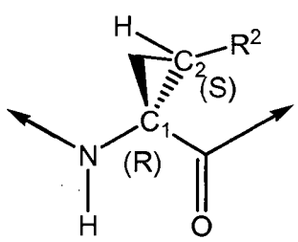


Asymmetric centers exist in the compounds of the present disclosure. For example, the compounds may include P1 cyclopropyl element of formula

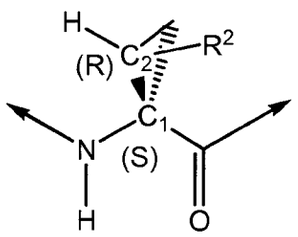


P1

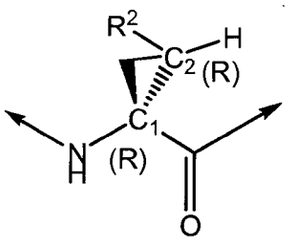
wherein C_1 and C_2 each represent an asymmetric carbon atom at positions 1 and 2 of the cyclopropyl ring.



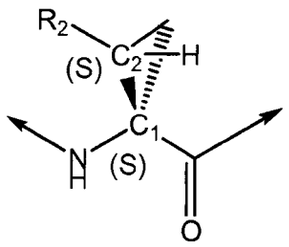
(1R, 2S)
R^2 is syn to carbonyl



(1S, 2R)
R^2 is syn to carbonyl



(1R, 2R)
R^2 is syn to amide



(1S, 2S)
R^2 is syn to amide

It should be understood that the disclosure encompasses all stereochemical forms, or mixtures thereof, which possess the ability to inhibit HCV protease.

Certain compounds of the present disclosure may also exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present disclosure includes each conformational isomer of these compounds and mixtures thereof.

Certain compounds of the present disclosure may exist in zwitterionic form and the present disclosure includes each zwitterionic form of these compounds and mixtures thereof.

When it is possible that, for use in therapy, therapeutically effective amounts of a compound of formula (I), as well as pharmaceutically acceptable salts thereof, may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. Accordingly, the disclosure further

provides pharmaceutical compositions, which include therapeutically effective amounts of compounds of formula (I) or pharmaceutically acceptable salts thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The compounds of formula (I) and pharmaceutically acceptable salts thereof, are as described above. The carrier(s), diluent(s), or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the disclosure there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of formula (I), or a pharmaceutically acceptable salt thereof, with one or more pharmaceutically acceptable carriers, diluents, or excipients.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Dosage levels of between about 0.01 and about 250 milligram per kilogram ("mg/kg") body weight per day, preferably between about 0.05 and about 100 mg/kg body weight per day of the compounds of the disclosure are typical in a monotherapy for the prevention and treatment of HCV mediated disease. Typically, the pharmaceutical compositions of this disclosure will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending on the condition being treated, the severity of the condition, the time of administration, the route of administration, the rate of excretion of the compound employed, the duration of treatment, and the age, gender, weight, and condition of the patient. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Generally, treatment is initiated with small dosages substantially less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compound is most desirably administered at a concentration level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

When the compositions of this disclosure comprise a combination of a compound of the disclosure and one or more additional therapeutic or prophylactic

agent, both the compound and the additional agent are usually present at dosage levels of between about 10 to 150%, and more preferably between about 10 and 80% of the dosage normally administered in a monotherapy regimen.

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual, or transdermal), vaginal, or parenteral (including subcutaneous, intracutaneous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional, intravenous, or intradermal injections or infusions) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil emulsions.

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

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

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, and the like.

Lubricants used in these dosage forms include sodium oleate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, betonite, xanthan gum, and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant, and pressing into tablets. A powder mixture is prepared by mixing the compound, suitable comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelating, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or and absorption agent such as betonite, kaolin, or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage, or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc, or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present disclosure can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material, and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

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

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

wax, or the like.

The compounds of formula (I), and pharmaceutically acceptable salts thereof, can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phopholipids, such as cholesterol, stearylamine, or phophatidylcholines.

The compounds of formula (I) and pharmaceutically acceptable salts thereof may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

Pharmaceutical formulations adapted for topical administration may be formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols, or oils.

For treatments of the eye or other external tissues, for example mouth and skin, the formulations are preferably applied as a topical ointment or cream. When formulated in an ointment, the active ingredient may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredient may be formulated in a cream with an oil-in-water cream base or a water-in oil base.

Pharmaceutical formulations adapted for topical administrations to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent.

Pharmaceutical formulations adapted for topical administration in the mouth include lozenges, pastilles, and mouth washes.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical formulations adapted for nasal administration wherein the carrier is a solid include a course powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, i.e., by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or nasal drops, include aqueous or oil solutions of the active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered, dose pressurized aerosols, nebulizers, or insufflators.

Pharmaceutical formulations adapted for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats, and soutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

Table 1 below lists some illustrative examples of compounds that can be administered with the compounds of this disclosure. The compounds of the disclosure can be administered with other anti-HCV activity compounds in

combination therapy, either jointly or separately, or by combining the compounds into a composition.

Table 1

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
NIM811		Cyclophilin Inhibitor	Novartis
Zadaxin		Immunomodulator	Sciclone
Suvus		Methylene blue	Bioenvision
Actilon (CPG10101)		TLR9 agonist	Coley
Batabulin (T67)	Anticancer	β-tubulin inhibitor	Tularik Inc., South San Francisco, CA
ISIS 14803	Antiviral	antisense	ISIS Pharmaceuticals Inc, Carlsbad, CA/Elan Phamaceuticals Inc., New York, NY
Summetrel	Antiviral	antiviral	Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA
GS-9132 (ACH-806)	Antiviral	HCV Inhibitor	Achillion / Gilead
Pyrazolopyrimidine compounds and salts From WO-2005047288 26 May 2005	Antiviral	HCV Inhibitors	Arrow Therapeutics Ltd.
Levovirin	Antiviral	IMPDH inhibitor	Ribapharm Inc., Costa Mesa, CA
Merimepodib (VX-497)	Antiviral	IMPDH inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA
XTL-6865 (XTL-002)	Antiviral	monoclonal antibody	XTL Biopharmaceuticals Ltd., Rehovot, Isreal

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Telaprevir (VX-950, LY-570310)	Antiviral	NS3 serine protease inhibitor	Vertex Pharmaceuticals Inc., Cambridge, MA/ Eli Lilly and Co. Inc., Indianapolis, IN
HCV-796	Antiviral	NS5B Replicase Inhibitor	Wyeth / Viropharma
NM-283	Antiviral	NS5B Replicase Inhibitor	Idenix / Novartis
GL-59728	Antiviral	NS5B Replicase Inhibitor	Gene Labs / Novartis
GL-60667	Antiviral	NS5B Replicase Inhibitor	Gene Labs / Novartis
2'C MeA	Antiviral	NS5B Replicase Inhibitor	Gilead
PSI 6130	Antiviral	NS5B Replicase Inhibitor	Roche
R1626	Antiviral	NS5B Replicase Inhibitor	Roche
2'C Methyl adenosine	Antiviral	NS5B Replicase Inhibitor	Merck
JTK-003	Antiviral	RdRp inhibitor	Japan Tobacco Inc., Tokyo, Japan
Levovirin	Antiviral	ribavirin	ICN Pharmaceuticals, Costa Mesa, CA
Ribavirin	Antiviral	ribavirin	Schering-Plough Corporation, Kenilworth, NJ
Viramidine	Antiviral	Ribavirin Prodrug	Ribapharm Inc., Costa Mesa, CA
Heptazyme	Antiviral	ribozyme	Ribozyme Pharmaceuticals Inc., Boulder, CO
BILN-2061	Antiviral	serine protease inhibitor	Boehringer Ingelheim Pharma KG, Ingelheim, Germany
SCH 503034	Antiviral	serine protease inhibitor	Schering Plough

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Zadazim	Immune modulator	Immune modulator	SciClone Pharmaceuticals Inc., San Mateo, CA
Ceplene	Immunomodulator	immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
CellCept	Immunosuppressant	HCV IgG immunosuppressant	F. Hoffmann-La Roche LTD, Basel, Switzerland
Civacir	Immunosuppressant	HCV IgG immunosuppressant	Nabi Biopharmaceuticals Inc., Boca Raton, FL
Albuferon - α	Interferon	albumin IFN-α2b	Human Genome Sciences Inc., Rockville, MD
Infergen A	Interferon	IFN alfacon-1	InterMune Pharmaceuticals Inc., Brisbane, CA
Omega IFN	Interferon	IFN-ω	Intarcia Therapeutics
IFN-β and EMZ701	Interferon	IFN-β and EMZ701	Transition Therapeutics Inc., Ontario, Canada
Rebif	Interferon	IFN-β1a	Serono, Geneva, Switzerland
Roferon A	Interferon	IFN-α2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Intron A	Interferon	IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
Intron A and Zadaxin	Interferon	IFN-α2b/α1-thymosin	RegeneRx Biopharmiceuticals Inc., Bethesda, MD/ SciClone Pharmaceuticals Inc, San Mateo, CA
Rebetron	Interferon	IFN-α2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ
Actimmune	Interferon	INF-γ	InterMune Inc., Brisbane, CA
Interferon-β	Interferon	Interferon-β-1a	Serono
Multiferon	Interferon	Long lasting IFN	Viragen/Valentis
Wellferon	Interferon	lymphoblastoid IFN-αn1	GlaxoSmithKline plc, Uxbridge, UK
Omniferon	Interferon	natural IFN-α	Viragen Inc., Plantation, FL
Pegasys	Interferon	PEGylated IFN-α2a	F. Hoffmann-La Roche LTD, Basel, Switzerland
Pegasys and Ceplene	Interferon	PEGylated IFN-α2a/ immune modulator	Maxim Pharmaceuticals Inc., San Diego, CA
Pegasys and Ribavirin	Interferon	PEGylated IFN-α2a/ribavirin	F. Hoffmann-La Roche LTD, Basel, Switzerland
PEG-Intron	Interferon	PEGylated IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron / Ribavirin	Interferon	PEGylated IFN-α2b/ribavirin	Schering-Plough Corporation, Kenilworth, NJ

Brand Name	*Physiological Class*	*Type of Inhibitor or Target*	*Source Company*
IP-501	Liver protection	antifibrotic	Indevus Pharmaceuticals Inc., Lexington, MA
IDN-6556	Liver protection	caspase inhibitor	Idun Pharmaceuticals Inc., San Diego, CA
ITMN-191 (R-7227)	Antiviral	serine protease inhibitor	InterMune Pharmaceuticals Inc., Brisbane, CA
GL-59728	Antiviral	NS5B Replicase Inhibitor	Genelabs
ANA-971	Antiviral	TLR-7 agonist	Anadys
TMC-465350	Antiviral	serine protease inhibitor	Medivir/ Tibotec

The compounds of the disclosure may also be used as laboratory reagents. Compounds may be instrumental in providing research tools for designing of viral replication assays, validation of animal assay systems and structural biology studies to further enhance knowledge of the HCV disease mechanisms. Further, the compounds of the present disclosure are useful in establishing or determining the binding site of other antiviral compounds, for example, by competitive inhibition.

The compounds of this disclosure may also be used to treat or prevent viral contamination of materials and therefore reduce the risk of viral infection of laboratory or medical personnel or patients who come in contact with such materials, e.g., blood, tissue, surgical instruments and garments, laboratory instruments and garments, and blood collection or transfusion apparatuses and materials.

This disclosure is intended to encompass compounds having formula (I) when prepared by synthetic processes or by metabolic processes including those occurring in the human or animal body (*in vivo*) or processes occurring *in vitro*.

The abbreviations used in the present application, including particularly in the illustrative schemes and examples which follow, are well-known to those skilled in the art. Some of the abbreviations used are as follows: 4-DMAP or DMAP for 4-*N,N*-dimethylaminopyridine; Boc or BOC for *tert*-butoxycarbonyl; Fmoc for 9-fluorenylmethyloxycarbonyl; CDI for 1,1'-carbonyldiimidazole; EDAC or EDC for

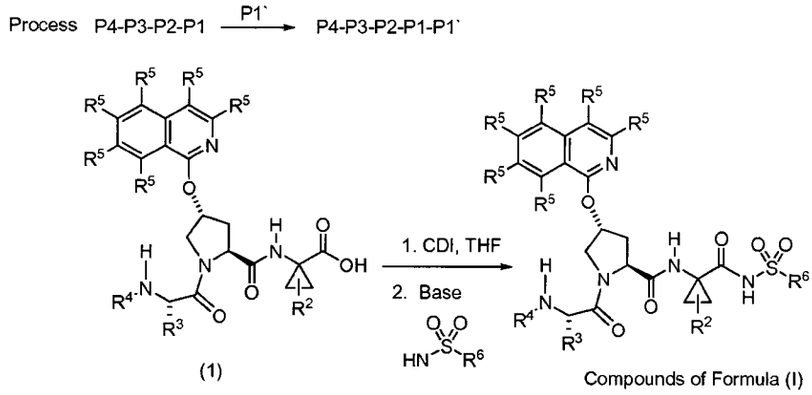
1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; THF for tetrahydrofuran; DBU for 1,8-diazabicyclo[5.4.0]undec-7-ene; TFA for trifluoroacetic acid; HATU for *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium phosphate; PyBOP for benzotriazol-1-yl-oxy-tris-pyrrolidino-phosphoniumhexafluorophosphate; Me for methyl; MeI for methyl iodide; MOtBu for potassium, sodium, or lithium *tert*-butoxide; TBME or MTBE for *tert*-butyl methyl ether; DMF for *N,N*-dimethylformamide; DMSO for dimethylsulfoxide; Ph for phenyl; DEAD for diethylazodicarboxylate; POPd for $[(t\text{-Bu})_2\text{POH}]_2\text{PdCl}_2$; NaOBu for sodium *tert*-butoxide; OAc for acetate; TBMDSCl for *tert*-butyldimethylsilyl chloride; 1,2-DME for 1,2-dimethoxyethane; DMA for *N,N*-dimethylacetamide; *n*-BuLi for n-butyllithium; *t*-BuLi or *t*BuLi for tert-butyllithium; DPPA for diphenylphosphoryl azide; TBAF for tetrabutylammonium fluoride; LiO*t*-Bu for lithium *tert*-butoxide; MeOH for methanol; DCM for dichloromethane; *t*-BuOK for potassium *tert*-butoxide; DIEA or DIPEA for diisopropylethylamine; MeCN for acetonitrile; NMM for N-methylmorpholine; DCE for 1,2-dichloroethane; LDA for lithium diisopropylamide; DMPU for 1, 3-dimethyl-3, 4, 5, 6-tetrahydro-2(*1H*)-pyrimidinone; EtOAc for ethyl acetate; and TEA for triethylamine.

The starting materials useful to synthesize the compounds of the present disclosure are known to those skilled in the art and can be readily manufactured or are commercially available.

The following methods set forth below are provided for illustrative purposes and are not intended to limit the scope of the claims. It will be recognized that it may be necessary to prepare such a compound in which a functional group is protected using a conventional protecting group then to remove the protecting group to provide a compound of the present disclosure. The details concerning the use of protecting groups in accordance with the present disclosure are known to those skilled in the art.

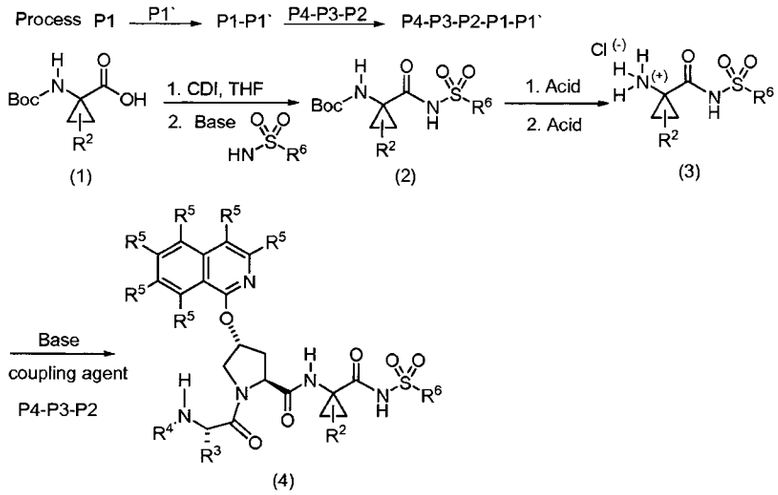
Scheme I shows the general process wherein compounds of Formula (I) are constructed by the coupling of tripeptide carboxylic acid intermediate (1) with a P1` sulfonamide. Said coupling reaction requires treatment of carboxylic acid (1) with a coupling reagent such as carbonyl diimidazole in a solvent such as THF, which can be heated to reflux, followed by the addition of the formed derivative of (1), to the P1` sulfonamide, in a solvent such as THF or methylene chloride in the presence of a base such as DBU.

Scheme I



An alternative process for the construction of compounds of Formula (I) is shown in Scheme II. Therein the P1` sulfonamide element is coupled to the P1 element using the process employed in Scheme 1. The resulting P1-P1` moiety can then be deprotected at its amino terminus. In this general example a Boc protecting group is employed but one skilled in the art would recognize that a number of suitable amino protecting groups could be employed in this process. The Boc protecting group can be removed using acid such as trifluoroacetic acid in a solvent such as dichloroethane to provide the deprotected amine as the TFA salt. Said TFA amine salt can be directly employed in the subsequent coupling reaction or as an alternative the TFA amine salt can be first converted to the HCl amine salt, and this HCl amine salt is used in said coupling reaction as shown in Scheme II. The coupling of said HCl amine salt (3) with the carboxyl terminus of a P4-P3-P2 intermediate can be achieved using coupling reagents, such as HATU, in solvents such as dichloromethane to provide compounds of Formula (I) (4).

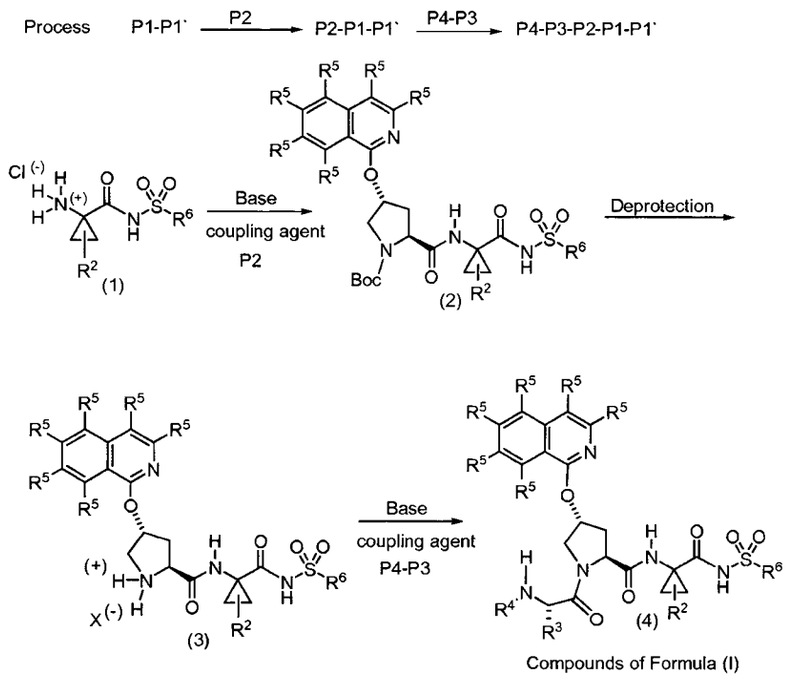
Scheme II



Compounds of Formula (I)

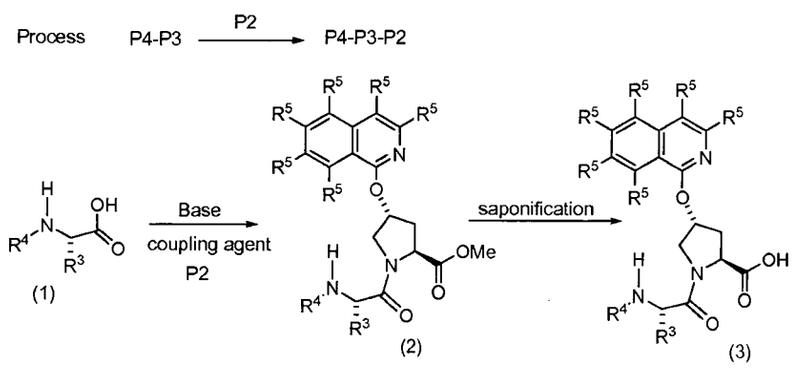
An alternative process for the construction of compounds of Formula (I) is shown in Scheme III. Here the hydrochloride salt of the P1-P1` terminal amine (1) is coupled to the free carboxyl group of the P2 element using coupling agents such as PyBOP, in the presence of a base such as diisopropylamine, and in a solvent such as methylene chloride. The resulting P2-P1-P1` intermediate can be converted to compounds of Formula (I) in a two step process wherein the first step is deprotection of the P2 amine terminus using an acid such as TFA in a solvent such as methylene chloride. The resulting trifluoroacetic acid salt can be coupled with the carboxyl terminus of the P4-P3 element using standard coupling agents such as PyBop in the presence of base such as diisopropyl amine, and using solvents such methylene chloride to provide compounds of Formula (I) (4).

Scheme III



The P4-P3-P2 intermediate utilized in the above schemes can be constructed as previously described with a further description of this process shown in general Scheme IV. The free carboxyl terminus of the P4-P3 intermediate (1), can be coupled to the amino terminus of the P2 element to provide the P4-P3-P2 dipeptide (2). The carboxyl terminus of the P4-P3-P2 intermediate can be deprotected by saponification of the ester group to provide P4-P3-P2 as the free carboxylic acid (3). Intermediates like (3) can be converted to compounds of Formula (I) using the methods described herein.

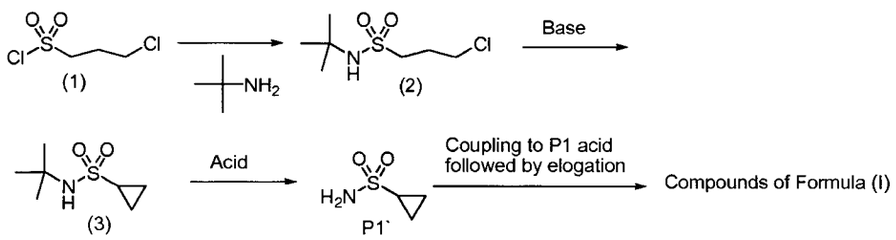
Scheme IV



In the construction of compounds of Formula (I), the P1` terminus is

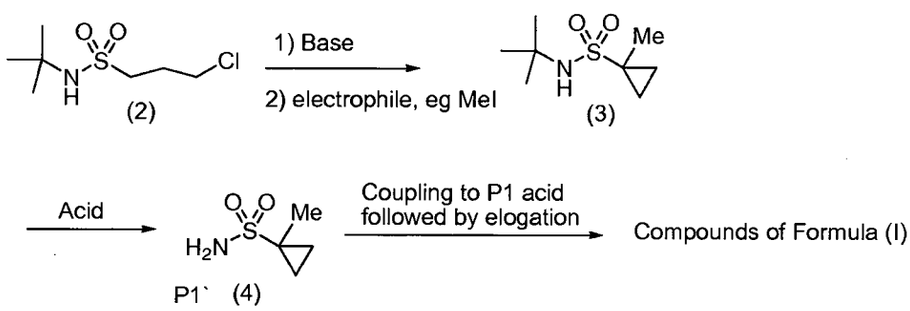
incorporated into the molecules using one of the general processes outlined above and described in more detail below. In some examples the P1` elements, that is the cycloalkyl or alkyl sulfonamides, are commercially available or can be prepared from the corresponding alkyl- or cycloalkylsulfonyl chloride by treating the sulfonyl chloride with ammonia. Alternatively, these sulfonamides can be synthesized using the general process outline in Scheme V. Commercially available 3-chloropropylsulfonyl chloride (1) is converted to a suitably protected sulfonamide, for example, by treatment with tert-butyl amine. The sulfonamide obtained (2) is then converted to the corresponding cycloalkylsulfonamide by treatment with two equivalents of a base such as butyllithium in a solvent such as THF at low temperature. The resulting cycloalkylsulfonamide can be deprotected by treatment with an acid to provide the desired unprotected cycloalkylsulfoamide.

Scheme V



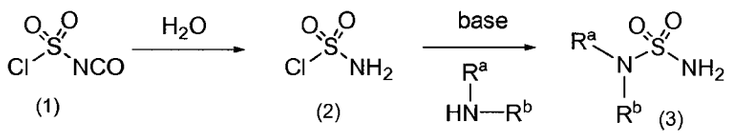
Substituted cycloalkylsulfonamides can also be incorporated into compounds of Formula (I) using a modification of the above said procedure. For example, intermediate 2 of Scheme VI can be treated with two equivalents of base such as butyllithium and the resulting reaction mixture can be treated with an electrophile such as methyl iodide to provide a substituted cycloalkylsulfonamide (3). This intermediate (3) can be deprotected at the N-terminus and the resulting compound (4) utilized as an intermediate in the preparation of compounds of Formula (I).

Scheme VI



The P1` intermediates employed in generating compounds of Formula (I) are in some cases derived from sulfamide derivatives. In such cases the sulfamide intermediates are available by several synthetic routes as, for example, by the pathway outlined in Scheme VII.

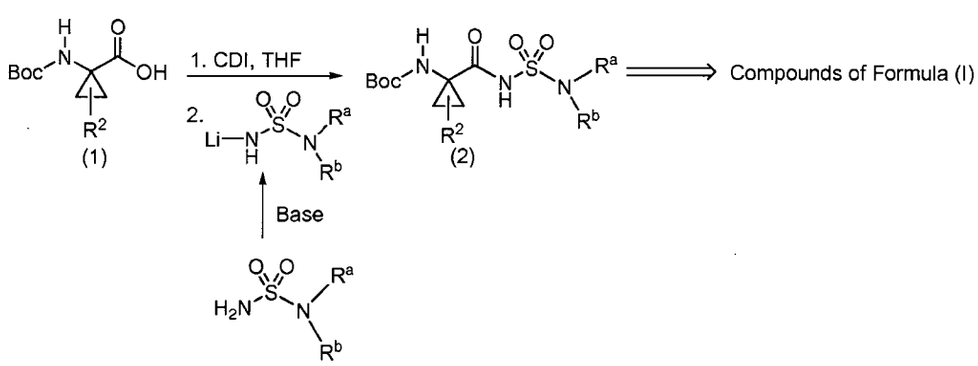
Scheme VII



Sulfamoyl chloride (2) can be prepared *in situ* by the addition of water (e.g., 1 equivalent) to chlorosulfonyl isocyanate 1 (e.g., 1 equivalent) in a solvent such as THF while maintained at a low temperature such as -20 °C. The resulting solution is then allowed to warm to 0 °C. To this solution a base, such as anhydrous triethylamine (eg., 1 equivalent), is added followed by an amine (eg., 1 equivalent). The reaction mixture is then warmed to room temperature, filtered, and the filtrate concentrated to provide the desired sulfamides (3).

The sulfamides can be incorporated into compounds of Formula (I) by several processes as, for example, by following the synthetic pathway defined in Scheme VIII. A carboxylic acid P1 element (1) is treated with an activating agent such as CDI. In a separate flask, a strong base is added to a solution of the above described sulfamide and the resulting reaction mixture is stirred for several hours after which this reaction mixture is added to the flask containing the activated carboxylic acid, to provide acylsulfamide derivatives (2). Intermediates like 2 can be converted to compounds of Formula (I) as described herein.

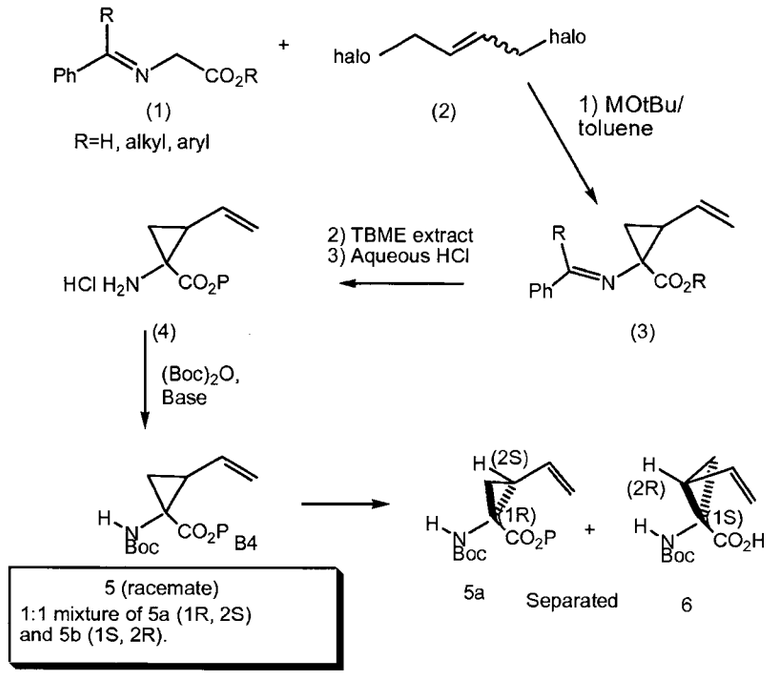
Scheme VIII



The P1 elements utilized in generating compounds of Formula (I) are in some cases commercially available, but are otherwise synthesized using the methods described herein and are subsequently incorporated into compounds of Formula (I) using the methods described herein. The substituted P1 cyclopropylamino acids can be synthesized following the general process outline in Scheme IX.

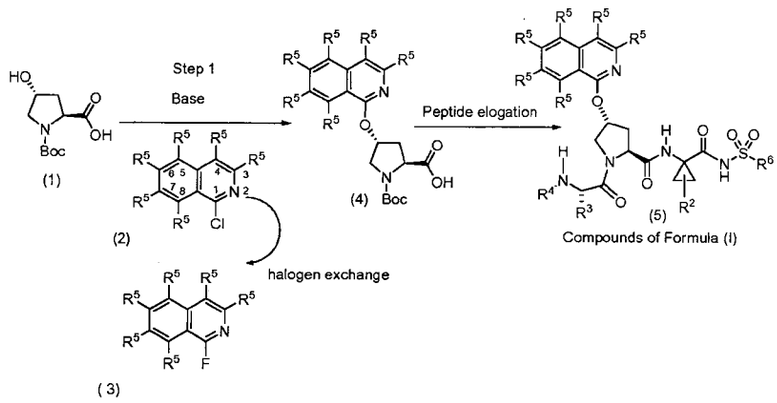
Treatment of commercially available or easily synthesized imine (1) with 1,4-dihalobutene (2) in presence of a base provides the resulting imine (3). Acid hydrolysis of 3 then provides 4, which has an allyl substituent syn to the carboxyl group, as a major product. The amine moiety of 4 can protected using a Boc group to provide the fully protected amino acid 5. This intermediate is a racemate which can be resolved by an enzymatic process wherein the ester moiety of 5 is cleaved by a protease to provide the corresponding carboxylic acid. Without being bound to any particular theory, it is believed that this reaction is selective in that one of the enantiomers undergoes the reaction at a much greater rate than its mirror image providing for a kinetic resolution of the intermediate racemate. In the examples cited herein, the more preferred stereoisomer for integration into compounds of Formula (I) is 5a which houses the (1R, 2S) stereochemistry. In the presence of the enzyme, this enantiomer does not undergo ester cleavage and thereby this enantiomer,5a, is recovered from the reaction mixture. However, the less preferred enantiomer ,5b, which houses the (1S, 2R) stereochemistry, undergoes ester cleavage, i.e., hydrolysis, to provide the free acid 6. Upon completion of this reaction, the ester 5a can be separated from the acid product 6 by routine methods such as, for example, aqueous extraction methods or chromotography.

Scheme IX



Procedures for making P2 intermediates and compounds of Formula (I) are shown in the schemes below. It should be noted that in many cases reactions are depicted for only one position of an intermediate. However, it is to be understood that such reactions could be used to impart modifications to other positions within this intermediate. Moreover, said intermediates, reaction conditions, and methods given in the specific examples are broadly applicable to compounds with other substitution patterns. Both general and specific examples are non-limiting.

Scheme X

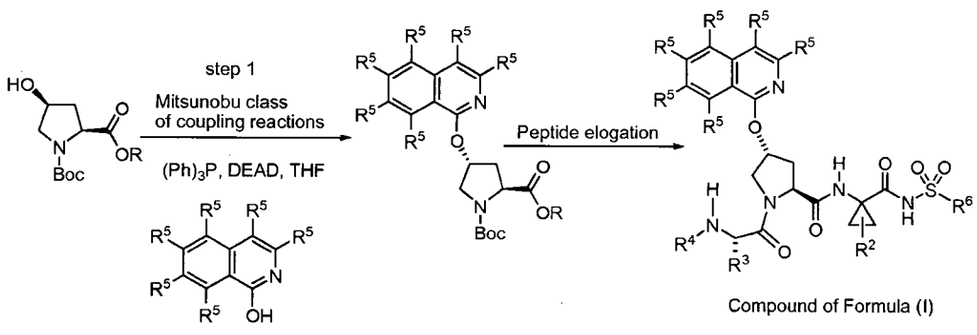


Scheme X shows the coupling of an N-protected C4-hydroxyproline moiety

with a heterocycle to form intermediate (4) and the subsequent modification of said intermediate (4) to a compound of Formula (I) by the process of peptide elongation as described herein. It should be noted that in the first step, that is the coupling of the C4-hydroxy proline group with the heteroaryl element, a base is employed. One skilled in the art would recognized that this coupling can be done using bases such as potassium tert-butoxide, or sodium hydride, in a solvent such as DMF or DMSO or THF. This coupling to the isoquinoline ring system occurs at the C1 position (numbering for isoquinoline ring system shown in intermediate 2 of Scheme XI) and is directed by the chloro group which is displaced in this process. It should be noted that alternative leaving groups can be utilized at this position (e.g., fluoro) as shown in the scheme. Said fluoro intermediates (3) are available from the corresponding chloro compound using literature procedures described herein.

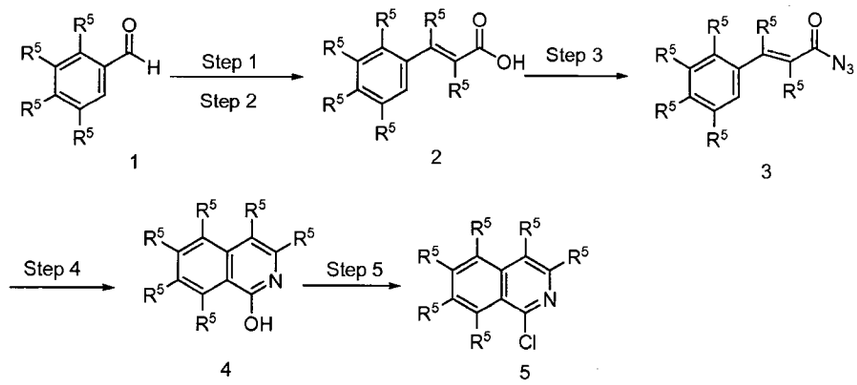
An alternative to the method described above for the coupling of the C4-hydroxyproline to the isoquinoline nucleus is provided in the Mitsunobu reaction as depicted in step 1 of Scheme XI. In this general reaction scheme a C4-hydroxy proline derivative is coupled to an isoquinoline ring system. This reaction makes use of reagents such as triphenylphosphine and DEAD (diethylazodicarboxylate) in aprotic solvents such as THF or dioxane and can be used for the formation of heteroaryl ethers. Note that in the course of this coupling reaction the stereochemistry of the C4 chiral center in the C4-hydroxyproline derivative is inverted and thereby it is necessary to use the C4-hydroxyproline derivative housing the (S) stereochemistry at the C4 position as starting material (as shown in Scheme XI). It should be noted that numerous modifications and improvements of the Mitsunobu reaction have been described in the literature, the teachings of which are incorporated herein.

Scheme XI



In examples herein, isoquinolines are incorporated into the final compounds and specifically into the P2 region of said compounds. One skilled in the art would recognize that a number of general methods are available for the synthesis of isoquinolines. Moreoever, the isoquinolines generated by these methods can be readily incorporated into final compounds of Formula (I) using the processes described herein. One general methodology for the synthesis of isoquinolines is shown in Scheme XII, wherein cinnamic acid derivatives, shown in general form as structure (2), are converted to 1-chloroisoquinolines in a four step process. The chloroisoquinolines can be subsequently used in coupling reactions to C4-hydroxyproline derivatives as described herein. The conversion of cinnamic acids to chloroquinolines begins with the treatment of cinnamic acid with an alkylcholorformate in the presence of a base. The resulting anhydride is then treated with sodium azide which results in the formation of an acylazide (3) as shown in the scheme. Alternate methods are available for the formation of acylazides from carboxylic acids as for example said carboxylic acid can be treated with diphenylphosphorylazide (DPPA) in an aprotic solvent such as methylene chloride in the presence of a base. In the next step of the reaction sequence the acylazide (3) is coverted to the corresponding isoquinolone (4) while heating to a temperature of approximately 190 °C in a high boiling solvent such a diphenylmethane. This reaction is general and provides moderate to good yields of substituted isoquinolone from the corresponding cinnamic acid derivatives. It should noted that said cinnamic acid derivatives are available commercially or can be obtained from the corresponding benzaldehyde (1) derivative by direct condensation with malonic acid or derivatives thereof and also by employing a Wittig reaction. The intermediate isoquinolones (4) of Scheme XII can be converted to the corresponding 1-chloroisoquinoline by treatment with phosphorous oxychloride. This reaction is general and can be applied to the isoquinolones shown herein.

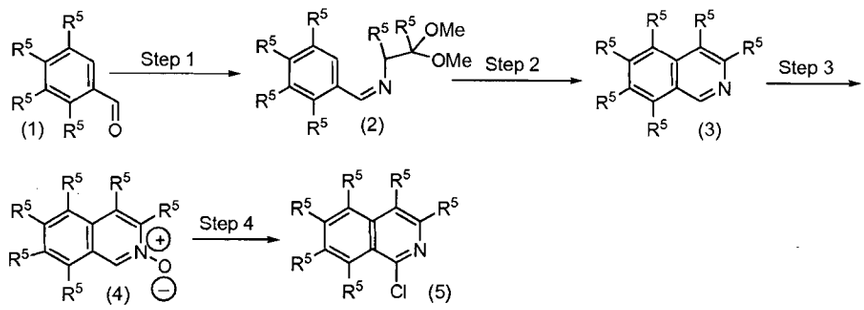
Scheme XII



Reference: N. Briet at al, Tetrahedron, 2002, 5761

An alternative method for the synthesis of the isoquinoline ring system is the Pomeranz-Fritsh procedure. This general method is outlined in Scheme XIII. The process begins with the conversion of a benzaldehyde derivative (1) to a functionalized imine (2). The imine is then converted to the isoquinoline ring system by treatment with acid at elevated temperature. This isoquinoline synthesis of Scheme XIII is general, and it should be noted that this process is particularly useful in procuring isoquinoline intermediates that are substituted at the C8 position. The intermediate isoquinolines (3) can be converted to the corresponding 1-chloroquinolines (5) in a two step process as shown. The first step in this sequence is the formation of the isoquinoline N-oxide(4) by treatment of isoquinoline (3) with meta-chloroperbenzoic acid in an aprotic solvent such as dichloromethane. Intermediate (4) can be converted to the corresponding 1-chloroquinoline by treatment with phosphorous oxychloroide in refluxing chloroform. Note that this two step process is general for the formation of chloroisoquinolines from isoquinolones.

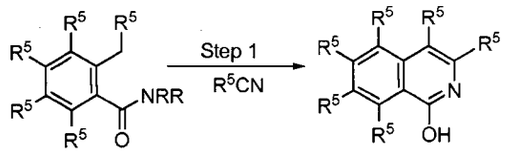
Scheme XIII



Pomeranz-Fritsch synthesis
K. Hirao, R. Tsuchiya, Y. Yano, H. Tsue, Heterocycles 42(1) 1996, 415-422

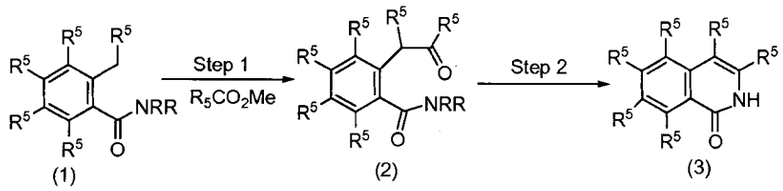
Another method for the synthesis of the isoquinoline ring system is shown in Scheme XIV. In this process an ortho-alkylbenzamide derivative (1) is treated with a strong base such as tert-butyllithium in a solvent such as THF at low temperature. To this reaction mixture is then added a nitrile derivative, which undergoes an addition reaction with the anion derived from deprotonation of (1), resulting in the formation of (2). This reaction is general and can be used for the formation of substituted isoquinolines. Intermediate (2) of Scheme XIV can be converted to the corresponding 1-chloroquinoline by the methods described herein.

Scheme XIV



An additional method for the synthesis of isoquinolines is shown in Scheme XV. The deprotonation of intermediate (1) using tert-butyllithium is described above. In the present method however, the intermediate anion is trapped by an ester, resulting in the formation of intermediate (2) as shown below. In a subsequent reaction, ketone (2) is condensed with ammoniumn acetate at elevated temperature providing for the formation of quinolone (3). This reaction is general and can be applied to the construction of substituted isoquinolones which can then be converted to the corresponding 1-chloroisoquinolines as described herein.

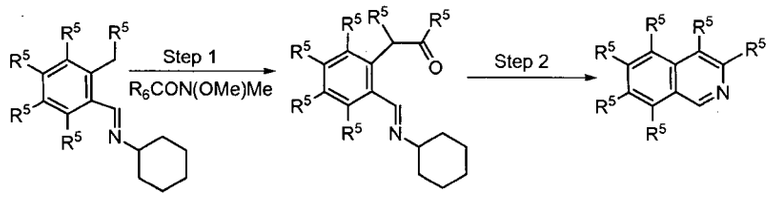
Scheme XV



Another method for the construction of isoquinolines is found in Scheme XVI. In the first step of this process an ortho-alkylarylimine derivatives such as (1) are subjected to deprotonation conditions (sec-butyl lithium, THF) and the resulting anion is quenched by the addition of an activated carboxylic acid derivative such as a Weinreb amide. The resulting ketoimine (2) can be converted to the corresponding isoquinoline by condensation with ammonium acetate at elevated temperatures. This

method is general and can be used for the synthesis of substituted isoquinolines. The isoquinolines can be converted to the corresponding 1-chloroquinoline by the methods described herein.

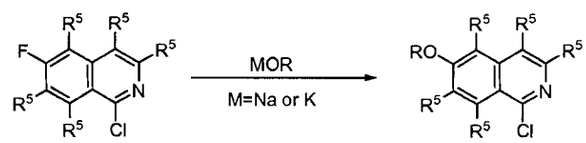
Scheme XVI



L. Flippin, J. Muchowski, JOC, 1993, 2631-2632

The isoquinolines described herein, and which are incorporated into the compounds of Formula (I), can be further functionalized. It is obvious to one skilled in the art that additional functionalization of said heterocycles can be done either before or after incorporation of these functionalities into compounds of Formula (I). The following schemes illustrate this point. For example Scheme XVII shows the conversion of a 1-chloro-6-fluoro-isoquinoline to the corresponding 1-chloro-6-alkoxy-isoquinoline species, by treatment of (1) with a sodium or potassium alkoxide species in the alcohol solvent from which the alkoxide is derived at room temperature. In some cases it may be necessary to heat the reaction to drive it to completion. The chloroquinoline can be incorporated into a compound of Formula (I) using the art described herein.

Scheme XVII

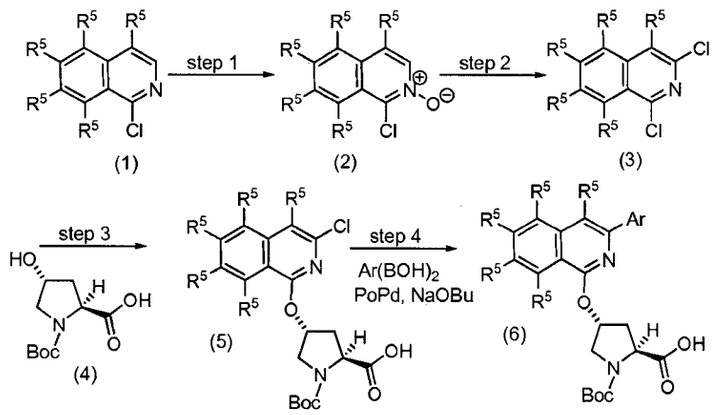


(1) (2)

Scheme XVIII provides a general example for the modification of isoquinolines as defined herein by employing palladium mediated coupling reactions. The couplings can be employed to functionalize a heterocycle at each position of the ring system provided the ring is suitably activated or functionalized, as for example with a chloride as shown in the scheme. This sequence begins with 1-chloroisoquinoline (1) which upon treatment with metachloroperbenzoic acid can be converted to the corresponding N-oxide (2). Intermediate (2) can be converted to the

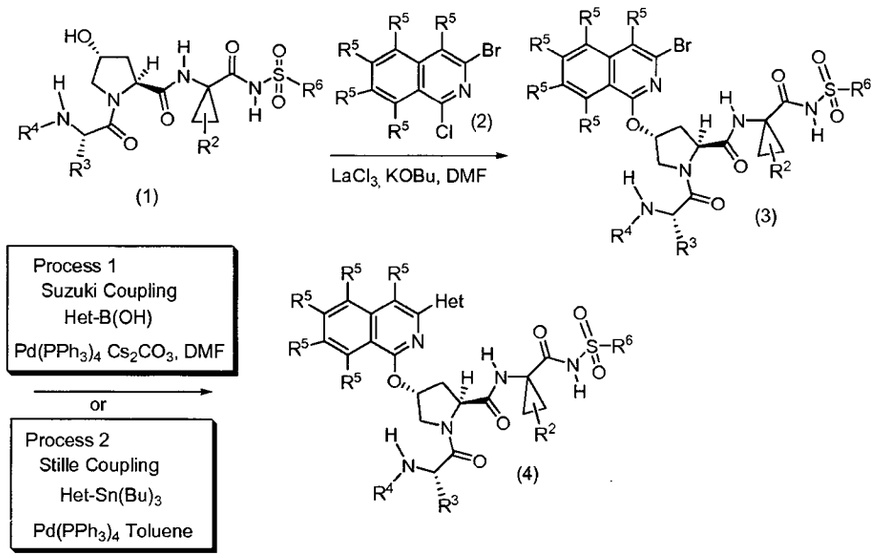
corresponding 1,3-dichloroisoquinoline (3) by treatment with phosphorous oxychloride in refluxing chloroform. Intermediate (3) can be coupled with N-Boc-4-hydroxyproline by the methods described herein to provide intermediate (5) as shown in the scheme. Intermediate (5) can undergo a Suzuki coupling with an aryl boronic acid, in the presence of a palladium reagent and base, and in a solvent such as THF or toluene or DMF to provide the C3-arylisoquinoline intermediate (6). Heteroarylboronic acids can also be employed in this palladium-mediated coupling process to provide C3-heteroarylisoquinolines. Intermediate (6) can be converted into final compounds of Formula (I) by the methods described herein.

Scheme XVIII



Palladium mediated couplings of isoquinoline systems with aryl or heteroaryl elements can also be employed at a later synthetic stage in the construction of compounds of Formula (I) as shown in Scheme XIX. Tripeptide acylsulfonamide intermediate (1) is coupled to a 1-chloro-3-bromoisoquinoline (2) using the previously described process to provide intermediate (3). The coupling of (1) and (2) is most efficient in the presence of a catalyst such as lanthanum chloride as described herein. The isoquinoline ring system of intermediate (3) can be further functionalized by employing either Suzuki couplings (Process 1: subjecting (3) to heteroaryl or aryl boronic acids in the presence of a palladium catalyst such as palladium tetrakistriphenylphosphine and a base such as cesium carbonate in solvents such as DMF) or Stille couplings (Process 2: subjecting (3) to heteraryl or aryl tin dervatives in the presence of a palladium catalyst such as palladium tetrakistriphenylphosphine in solvents such as toluene).

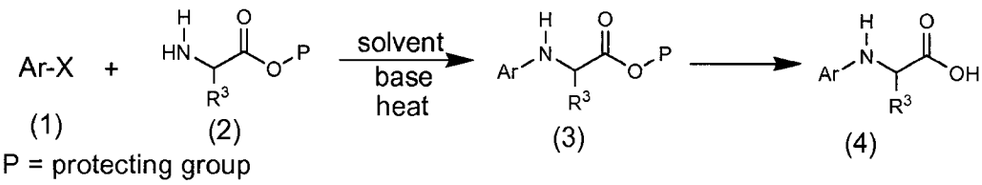
Scheme XIX



The P3 amino acids employed in the present invention are either commercially available or can be prepared using methods known to those of ordinary skill in the art. Non-limiting routes for the preparation of the P3 amino acid include:

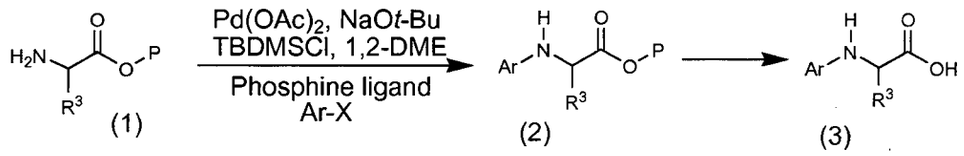
Route 1: Nucleophilic aromatic substitution of a sufficiently electrophilic aromatic or heteroaromatic species (1) with an amino acid ester (2) as shown in Scheme XX. This reaction is then followed by a simple ester cleavage of 3 to provide the desired amino acid (4).

Scheme XX



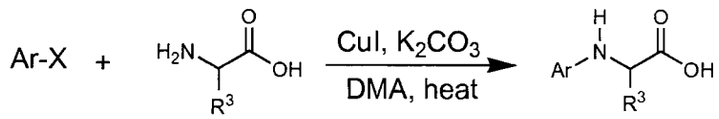
Route 2: A Buchwald-Hartwig type reaction which involves palladium-catalyzed coupling an aryl or heteroaryl halide bond with a suitably protected amino acid (1) as shown in Scheme XXI. Simple saponification of intermediate 2 provides the desired amino acid (3). (Shen, Q.; Shekhar, S; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2005**, *44*, 1371-1375.):

Scheme XXI

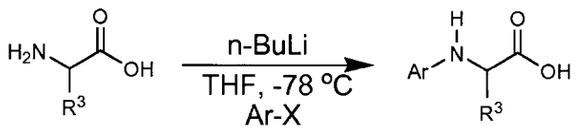


Route 3: A coupling process whereby an aryl or heteroaryl halide and a free amino acid are coupled *via* a CuI mediated process to give the arylamino acid directly as shown in Scheme XXII (Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459-12467.)

Scheme XXII

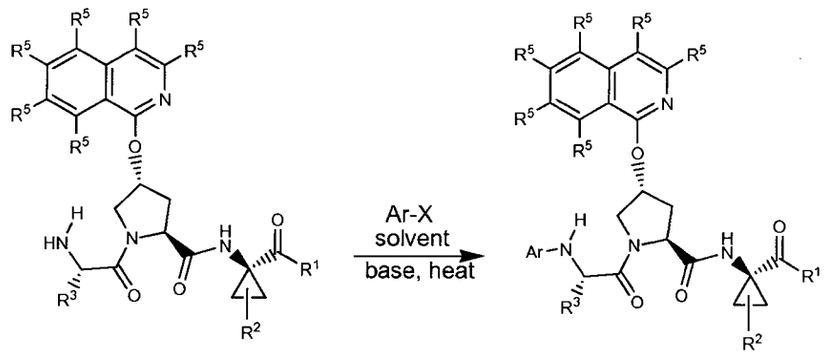


Route 4: A process which employs nucleophilic displacement of the dianion of a free amino acid and an aryl or heteroaryl halide, typically a fluoride (similar to Saitton, S.; Kihlberg, J.; Luthman, K. *Tetrahedron* **2004**, *60*, 6113-6120.):



In some cases, as shown in Scheme XXIII, access to the aminoaryl final products can be achieved by direct nucleophilic aromatic substitution of the aryl ring with a fully assembled core tripeptide having a free amino group at the terminus of the P3 subregion.

Scheme XXIII



EXAMPLES

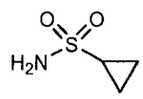
The present disclosure will now be described in connection with certain embodiments which are not intended to limit its scope. On the contrary, the present disclosure covers all alternatives, modifications, and equivalents as can be included within the scope of the claims. Thus, the following examples, which include specific embodiments, will illustrate one practice of the present disclosure, it being understood that the examples are for the purposes of illustration of certain embodiments and are presented to provide what is believed to be the most useful and readily understood description of its procedures and conceptual aspects.

Solution percentages express a weight to volume relationship, and solution ratios express a volume to volume relationship, unless stated otherwise. Nuclear magnetic resonance (NMR) spectra were recorded either on a Bruker 300, 400 or 500 MHz spectrometer; the chemical shifts (δ) are reported in parts per million. Flash chromatography was carried out on silica gel (SiO_2) according to Still's flash chromatography technique (*J. Org. Chem.* **1978**, *43*, 2923).

I. Preparation of P1` Intermediates

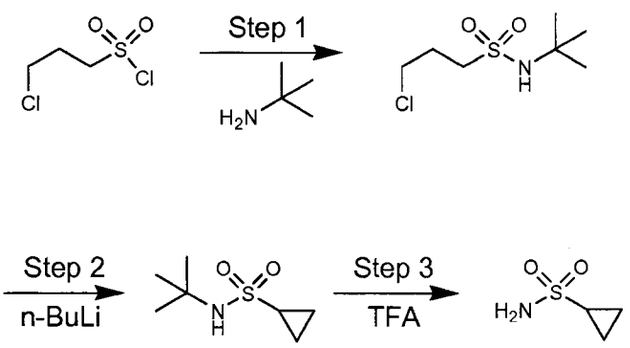
1. Preparation of cyclopropylsulfonamide

Method 1:



cyclopropylsulfonamide

Scheme 1



Step 1:

tert-Butylamine (3.0 mol, 315 mL) was dissolved in THF (2.5 L). The solution was cooled to –20 °C. 3-Chloropropanesulfonyl chloride (1.5 mol, 182 mL) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for 24 hours. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (2.0 L). The resulting solution was washed with 1.0M HCl (1.0 L), water (1.0 L), and brine (1.0 L), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a slightly yellow solid, which was crystallized from hexane to provide the product as a white solid (316.0 g, 99%). ^1H NMR ($CDCl_3$) δ 1.38 (s, 9H), 2.30-2.27 (m, 2H), 3.22 (t, J = 7.35 Hz, 2H), 3.68 (t, J = 6.2 Hz, 2H), 4.35 (b, 1H).

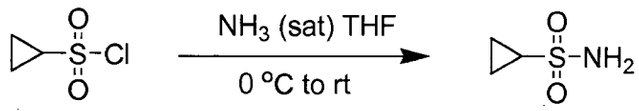
Step 2:

To a solution of the product of Step 1 (2.14 g, 10.0 mmol) in THF (100 mL) was added n-BuLi (2.5 M in hexane, 8.0 mL, 20.0 mmol) at -78 °C. The reaction mixture was allowed to warm up to room temperature over period of 1 hour and concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water (200 mL each). The separated organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was recrystallized from hexane to provide the desired product as a white solid (1.0 g, 56%). ^1H NMR ($CDCl_3$) δ 0.98-1.00 (m, 2H), 1.18-1.19 (m, 2H), 1.39 (s, 9H), 2.48-2.51 (m, 1H), 4.19 (b, 1H).

Step 3:

A solution of the product of Step 2 (110 g, 0.62 mmol) in TFA (500 mL) was stirred at room temperature for 16 hours. The volatiles were removed *in vacuo*. The residue was recrystallized from ethyl acetate/hexane (60 mL/240 mL) to provide the desired product as a white solid (68.5 g, 91%). ^{1}H NMR (DMSO-d_6) δ 0.84-0.88 (m, 2H), 0.95-0.98 (m, 2H), 2.41-2.58 (m, 1H), 6.56 (b, 2H).

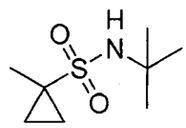
Method 2:



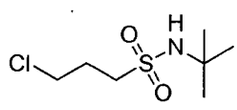
To a solution of 100 mL of THF cooled to 0 °C was bubbled in gaseous ammonia until saturation was reached. To this solution was added a solution of 5 g (28.45 mmol) of cyclopropylsulfonyl chloride (purchased from Array Biopharma) in 50 mL of THF. The solution was warmed to room temperature overnight and stirred one additional day. The mixture was concentrated until 1-2 mL of solvent remained and poured onto a 30 g plug of SiO_2 (eluted with 30% to 60% ethyl acetate/hexanes) to provide 3.45g (100%) of cyclopropylsulfonamide as a white solid. ^{1}H NMR (methanol-d_4) δ 0.94-1.07 (m, 4H), 2.52-2.60 (m, 1H); ^{13}C NMR (methanol-d_4) δ 5.92, 33.01.

2. Preparation of C1-substituted cyclopropylsulfonamides

2a. Preparation of *N-tert*-butyl-(1-methyl)cyclopropyl-sulfonamide

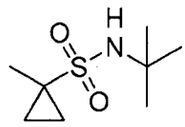


Step 1: Preparation of *N-tert*-butyl-(3-chloro)propylsulfonamide



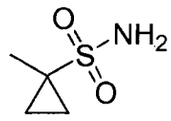
Prepared as described above.

Step 2: Preparation of *N-tert*-butyl-(1-methyl)cyclopropyl-sulfonamide



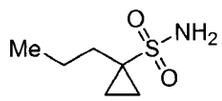
A solution of the product of Step 1 (4.3 g, 20 mmol) was dissolved in dry THF (100 mL) and cooled to – 78 °C. To this solution was added *n*-butyllithium (17.6 mL, 44 mmol, 2.5M in hexane) slowly. The dry ice bath was removed and the reaction mixture was warmed to room temperature over a period of 1.5 hours. This mixture was cooled to – 78 °C and a solution of *n*-butyllithium (20 mmol, 8 mL, 2.5M in hexane) was added. The reaction mixture was warmed to room temperature, cooled to –78 °C over a period of 2 hours, and treated with a neat solution of methyl iodide (5.68 g, 40 mmol). The reaction mixture was warmed to room temperature overnight, then quenched with saturated NH_4Cl (100 mL) at room temperature and extracted with ethyl acetate (100 mL). The organic phase was washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide a yellow oil which was crystallized from hexane to provide the desired product as a slightly yellow solid (3.1 g, 81%): ^{1}H NMR ($CDCl_3$) δ 0.79 (m, 2H), 1.36 (s, 9H), 1.52 (m, 2H), 1.62 (s, 3H), 4.10 (br s, 1H).

Step 3: Preparation of 1-methylcyclopropylsulfonamide



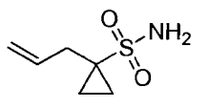
A solution of the product of Step 2 (1.91 g, 10 mmol) was dissolved in TFA (30 mL), and the reaction mixture stirred at room temperature for 16 hours. The solvent was removed *in vacuo* to provide a yellow oil which was crystallized from ethyl acetate/hexane (1:4, 40 mL) to provide the desired product as a white solid (1.25 g, 96%): ^{1}H NMR ($CDCl_3$) δ 0.84 (m, 2H), 1.41 (m, 2H), 1.58 (s, 3H), 4.65 (br s, 2H). Anal. Calcd. For $C_4H_9NO_2S$: C, 35.54; H, 6.71; N, 10.36. Found: C, 35.67; H, 6.80; N, 10.40.

2b. Preparation of 1-propylcyclopropylsulfonamide

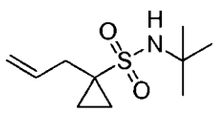


This compound was prepared using the procedure described for the preparation of 1-methylcyclopropylsulfonamide substituting propyl halide for methyl iodide in the second step of this process.

2c. Preparation of 1-allylcyclopropylsulfonamide

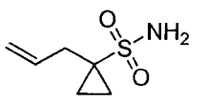


Step 1: Preparation of *N-tert*-butyl-(1-allyl)cyclopropylsulfonamide



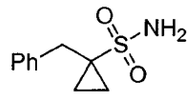
This compound was obtained in 97% yield according to the procedure described in the synthesis of *N-tert*-butyl-(1-methyl)cyclopropylsulfonamide using 1.25 equivalents of allyl bromide as the electrophile. The compound was used in the next reaction without further purification: ^{1}H NMR ($CDCl_3$) δ 0.83 (m, 2H), 1.34 (s, 9H), 1.37 (m, 2H), 2.64 (d, J = 7.3 Hz, 2H), 4.25 (br s, 1H), 5.07-5.10 (m, 2H), 6.70-6.85 (m, 1H).

Step 2: Preparation of 1-allylcyclopropylsulfonamide

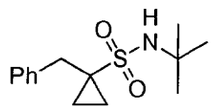


This compound was obtained in 40% yield from the product of Step 1 according to the procedure described in the synthesis of 1-methylcyclopropylsulfonamide. The compound was purified by column chromotography over SiO_2 using 2% methanol in dichloromethane as the eluent: ^{1}H NMR ($CDCl_3$) δ 0.88 (m, 2H), 1.37 (m, 2H), 2.66 (d, *J*=7.0 Hz, 2H), 4.80 (s, 2H), 5.16 (m, 2H), 5.82 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 11.2, 35.6, 40.7, 119.0, 133.6.

2d. Preparation of 1-Benzylcyclopropylsulfonamide

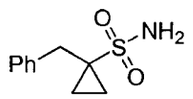


Step 1: Preparation of *N-tert*-butyl-(1-benzyl)cyclopropyl-sulfonamide.



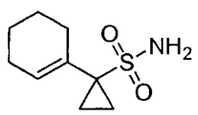
This compound was obtained in 60% yield using the procedure described for the synthesis of *N-tert*-butyl-(1-methyl)cyclopropylsulfonamide except 1.05 equivalents of benzyl bromide were used, followed by trituration with 10% ethyl acetate in hexane: ^{1}H NMR ($CDCl_3$) δ 0.92 (m, 2H), 1.36 (m, 2H), 1.43 (s, 9H), 3.25 (s, 2H), 4.62 (br s, 1H), 7.29-7.36 (m, 5H).

Step 2: Preparation of 1-Benzylcyclopropylsulfonamide

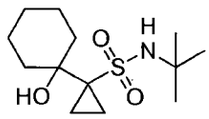


This compound was obtained in 66% yield from *N-tert*-butyl(1-benzyl)cyclopropylsulfonamide using the procedure described for the synthesis of 1-methylcyclopropylsulfonamide, followed by recrystallization from the minimum amount of 10% ethyl acetate in hexane: ^{1}H NMR ($CDCl_3$) δ 0.90 (m, 2H), 1.42 (m, 2H), 3.25 (s, 2H), 4.05 (s, 2H), 7.29 (m, 3H), 7.34 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 11.1, 36.8, 41.9, 127.4, 128.8, 129.9, 136.5.

2e. Preparation of 1-(1-cyclohexenyl)cyclopropyl-sulfonamide

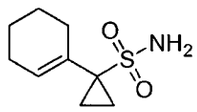


Step 1: Preparation of *N-tert*-butyl-[1-(1-hydroxy)cyclohexyl]-cyclopropylsulfonamide



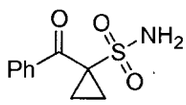
This compound was obtained in 84% yield using to the procedure described for the synthesis of *N-tert*-butyl-(1-methyl)cyclopropylsul-fonamide except 1.30 equivalents of cyclohexanone were used, followed by recrystallization from the minimum amount of 20% ethyl acetate in hexane: ^{1}H NMR ($CDCl_3$) δ 1.05 (m, 4H), 1.26 (m, 2H), 1.37 (s, 9H), 1.57-1.59 (m, 6H), 1.97 (m, 2H), 2.87 (br s, 1H), 4.55 (br s, 1H).

Step 2: Preparation of 1-(1-cyclohexenyl)cyclopropyl-sulfonamide

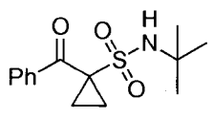


This compound, 1-(1-cyclohexenyl)-cyclopropylsulfonamide was obtained in 85% yield from *N-tert*-butyl-[1-(1-hydroxy)cyclohexyl]-cyclopropylsulfonamide using the procedure described for the synthesis of 1-methylcyclopropylsulfonamide, followed by recrystallization from the minimum amount of ethyl acetate and hexane: ^{1}H NMR (DMSO-d_6) δ 0.82 (m, 2H), 1.28 (m, 2H), 1.51 (m, 2H), 1.55 (m, 2H), 2.01 (s, 2H), 2.16 (s, 2H), 5.89 (s, 1H), 6.46 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 11.6, 21.5, 22.3, 25.0, 27.2, 46.9, 131.6, 132.2; LR-MS (ESI): 200 (M^+-1).

2f. Preparation of 1-benzoylcyclo-propylsulfonamide



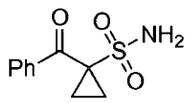
Step 1: Preparation of *N-tert*-butyl-(1-benzoyl)cyclopropyl-sulfonamide



This compound was obtained in 66% yield using the procedure described for

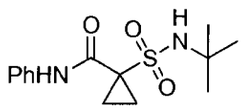
the synthesis of *N-tert*-butyl-(1-methyl)cyclopropylsulfonamide except 1.2 equivalents of methyl benzoate was used as the electrophile. The compound was purified by column chromatography over SiO_2 using 30% to 100% dichloromethane in hexane: ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.52 (m, 2H), 1.81 (m, 2H), 4.16 (br s, 1H), 7.46 (m, 2H), 7.57 (m, 1H), 8.05 (d, J = 8.5 Hz, 2H).

Step 2: Preparation of 1-benzoylcyclo-propylsulfonamide



This compound was obtained in 87% yield from *N-tert*-butyl(1-benzoyl)cyclopropylsul-fonamide using the process described for the synthesis of 1-methylcyclopropylsulfonamide, followed by recrystallization from the minimum amount of ethyl acetate in hexane: ^{1}H NMR (DMSO-d_6) δ 1.39 (m, 2H), 1.61 (m, 2H), 7.22 (s, 2H), 7.53 (t, *J*=7.6 Hz, 2H), 7.65 (t, *J*=7.6 Hz, 1H), 8.06 (d, *J*=8.2 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 12.3, 48.4, 128.1, 130.0, 133.4, 135.3, 192.0.

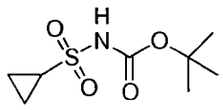
2g. Preparation of *N-tert*-butyl-(1-phenylaminocarboxy)-cyclopropylsulfonamide



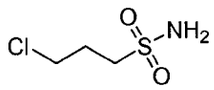
This compound was obtained in 42% yield using the procedure described for the synthesis of *N-tert*-butyl-(1-methyl)cyclopropylsulfonamide using 1 equivalent of phenylisocyanate, followed by recrystallization from the minimum amount of ethyl acetate in hexane ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 9H), 1.67-1.71 (m, 4H), 4.30 (br s, 1H), 7.10 (t, J = 7.5 Hz, 1H), 7.34 (t, J = 7.5 Hz, 2H), 7.53 (t, J = 7.5 Hz, 2H).

3. Preparation of C1-Substituted cyclopropanesulfonamides: The use of an *N*-Boc protecting group

3a. Preparation of cyclopropylsulfonylamine *tert*-butyl carbamate, a key intermediate in the preparation of C1-substituted cyclopropylsulfonamides

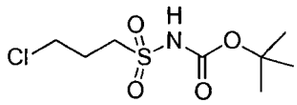


Step 1: Preparation of 3-chloropropylsulfonamide



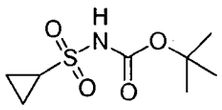
A solution of 3-chloropropanesulfonyl chloride (55 g, 310.7 mmol) was dissolved in THF (200 mL) and added dropwise over 30 minutes to a solution of NH_4OH (200 mL) at 0 °C. The reaction mixture was warmed to room temperature, stirred 1 hour, and the aqueous layer extracted with dichloromethane (4 x 500 mL). The combined extracts were washed with 1N HCl (150 mL), water (150 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude solid was recrystallized from the minimum amount of dichloromethane in hexanes to provide the desired product as a white solid (45.3 g, 93%). ^{1}H NMR ($CDCl_3$) δ 2.34 (m, 2H), 3.32 (t, J=7.3 Hz, 2H), 3.70 (t, J=6.2 Hz, 2H), 4.83 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 27.10, 42.63, 52.57.

Step 2: Preparation of 3-chloropropylsulfonylamine *tert*-butylcarbamate



A solution of the product of Step 1 (30.2 g, 191.5 mmol), triethylamine (30.2 mL, 217.0 mmol), and 4-DMAP (2.40g, 19.6 mmol) in dichloromethane (350 mL) at 0 °C was treated dropwise with a solution of di-*tert*-butyldicarbonate (47.2g, 216.9 mmol) in dichloromethane (250 mL) over 30 minutes. The reaction mixture was warmed to room temperature, stirred an additional 3 hours, and was washed with 1N HCl (300 mL), water (300 mL), and brine (300 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide the crude product. This material was triturated with 70 mL of 5% dichloromethane in hexanes to provide the desired product as an off-white solid (47.2 g, 96%): ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 9H), 2.33 (m, 2H), 3.60 (t, J=7.3 Hz, 2H), 3.68 (t, J=6.21 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 26.50, 27.95, 42.37, 50.40, 84.76, 149.53.

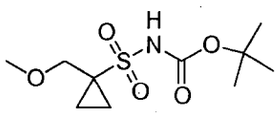
Step 3: Preparation of cyclopropylsulfonylamine *tert*-butyl carbamate



A solution of *n*-butyllithium (74.7 mL, 119.5 mmol, 1.6M in hexane) was dissolved in dry THF (105 mL) and cooled to –78 °C under an argon atmosphere. To this solution was added a solution of the product of Step 2 (14 g, 54.3 mmol) in dry THF (105 mL) dropwise over 20-30 minutes. The dry ice bath was removed and the reaction mixture was allowed to warm to room temperature over a period of 2 hours. The reaction mixture was quenched with glacial acetic acid (3.4 mL), concentrated *in vacuo*, and partitioned between dichloromethane (100 mL) and water (100 mL). The organic phase was washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide the desired product as a waxy off-white solid (12.08 g, 100%): ^{1}H NMR ($CDCl_3$) δ 1.10 (m, 2H), 1.34 (m, 2H), 1.50 (s, 9H), 2.88 (m, 1H), 7.43 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 6.21, 28.00, 31.13, 84.07, 149.82.

3b. Preparation of 1-methoxy-methylcyclopropy-sulfonamide

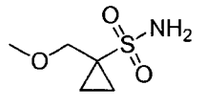
Step 1: Preparation of 1-methoxymethylcyclopropylsulfonylamine *tert*-butylcarbamate



To a solution of cyclopropylsulfonylamine *tert*-butyl carbamate (1.0 g, 4.5 mmol) dissolved in THF (30 mL) cooled to –78 °C, was added *n*-butyllithium (6.4 mL, 10.2 mmol, 1.6M in hexane) and the reaction mixture was stirred for 1 hour. To this solution was added a neat solution of chloromethyl methyl ether (0.40 mL, 5.24 mmol), and the mixture was slowly allowed to warm to room temperature overnight. The solution pH was adjusted to 3 using 1N aqueous HCl and was then extracted with ethyl acetate (4 x 50 mL portions). The combined extracts were dried ($MgSO_4$), filtered, and concentrated to afford 1-methoxymethylcyclopropylsulfonylamine *tert*-butylcarbamate, as a waxy solid (1.20 g, 100%) which was taken directly into the next reaction without further purification: ^{1}H NMR ($CDCl_3$) δ 1.03 (m, 2H), 1.52 (s, 9H), 1.66 (m, 2H), 3.38 (s, 3H), 3.68 (s, 2H), 7.54 (s, 1H); ^{13}C NMR ($CDCl_3$) δ

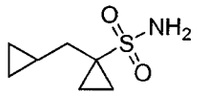
11.37, 28.29, 40.38, 58.94, 73.43, 83.61, 149.57.

Step 2: Preparation of 1-methoxymethylcyclopropysulfonamide

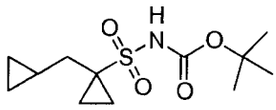


A solution of 1-methoxymethylcyclopropylsulfonylamine *tert*-butylcarbamate (1.14 g, 4.30 mmol) was dissolved in a solution of 50%TFA/dichloromethane (30 mL) and was stirred stirred at room temperature for 16 hours. The solvent was removed *in vacuo* and the residue chromatographed over 80g of SiO_2 (eluting with 0% to 60% ethyl acetate/hexanes to 1-methoxymethylcyclopropylsulfonamide as a white solid (0.55 g, 77% overall over two steps): ^{1}H NMR ($CDCl_3$) δ 0.95 (m, 2H), 1.44 (m, 2H), 3.36 (s, 3H), 3.65 (s, 2H), 4.85 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 11.17, 40.87, 59.23, 74.80; LRMS m/z 183 (M^++NH_4).

3c. Preparation of 1-cyclopropylmethylcyclopropylsulfonamide

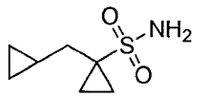


Step 1: Preparation of 1-cyclopropylmethylcyclopropylsulfonylamine *tert*-butylcarbamate



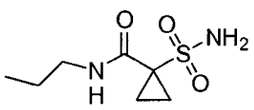
1-Cyclopropylmethylcyclopropylsulfonylamine *tert*-butylcarbamate was obtained in 92% yield according to the procedure described in the synthesis of 1-methoxymethylcyclopropylsulfonylamine *tert*-butylcarbamate, except 1.10 equivalents of cyclopropylmethyl bromide were used as electrophile. The compound was taken directly into the next reaction without purification: ^{1}H NMR ($CDCl_3$) δ 0.10 (m, 2H), 0.51 (m, 2H), 0.67 (m, 1H), 1.10 (m, 2H), 1.49 (s, 9H), 1.62 (m, 2H), 1.87 (d, J=7.0 Hz, 2H).

Step 2: Preparation of 1-cyclopropylmethyl-cyclopropylsulfonamide

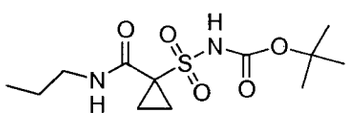


This compound was obtained in 65% yield from 1-cyclopropylmethylcyclopropylsulfonylamine *tert*-butylcarbamate according to the procedure described for the synthesis of 1-methoxymethylcyclopropylsulfonamide. The compound was purified by column chromotography over SiO_2 using 0% to 60% ethyl acetate in hexanes as the eluent: ^{1}H NMR ($CDCl_3$) δ 0.15 (m, 2H), 0.51 (m, 2H), 1.01 (m, 2H), 1.34 (m, 3H), 1.86 (d, *J*=7.0 Hz, 2H), 4.83 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 4.65, 7.74, 11.26, 35.62, 41.21; LRMS m/z 193 (M^++NH_4).

3d. Preparation of 1-propylcarbamoylcyclopropane-sulfonamide

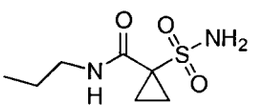


Step 1: Preparation of 1-propylcarbamoylcyclopropanesulfonamide *tert*-butylcarbamate



This compound was obtained in a crude 100% yield according to the procedure described for the synthesis of 1-methoxymethylcyclopropylsulfonylamine *tert*-butyl-carbamate except that 1.10 equivalents of *n*-propyl isocyanate was used as the electrophile. The compound was taken directly into the next reaction without purification: ^{1}H NMR ($CDCl_3$) δ 0.10 (m, 2H), 0.51 (m, 2H), 0.67 (m, 1H), 1.10 (m, 2H), 1.49 (s, 9H), 1.62 (m, 2H), 1.87 (d, *J*=7.0 Hz, 2H).

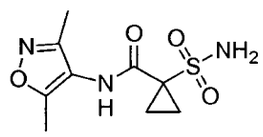
Step 2: Preparation of 1-propylcarbamoylcyclopropane-sulfonamide



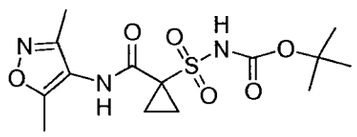
This compound was obtained in 50% yield from 1-propylcarbamoylcyclopropanesulfonamide *tert*-butylcarbamate according to the

procedure described for the synthesis of 1-methoxymethylcyclopropylsulfonamide, except that no chromatography was used as the material was recrystallized from the minimum amount of dichloromethane/hexanes: ^{1}H NMR ($CDCl_3$) δ 0.15 (m, 2H), 0.51 (m, 2H), 1.01 (m, 2H), 1.34 (m, 3H), 1.86 (d, J=7.0 Hz, 2H), 4.83 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 4.65, 7.74, 11.26, 35.62, 41.21; LRMS m/z 193 (M^++NH_4).

3e. Preparation of 1-(3,5-dimethylisoxazol-4yl)carbamoylcyclopropanesulfonamide

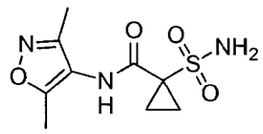


Step 1: Preparation of 1-(3,5-dimethylisoxazol-4-yl)carbamoylcyclopropanesulfonamide *tert*-butylcarbamate



This compound was obtained in a crude 100% yield according to the procedure described for the synthesis of 1-methoxymethylcyclopropylsulfonylamine *tert*-butylcarbamate except that 1.20 equivalents of 3,5-dimethylisoxazole-4-isocyanate was used as the electrophile. The compound was taken directly into the next reaction without purification.

Step 2: Preparation of 1-(3,5-dimethylisoxazol-4yl)carbamoylcyclopropanesulfonamide

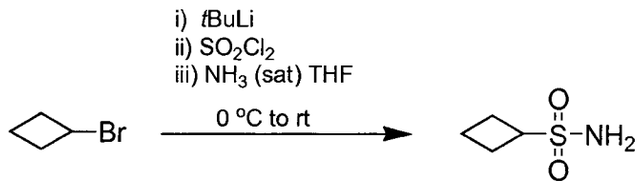


This compound was obtained in 50% yield (580 mg) from 1.62g (4.52 mmol) of 1-(3,5-dimethylisoxazol-4-yl)carbamoylcyclo-propanesulfonamide *tert*-butylcarbamate using 30 mL (120 mmol) of 4N HCl/dioxanes, stirring overnight, concentration and chromatography over a Biotage 40M column (eluting with 0% to 5% methanol/dichloromethane: ^{1}H NMR (methanol-d_4) δ 1.57 (m, 2H), 1.61 (m 2H),

2.15 (s, 3H), 2.30 (s, 3H), 4.84 (s, 3H); ^{13}C NMR (methanol-d_4) δ 9.65, 10.94, 15.01, 46.11, 114.82, 159.45, 165.55, 168.15; LRMS m/z 260 (M^++H).

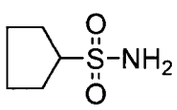
4. Preparation of cycloalkylsulfonamides from cyloalkylbromides

4a. Preparation of cyclobutylsulfonamide from cylobutyl bromide



To a solution of 5.0 g (37.0 mmol) of cyclobutyl bromide in 30 mL of anhydrous diethyl ether (diethyl ether) cooled to –78 °C was added 44 mL (74.8 mmol) of 1.7M tert-butyllithium in pentanes. The solution was slowly warmed to –35 °C over 1.5 hours. This mixture was cannulated slowly into a solution of 5.0 g (37.0 mmol) of freshly distilled sulfuryl chloride in 100 mL of hexanes cooled to –40 °C, warmed to 0 °C over 1 hour and carefully concentrated in vacuo. This mixture was redissolved in diethyl ether, washed once with some ice-cold water, dried ($MgSO_4$), filtered, and concentrated carefully. This mixture was redissolved in 20 mL of THF, added dropwise to 500 mL of saturated NH_3 in THF, and was allowed to stir overnight. The mixture was concentrated in vacuo to a crude yellow solid and was recrystallized from the minimum amount of dichloromethane in hexanes with 1-2 drops of methanol to provide 1.90 g (38%) of the desired product as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.95-2.06 (m, 2H), 2.30-2.54 (m, 4H), 3.86 (p, J=8 Hz, 1H), 4.75 (brs, 2H); ^{13}C NMR ($CDCl_3$) δ 16.43, 23.93, 56.29. HRMS m/z $(M-H)^-$ calcd for $C_4H_8NSO_2$: 134.0276, found 134.0282.

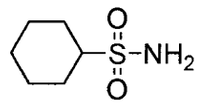
4b. Preparation of cyclopentyl sulfonamide



A solution of 18.5 mL (37.0 mmol) of 2M cyclopentylmagnesium chloride in ether was added dropwise to a solution of 3.0 mL (37.0 mmol) freshly distilled sulfuryl chloride (obtained from Aldrich) in 100 mL of hexanes cooled to –78 °C.

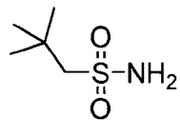
The mixture was warmed to 0 °C over 1 hour and was then carefully concentrated *in vacuo*. This mixture was redissolved in diethyl ether (200 mL), washed once with some ice-cold water (200 mL), dried ($MgSO_4$), filtered, and concentrated carefully. This mixture was redissolved in 35 mL of THF, added dropwise to 500 mL of saturated NH_3 in THF and was allowed to stir overnight. The mixture was concentrated *in vacuo* to a crude yellow solid, the residue filtered through 50g of silica gel using 70% ethyl acetate-hexanes as the eluent and the solution was then concentrated. The residue was recrystallized from the minimum amount of dichloromethane in hexanes with 1-2 drops of methanol to provide 2.49 g (41%) of the desired product as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.58-1.72 (m, 2H), 1.74-1.88 (m, 2H), 1.94-2.14 (m, 4H), 3.48-3.59 (m, 1H), 4.80 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 25.90, 28.33, 63.54; MS m/e 148 $(M-H)^-$.

4c. Preparation of cyclohexyl sulfonamide



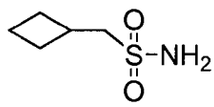
A solution of 18.5 mL (37.0 mmol) of 2M cyclohexylmagnesium chloride (TCI Americas) in diethyl ether was added dropwise to a solution of 3.0 mL (37.0 mmol) freshly distilled sulfuryl chloride in 100 mL of hexanes cooled to –78 °C. The mixture was warmed to 0 °C over 1 hour and was then carefully concentrated *in vacuo*. This mixture was redissolved in diethyl ether (200 mL), washed once with some ice-cold water (200 mL), dried ($MgSO_4$), filtered, and concentrated carefully. This mixture was redissolved in 35 mL of THF, added dropwise to 500 mL of saturated NH_3 in THF and was allowed to stir overnight. The mixture was concentrated *in vacuo* to a crude yellow solid, the residue filtered through 50g of silica gel using 70% ethyl acetate-hexanes as the eluent and was concentrated. The concentrate was recrystallized from the minimum amount of dichloromethane in hexanes with 1-2 drops of methanol to provide 1.66 g (30%) of the desired product as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.11-1.37 (m, 3H), 1.43-1.56 (m, 2H), 1.67-1.76 (m, 1H), 1.86-1.96 (m, 2H), 2.18-2.28 (m, 2H), 2.91 (tt, J=12, 3.5 Hz, 1H), 4.70 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 25.04, 25.04, 26.56, 62.74; MS m/e 162 $(M-1)^-$.

4d. Preparation of neopentylsulfonamide



Following the procedure for the preparation of cyclohexylsulfonamide, 49 mL (37 mmol) of 0.75M neopentylmagnesium chloride (Alfa) in diethyl ether was converted to 1.52g (27%) of the desired product as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.17 (s, 9H), 3.12 (s, 2H), 4.74 (brs, 2H); ^{13}C NMR ($CDCl_3$) δ 29.46, 31.51, 67.38; MS m/e 150 $(M-1)^-$.

4e. Preparation of cyclobutylcarbinylsulfonamide

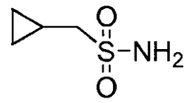


A solution of 12.3 g (83 mmol) of cyclobutylcarbinyl bromide (Aldrich) and 13.7g (91 mmol) of sodium iodide in 150 mL of acetone was heated to reflux overnight and then cooled to room temperature. The inorganic solids were removed by filtration and the acetone and cyclopropylcarbinyl iodide (8.41g, 46%) were removed by distillation (ambient temperature and 150 torr at 80 °C, respectively).

A solution of 4.0 g (21.98 mmol) of cyclobutyl carbinyl iodide in 30 mL of anhydrous diethyl ether cooled to –78 °C was cannulated into a solution of 17 mL (21.98 mmol) of 1.3M sec-butyllithium in cyclohexanes and the solution was stirred for 5 minutes. To this mixture was cannulated a solution of 3.0 g (21.98 mmol) of freshly distilled sulfuryl chloride in 110 mL of hexanes cooled to –78 °C, the mixture warmed to room temperature over 1 hour and was then carefully concentrated *in vacuo*. This mixture was redissolved in diethyl ether, washed once with some ice-cold water, dried ($MgSO_4$), filtered, and concentrated carefully. This mixture was redissolved in 30 mL of THF, added dropwise to 500 mL of saturated NH_3 in THF and was allowed to stir overnight. The mixture was concentrated *in vacuo* to a crude yellow solid and was recrystallized from the minimum amount of dichloromethane in hexanes with 1-2 drops of methanol to provide 1.39 g (42%) of the desired product as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.81-2.03 (m, 4H), 2.14-2.28 (m, 2H), 2.81-2.92 (m, 1H), 3.22 (d, J=7 Hz, 2H), 4.74 (brs, 2H); ^{13}C NMR ($CDCl_3$) δ 19.10, 28.21,

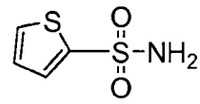
30.64, 60.93. MS m/e 148 $(M-H)^-$.

4f. Preparation of cyclopropylcarbinylsulfonamide



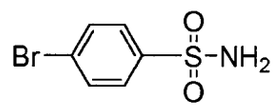
Using the procedure employed for the preparation of cyclobutylcarbinylsulfonamide, cyclopropylcarbinylsulfonamide was prepared from cyclopropylcarbinyl bromide (Aldrich) (see also *JACS* 1981, p.442-445). ^{1}H NMR ($CDCl_3$) δ 0.39-0.44 (m, 2H), 0.67-0.76 (m, 2H), 1.13-1.27 (m, 1H), 3.03 (d, J=7.3 Hz, 2H), 4.74 (brs, 2H); ^{13}C NMR ($CDCl_3$) δ 4.33, 5.61, 59.93; MS m/e 134 (M-1).

4g. Preparation of 2-thiophenesulfonamide



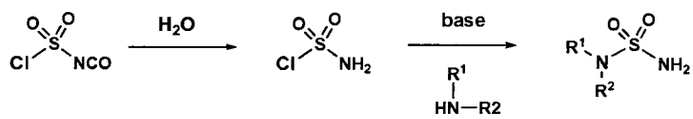
The desired product was prepared from 2-thiophenesulfonyl chloride (purchased from Aldrich) using the method described in *Justus Liebigs Ann. Chem.* **1933**, *501*, p.174-182.

4h. Preparation of 4-bromobenzenesulfonamide



4-Bromophenylsulfonamide was prepared by treatment of commercially available 4-bromosulfonyl chloride with saturated ammonia in THF.

5. General procedure for the preparation of sulfamides

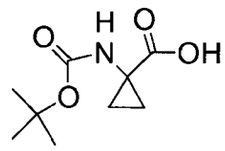


The intermediate sulfamoyl chloride was prepared by addition of water (1 equiv) in THF to a cold (-20 °C) stirred solution of chlorosulfonyl isocyanate (1 equiv) in THF and the resulting solution allowed to warm to 0 °C. To this solution was added anhydrous triethylamine (1 equiv) followed by requisite secondary amine

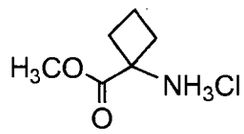
(1 equiv). The reaction mixture was warmed to room temperature, then filtered and the filtrate was concentrated to afford the desired sulfamides.

II Preparation of P1 Intermediates

5. 1-*tert*-Butoxycarbonylaminocyclopropane carboxylic acid is commercially available

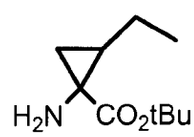


6. Preparation of 1-aminocyclobutanecarboxylic acid methyl ester·hydrochloride



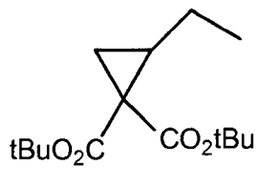
1-Aminocyclobutanecarboxylic acid (100 mg, 0.869 mmol)(Tocris) was dissolved in 10 mL of methanol. HCl gas was bubbled in for 2 hours. The reaction mixture was stirred for 18 hours, and then concentrated *in vacuo* to give 144 mg of a yellow oil. Trituration with 10 mL of diethyl ether provided 100 mg of the desired product as a white solid. ^{1}H NMR ($CDCl_3$) δ 2.10-2.25 (m, 1H), 2.28-2.42 (m, 1H), 2.64-2.82 (m, 4H), 3.87 (s, 3H), 9.21 (br s, 3H).

7a. Preparation of (1R,2R)/(1S,2S) 1-amino-2-ethylcyclopropanecarboxylic acid *tert*-butyl ester (racemic mixture)



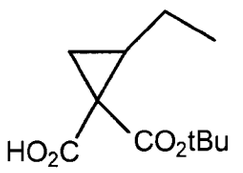
ethyl syn to carboxy

Step 1: Preparation of 2-ethylcyclopropane-1,1-dicarboxylic acid di-*tert*-butyl ester, shown below



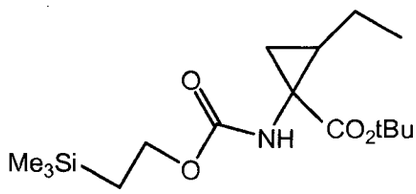
To a suspension of benzyltriethylammonium chloride (21.0 g, 92.2 mmol) in a 50% aqueous NaOH solution (92.4 g in 185 mL H_2O) was added 1,2-dibromobutane (30.0 g, 138.9 mmol) and di-*tert*-butylmalonate (20.0 g, 92.5 mmol). The reaction mixture was vigorously stirred for 18 hours at room temperature and treated with a mixture of ice and water. The crude product was extracted with dichloromethane (3x) and sequentially washed with water (3x), and brine. The organic extracts were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (100 g SiO_2, 3% diethyl ether in hexane) to provide the desired product (18.3 g, 67.8 mmol, 73% yield) which was used directly in the next reaction.

Step 2: Preparation of racemic 2-Ethylcyclopropane-1,1-dicarboxylic acid *tert*-butyl ester, shown below



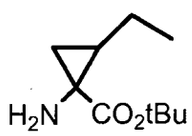
The product of Step 1 (18.3 g, 67.8 mmol) was added to a suspension of potassium *tert*-butoxide (33.55 g, 299.0 mmol) in dry diethyl ether (500 mL) at 0 °C, treated with H_2O (1.35 mL, 75.0 mmol), and was vigorously stirred overnight at room temperature. The reaction mixture was poured in a mixture of ice and water and washed with diethyl ether (3x). The aqueous layer was adjusted to acidic pH with a 10% aqueous citric acid solution at 0 °C and extracted with ethyl acetate (3x). The combined organic layers were washed with water (2x), brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide the desired product as a pale yellow oil (10 g, 46.8 mmol, 69% yield).

Step 3: Preparation of (1R,2R)/(1S,2S) 2-ethyl-1-(2-trimethylsilanylethoxycarbonylamino)cyclopropane-carboxylic acid *tert*-butyl ester, shown below



To a suspension of the product of Step 2 (10 g, 46.8 mmol) and 3g of freshly activated 4Å molecular sieves in dry benzene (160 mL) was added triethylamine (7.50 mL, 53.8 mmol) and DPPA (11 mL, 10.21 mmol). The reaction mixture was heated to reflux for 3.5 hours, treated with 2-trimethylsilylethanol (13.5 mL, 94.2 mmol), and heated to reflux overnight. The reaction mixture was filtered, diluted with diethyl ether, washed sequentially with 10% aqueous citric acid solution, water, saturated aqueous $NaHCO_3$, water (2x), and brine (2x), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was suspended with 10g of Aldrich polyisocyanate scavenger resin in 120 mL of dichloromethane, stirred at room temperature overnight, and filtered to provide the desired product (8 g, 24.3 mmol; 52%) as a pale yellow oil: ^1H NMR ($CDCl_3$) δ 0.03 (s, 9H), 0.97 (m, 5H), 1.20 (br m, 1H), 1.45 (s, 9H), 1.40-1.70 (m, 4H), 4.16 (m, 2H), 5.30 (br s, 1H).

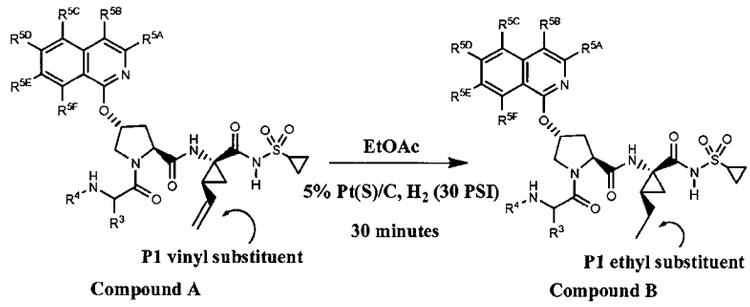
Step 4: Preparation of (1R,2R)/(1S,2S) 1-amino-2-ethylcyclopropanecarboxylic acid *tert*-butyl ester (racemic mixture), shown below



ethyl syn to carboxy

To the product of Step 3 (3 g, 9 mmol) was added a 1.0M TBAF solution in THF (9.3 mL, 9.3 mmol). The mixture was heated to reflux for 1.5 hours, cooled to room temperature, and diluted with 500 mL of ethyl acetate. The solution was successively washed with water (2x100 mL) and brine (2x100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide the desired product.

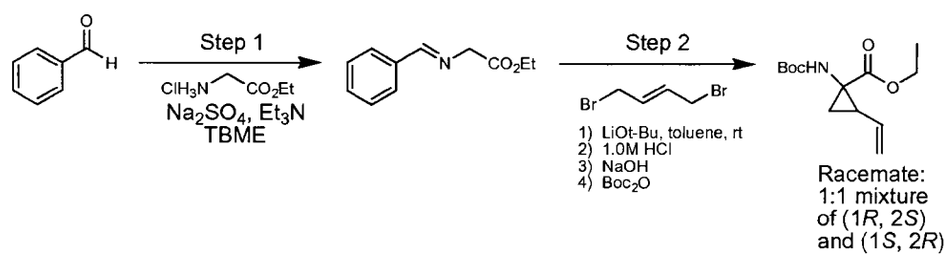
7b. A general method for the conversion of Compounds of Formula I bearing a P1 vinyl P1 substituent to the corresponding saturated P1 analogue as shown



A suspension of Compound A (approximately 100mg) and Pt(S)/C (5%, 10 mg) in approximately 15 mL of EtOAc was hydrogenated , H_2 (30 PSI) for 0.5 h. After filtration through a Ceilite plug, the filtrate was concentrated and purified to give the desired product, Compound B.

8. Preparation of racemic (1*R*,2*S*)/(1*S*,2*R*)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester:

Scheme 1



Step 1:

Glycine ethyl ester hydrochloride (304 g, 2.16 mole) was suspended in *tert*-butylmethyl ether (1.6 L). Benzaldehyde (231 g, 2.16 mole) and anhydrous sodium sulfate (155 g, 1.09 mole) were added, and the mixture was cooled to 0°C using an ice-water bath. Triethylamine (455 mL, 3.26 mole) was added dropwise over 30 minutes and the mixture was stirred for 48 hours at room temperature. The reaction was then quenched by addition of ice-cold water (1 L) and the organic layer was separated. The aqueous phase was extracted with *tert*-butylmethyl ether (0.5 L) and the organic phases were combined and washed with a mixture of saturated aqueous $NaHCO_3$ (1 L) and brine (1 L). The organic layer was dried over $MgSO_4$, filtered,

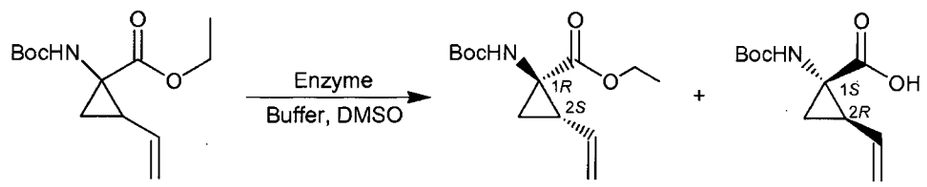
and concentrated *in vacuo* to provide 392.4 g of the *N*-benzyl imine product as a thick yellow oil that was used directly in the next step. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.32 (t, J = 7.1 Hz, 3H), 4.24 (q, J = 7.1 Hz, 2H), 4.41 (d, J = 1.1 Hz, 2H), 7.39-7.47 (m, 3H), 7.78-7.81 (m, 2H), 8.31 (s, 1H).

Step 2:

To a suspension of lithium *tert*-butoxide (84.1 g, 1.05 mol) in dry toluene (1.2 L), was added dropwise a mixture of the *N*-benzyl imine of glycine ethyl ester (100 g, 0.526 mol) and *trans*-1,4-dibromo-2-butene (107 g, 0.500 mol) in dry toluene (0.6 L) over 60 minutes. Upon completion of the addition, the deep red mixture was quenched by addition of water (1 L) and *tert*-butylmethyl ether (TBME, 1 L). The aqueous phase was separated and extracted a second time with TBME (1 L). The organic phases were combined, 1.0M HCl (1 L) was added and the mixture stirred at room temperature for 2 hours. The organic phase was separated and extracted with water (0.8 L). The aqueous phases were then combined, saturated with salt (700 g), and TBME (1 L) was added and the mixture was cooled to 0°C. The stirred mixture was then made basic to pH =14 by the dropwise addition of 10.0M NaOH, the organic layer was separated, and the aqueous phase was extracted with TBME (2 x 500 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated to a volume of 1 L. To this solution of free amine was added Boc_2O or di-*tert*-butyldicarbonate (131 g, 0.600 mol) and the mixture stirred for 4 days at room temperature. Additional di-*tert*-butyldicarbonate (50 g, 0.23 mol) was added to the reaction and the mixture was refluxed for 3 hours and was then allowed cool to room temperature overnight. The reaction mixture was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide 80 g of crude material. This residue was purified by flash chromatography (2.5 kg of SiO_2, eluted with 1% to 2% CH_3OH/CH_2C1_2) to provide 57 g (53%) of racemic *N*-Boc-(1*R*,2*S*)/(1*S*,2*R*)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester as a yellow oil which solidified while sitting in the refrigerator: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, J = 7.1 Hz, 3H), 1.46 (s, 9H), 1.43-1.49 (m, 1H), 1.76-1.82 (br m, 1H), 2.14 (q, J = 8.6 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 5.12 (dd J = 10.3, 1.7 Hz, 1H), 5.25 (br s, 1H), 5.29 (dd, J = 17.6, 1.7 Hz, 1H), 5.77 (ddd, J = 17.6, 10.3, 8.9 Hz, 1H); MS *m/z* 254.16 (M-1).

9. Resolution of *N*-Boc-(1*R*,2*S*)/(1*S*,2*R*)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester

Scheme 2

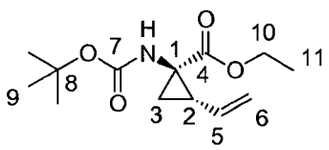


Racemate: 1:1 mixture of (1*R*, 2*S*) and (1*S*, 2*R*)

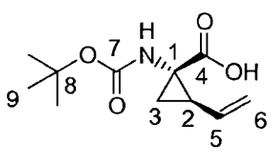
Resolution A

To an aqueous solution of sodium phosphate buffer (0.1 M, 4.25 liter ("L"), pH 8) housed in a 12 Liter jacked reactor, maintained at 39 °C, and stirred at 300 rpm was added 511 grams of Alcalase 2.4L (about 425 mL) (Novozymes North America Inc.). When the temperature of the mixture reached 39 °C, the pH was adjusted to 8.0 by the addition of a 50% NaOH in water. A solution of the racemic *N*-Boc-(1R,2S)/(1S,2R)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester (85g) in 850 mL of DMSO was then added over a period of 40 minutes. The reaction temperature was then maintained at 40 °C for 24.5 hours during which time the pH of the mixture was adjusted to 8.0 at the 1.5 hour and 19.5 hour time points using 50% NaOH in water. After 24.5 hours, the enantio-excess of the ester was determined to be 97.2%, and the reaction was cooled to room temperature (26 °C) and stirred overnight (16 hours) after which the enantio-excess of the ester was determined to be 100%. The pH of the reaction mixture was then adjusted to 8.5 with 50% NaOH and the resulting mixture was extracted with MTBE (2 x 2 L). The combined MTBE extract was then washed with 5% $NaHCO_3$ (3 x 100 mL), water (3 x 100 mL), and concentrated *in vacuo* to give the enantiomerically pure *N*-Boc-(1R,2S)/-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester as light yellow solid (42.55 g; purity: 97% @ 210 nm, containing no acid; 100% enantiomeric excess ("ee").

The aqueous layer from the extraction process was then acidified to pH 2 with 50% H_2SO_4 and extracted with MTBE (2 x 2 L). The MTBE extract was washed with water (3 x 100 mL) and concentrated to give the acid as light yellow solid (42.74 g; purity: 99% @ 210 nm, containing no ester).



1R, 2S-ester



1S,2R-acid

	ester	acid
High Resolution Mass Spec	(+) ESI, $C_{13}H_{22}NO_4$, $[M+H]^+$, calcd. 256.1549, found 256.1542	(-) ESI, $C_{11}H_{16}NO_4$, $[M-H]^-$, calcd. 226.1079, found 226.1089
NMR observed chemical shift Solvent: $CDCl_3$ (proton δ 7.24 ppm, C-13 δ 77.0 ppm) Bruker DRX-500C: proton 500.032 MHz, carbon 125.746 MHz		

Position	Proton (pattern) ppm	C-13 ppm	Proton (pattern) ppm	C-13 ppm
1	----	40.9	----	40.7
2	2.10 (q, J = 9.0 Hz)	34.1	2.17 (q, J = 9.0 Hz)	35.0
3a	1.76 (br)	23.2	1.79 (br)	23.4
3b	1.46 (br)		1.51, (br)	
4	----	170.8	----	175.8
5	5.74 (ddd, J = 9.0, 10.0, 17.0 Hz)	133.7	5.75 (m)	133.4
6a	5.25 (d, J = 17.0 Hz)	117.6	5.28 (d, J = 17.0 Hz)	118.1
6b	5.08 (dd, J = 10.0, 1.5 Hz)		5.12 (d, J = 10.5 Hz)	
7	----	155.8	----	156.2

8	----	80.0	----	80.6
9	1.43 (s)	28.3	1.43 (s)	28.3
10	4.16 (m)	61.3	----	----
11	1.23 (t, J = 7.5 Hz)	14.2	----	----

Resolution B

To 0.5 mL 100 mM Heps·Na buffer (pH 8.5) in a well of a 24 well plate (capacity: 10 mL/well), 0.1 mL of Savinase 16.0L (protease from Bacillus clausii) (Novozymes North America Inc.) and a solution of the racemic *N*-Boc-(1R,2S)/(1S,2R)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester (10 mg) in 0.1 mL of DMSO were added. The plate was sealed and incubated at 250 rpm at 40 °C. After 18 hours, enantio-excess of the ester was determined to be 44.3% as following: 0.1 mL of the reaction mixture was removed and mixed well with 1 mL ethanol; after centrifugation, 10 microliter ("μL") of the supernatant was analyzed with the chiral HPLC. To the remaining reaction mixture, 0.1 mL of DMSO was added, and the plate was incubated for additional 3 days at 250 rpm at 40 °C, after which four mL of ethanol was added to the well. After centrifugation, 10 μL of the supernatant was analyzed with the chiral HPLC and enantio-excess of the ester was determined to be 100%.

Resolution C

To 0.5 mL 100 mM Heps·Na buffer (pH 8.5) in a well of a 24 well plate (capacity: 10 mL/well), 0.1 mL of Esperase 8.0L, (protease from Bacillus halodurans) (Novozymes North America Inc.) and a solution of the racemic *N*-Boc-(1R,2S)/(1S,2R)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester (10 mg) in 0.1 mL of DMSO were added. The plate was sealed and incubated at 250 rpm at 40 °C. After 18 hour, enantio-excess of the ester was determined to be 39.6% as following: 0.1 mL of the reaction mixture was removed and mixed well with 1 mL ethanol; after cenrifugation, 10 μL of the supernatant was analyzed with the chiral HPLC. To the remaining reaction mixture, 0.1 mL of DMSO was added, and the plate was incubated for additional 3 days at 250 rpm at 40 °C, after which 4 mL of

ethanol was added to the well. After centrifugation, 10 μL of the supernatant was analyzed with the chiral HPLC and enantio-excess of the ester was determined to be 100%.

Samples analysis was carried out in the following manner:

1) Sample preparation: About 0.5 mL of the reaction mixture was mixed well with 10 volume of ethanol. After centrifugation, 10 μL of the supernatant was injected onto HPLC column.

2) Conversion determination:

Column: YMC ODS A, 4.6 x 50 mm, S-5 μm

Solvent: A, 1 mM HCl in water; B, CH_3CN

Gradient: 30% B for 1 min; 30% to 45% B over 0.5 min; 45% B for 1.5 min; 45% to 30% B over 0.5 minutes.

Flow rate: 2 mL/min

UV Detection: 210 nm

Retention time: acid, 1.2 min; ester, 2.8 minutes.

3) Enantio-excess determination for the ester:

Column: CHIRACEL OD-RH, 4.6 x 150 mm, S-5 μm

Mobile phase: CH_3CN/50 mM $HClO_4$ in water (67/33)

Flow rate: 0.75 mL/min.

UV Detection: 210 nm.

Retention time:

(1S,2R)-1-amino-2-vinylcyclopropane carboxylic acid 5.2 min;

Racemate (1R,2S)/(1S,2R)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester 18.5 minutes and 20.0 min;

(1R,2S)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester 18.5 minutes.

Resolution D

5 L of 0.3 M sodium phosphate buffer (pH 8) was maintained at 38 °C in a 20 Liter jacked reactor, stirred at 130 rpm. Four liters of Alcalase 2.4L (Novozymes North America Inc.) and 1 liter of DI water were added to the reactor. When temperature of the mixture closed to 38 °C, pH was adjusted to 7.8 with 10 N NaOH. A solution of the racemic *N*-Boc-(1R,2S)/(1S,2R)-1-amino-2-vinylcyclopropane

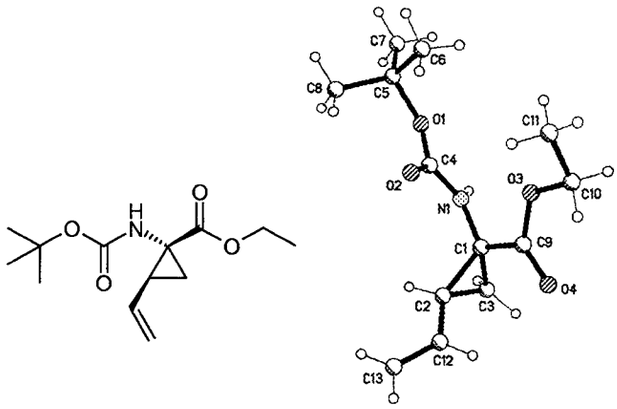
carboxylic acid ethyl ester (500 grams) in 5 liters DMSO was added to the reactor over a period of 1 hour *via* an addition funnel. The reaction temperature was then adjusted to 48 °C. After 21 hours, enantio-excess of the ester reached 99.3%. Heating was stopped at 24 hours and the reaction was slowly cooled down to room temperature (about 25 °C) and stirred overnight. The pH of the reaction mixture was adjusted to 8.5 with 10 N NaOH and the mixture was extracted with MTBE (2 x 4 L). The combined MTBE extract was washed with 5% $NaHCO_3$ (3 x 400 mL) and water (3 x 400 mL), and concentrated to give enantiomerically pure *N*-Boc-(1R,2S)/-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester as light yellow crystal (259 g; purity: 96.9% @ 210 nm, containing no acid; 100%ee).

Resolution E

10 L of 0.1 M sodium phosphate buffer (pH 8) was maintained at 40 °C in a 20 Liter jacked reactor, stirred at 360 rpm. 1.5 liters of Alcalase 2.4L (Novozymes North America Inc.) was added to the reactor. When the temperature of the mixture closed to 38 °C, the pH was adjusted to 8.0 with 10 N NaOH. A solution of the racemic *N*-Boc-(1R,2S)/(1S,2R)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester (200 grams) in 2 liters DMSO was added to the reactor over a period of 1 hour *via* an addition funnel. The reaction temperature was then adjusted to 40 °C. After 3 hours, the pH was adjusted to 8.0 with 10 N NaOH. After 21 hours, the reaction was cooled down to 25 °C, the pH of the reaction mixture was adjusted to 8.5 with 10 N NaOH and the mixture was extracted with MTBE (2 x 5 L). The combined MTBE extract was washed with 5% $NaHCO_3$ (3 x 500 mL) and water (3 x 200 mL), and concentrated to give 110 gram of yellow oil. The oil was set at room temperature under house vacuum and gave enantiomerically pure *N*-Boc-(1R,2S)/-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester as colorless long rod crystal (101 g; purity: 97.9% @ 210 nm, containing no acid; 100%ee).

The crystal structure enantiomerically pure *N*-Boc-(1R,2S)/-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester has been characterized by single crystal analysis (X-ray NB#: 52795-093, refcode: 634592N1). The absolute configuration is not established for lack of a known chiral center or heavier atom(s). A chain structure along the crystallographic a-axis is formed *via* intermolecular hydrogen bonding between the amide group and the carbonyl oxygen atom (N...O 3.159 Å).

Structure of *N*-Boc-(1R,2S)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester:



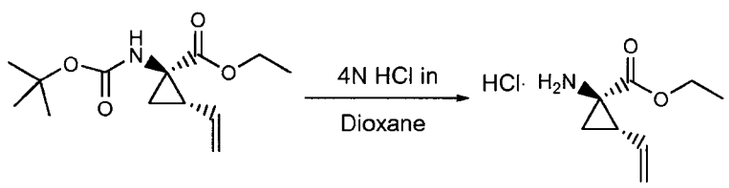
Crystal Data:	Experimental:
Chemical formula: C13H21N1O4	*Crystallization*
Crystal system: Orthorhombic	Crystal source: MTBE
Space Group: $P2_12_12_1$	Crystal description: Colorless rod
a = 5.2902(1) Å α=90°	Crystal size (mm): 0.12 X 0.26 X 0.30
b = 13.8946(2) Å β=90°	*Data Collection*
c = 19.9768(3) Å γ=90°	Temperature (K): 293
V = 1468.40(4) Å^3	θ_{max} (°): 65.2 (Cu Kα)
Z = 4 d_x = 1.155 g cm^{-3}	No. of reflections measured: 7518
No. of reflections for lattice parameters: 6817	No. of independent reflections: 2390 (R_{int} = 0.0776)
θrange for lattice parameters (°): 2.2-65.2	No. of observed reflections ($I \geq 2\sigma$: 2284
Absorption coefficient (mm^{-1}): 0.700	Absorption correction (T_{min}-T_{max}): 0.688-1.000

Resolution F

5 L of 0.2 M sodium borate buffer (pH 9) was maintained at 45°C in a 20 liter jacked reactor, and stirred at 400 rpm. Three liter of DI water and four liters of Savinase 16L, type EX (Novozymes North America Inc.) were added to the reactor. When temperature of the mixture closed to 45°C, pH was adjusted to 8.5 with 10 N NaOH. A solution of the racemic *N*-Boc-(1R,2S)/(1S,2R)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester (200 grams) in 2 liters DMSO was added to the reactor over a period of 40 minutes, *via* an addition funnel. The reaction temperature was then adjusted to 48 °C. After 2 hours, pH was adjusted to pH 9.0

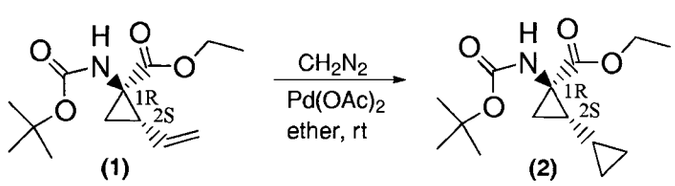
with 10 N NaOH. At 18 hour, enantio-excess of the ester reached 72%, pH was adjusted to 9.0 with 10 N NaOH. At 24 hours, temperature was lowered to 35 °C. At 42 hours, the temperature was raised to 48 °C and the pH was adjusted to 9.0 with 10 N NaOH. Heating was stopped at 48 hours and the reaction was slowly cooled down to room temperature (about 25 °C) and stirred overnight. At 66 hour, pH of the reaction mixture was 8.6. The mixture was extracted with MTBE (2 x 4 L). The combined MTBE extract was washed with 5% $NaHCO_3$ (6 x 300 mL) and water (3 x 300 mL), and concentrated to give enantiomerically pure *N*-Boc-(1R,2S)/-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester as light yellow crystal (101A g; purity: 95.9% @ 210 nm, containing no acid; 98.6%ee).

10. Preparation of chiral (1R,2S)-1-amino-2-vinylcyclopropane carboxylic acid ethyl ester hydrochloride



(1R,2S) *N*-Boc-1-amino-2-vinylcyclopropanecarboxylic acid ethyl ester (8.5 g, 33.3 mmol) was stirred under a nitrogen atmosphere with 200 mL of 4N HCl/dioxane (Aldrich) at room temperature for 3 hours. The solvent was removed under reduced pressure keeping the temperature below 40 °C. This gave 6.57 g (~100%) of (1R,2S)-1-amino-2-vinylcyclopropanecarboxylic acid ethyl ester hydrochloride as a light tan solid. ^{1}H NMR (300 MHz, CD_3OD) δ 1.31 (t, *J*=7.0 Hz, 3H), 1.69-1.82 (m, 2H), 2.38 (q, *J*=8.8 Hz, 1H), 4.29 (q, *J*=7.0 Hz, 2H), 5.22 (d, *J*=10.3 Hz, 1H), 5.40 (d, *J*=17.2 Hz, 1H), 5.69-5.81 (m, 1H). MS m/z 156 (M^++1).

11. Preparation of *N*-Boc-(1R,2S)-1-amino-2-cyclopropylcyclopropane carboxylic acid ethyl ester



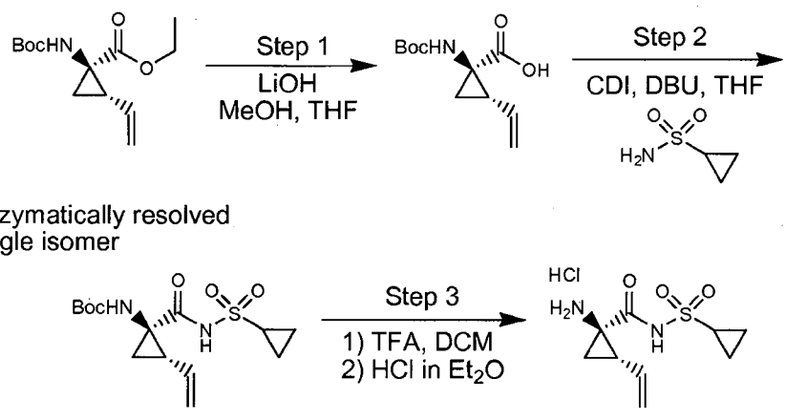
A solution of *N*-Boc-(1R,2S)-1-amino-2-vinylcyclopropane carboxylic acid

(255 mg, 1.0 mmol) in diethyl ether (10 mL) was treated with palladium acetate (5 mg, 0.022 mmol). The orange/red solution was placed under a nitrogen atmosphere. An excess of diazomethane in diethyl ether was added dropwise over the course of 1 hour. The resulting solution was stirred at room temperature for 18 hours. The excess diazomethane was removed using a stream of nitrogen and the resulting solution was concentrated by rotary evaporation to give the crude product. Flash chromatography (10% ethyl acetate/hexane) provided 210 mg (78%) of (1R,2S)-*N*-Boc-1-amino-2-cyclopropylcyclopropane carboxylic acid ethyl ester as a colorless oil. MS *m/z* 270 ($M^+ + H$).

III. Preparation of P1'-P1 intermediates

12. Preparation of P1P1':

Scheme 1



Step 1:

To a solution of 1(*R*)-tert-butoxycarbonylamino-2(*S*)-vinyl-cyclopropanecarboxylic acid ethyl ester (3.28 g, 13.2 mmol) in THF (7 mL) and methanol (7 mL) was added a suspension of LiOH (1.27 g, 53.0 mmol) in water (14 mL). The mixture was stirred overnight at room temperature. To the mixture was added 1.0M NaOH (15 mL), water (20 mL) and ethyl acetate (20 mL). The mixture was shaken, the phases were separated, and the organic phase was again extracted with 20 mL 0.5M NaOH. The combined aqueous phases were acidified with 1.0M

HCl until pH = 4 and extracted with ethyl acetate (3 x 40mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered to provide the desired product as a white solid (2.62 g, 87%). ^{1}H NMR: (DMSO-d_6) δ1.22-1.26 (m, 1H), 1.37 (s, 9H), 1.50-1.52 (m, 1H), 2.05 (q, J = 9 Hz, 1H), 5.04 (d, J = 10 Hz, 1H), 5.22 (d, J = 17 Hz, 1H), 5.64-5.71 (m, 1H), 7.18, 7.53 (s, NH (rotamers), 12.4 (br s, 1H)); LC-MS MS *m/z* 228 (M^+ + H).

Step 2:

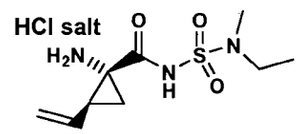
A solution of the product of Step 1 (2.62 g, 11.5 mmol) and CDI (2.43 g, 15.0 mmol) in THF (40 mL) was heated at reflux for 50 minutes under nitrogen. The solution was cooled to room temperature and transferred by cannula to a solution of cyclopropylsulfonamide (1.82 g, 15.0 mmol) in THF (10 mL). To the resulting solution was added DBU (2.40 mL, 16.1 mmol) and stirring was continued for 20 hours. The mixture was quenched with 1.0M HCl to pH = 1, and THF was evaporated *in vacuo*. The suspension was extracted with ethyl acetate (2 x 50 mL) and the organic extracts were combined and dried (Na_2SO_4). Filtration, concentration, and purification by recrystallization from hexanes-ethyl acetate (1:1) provideed the desired product (2.4 g) as a white solid. The mother liquor was purified by a Biotage 40S column (eluted 9% acetone in dichloromethane) to give a second batch of the desired product (1.1 g). Both batches were combined (total yield 92%). ^{1}H NMR: (DMSO-d_6) δ 0.96-1.10 (m, 4H), 1.22 (dd, J = 5.5, 9.5 Hz, 1H), 1.39 (s, 9H), 1.70 (t, J = 5.5 Hz, 1H), 2.19-2.24 (m, 1H), 2.90 (m, 1H), 5.08 (d, J = 10 Hz, 1H), 5.23 (d, J = 17 Hz, 1H), 5.45 (m, 1H), 6.85, 7.22 (s, NH (rotamers)); LC-MS, MS *m/z* 331 (M^+ + H).

Step 3:

A solution of the product of Step 2 (3.5 g, 10.6 mmol) in dichloromethane (35 mL) and TFA (32 mL) was stirred at room temperature for 1.5 hours. The volatiles were removed *in vacuo* and the residue suspended in 1.0M HCl in diethyl ether (20 mL) and concentrated *in vacuo*. This procedure was repeated once. The resulting mixture was triturated with pentane and filtered to give the title compound as a hygroscopic, off-white solid (2.60 g, 92%). ^{1}H NMR (DMSO-d_6) δ 1.01-1.15 (m,

4H), 1.69-1.73 (m, 1H), 1.99-2.02 (m, 1H), 2.38 (q, J = 9 Hz, 1H), 2.92-2.97 (m, 1H), 5.20 (d, J = 11 Hz, 1H), 5.33 (d, J = 17 Hz, 1H), 5.52-5.59 (m, 1H), 9.17 (br s, 3H); LC-MS, MS *m/z* 231 (M^+ + H).

13. Preparation of P1-P1' sulfamide derivative



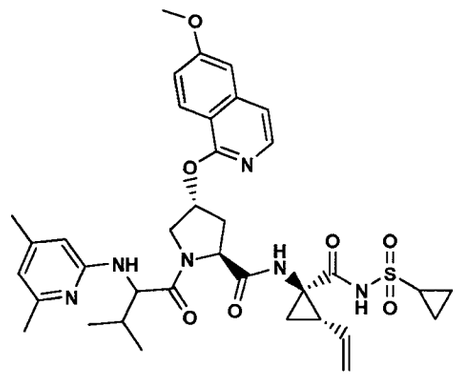
To a solution of (1R, 2S) 1-*tert*-butoxycarbonylamino-2-vinyl-cyclopropanecarboxylic acid (217 mg, 1.194 mmol) in THF (5 mL), was added CDI (290 mg, 1.791 mmol) and the reaction mixture was heated to reflux for 45 minutes. In another round-bottomed flask, LiHMDS (1.0M solution in hexanes, 2.4 mL, 2.4 mmol) was added to a solution of *N*-ethylmethylsulfamide (330 mg, 2.388 mmol) in THF (5 mL) and the reaction mixture was stirred at room temperature for 1 hour. The two reaction mixtures were combined and stirred at room temperature for 2 hours. Water was added to quench the reaction and the reaction solution was extracted with ethyl acetate. The organic layer was separated and dried over $MgSO_4$. Filtration and concentration gave crude product which was purified by preparative HPLC to provide the desired *N*-Boc protected *N*-acylsulfamide. The Boc protecting group was then removed as the compound was dissolved in 4N HCl solution in dioxane (2mL) and stirred at room temperature for 4 hours. Concentration provided a brownish oil as the HCl salt. (112mg, 33% yield). ^{1}H NMR (400Mz, CD_3OD) δ 1.16 (t, J=7.21 Hz, 3H), 1.68 (dd, J=10.03, 7.83 Hz, 1H), 2.15 (m, 1H), 2.37 (m, 1H), 2.89 (s, 3H), 3.30 (m, 2H), 5.31 (d, J=10.27 Hz, 1H), 5.42 (d, J=17.12 Hz, 3H), 5.68 (m, 1H). LC-MS (retention time: 0.883 minutes.), MS m/z 270 (M + Na^+).

Compound 1 Isomers:

N-(4,6-dimethyl-2-pyridinyl)-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide and

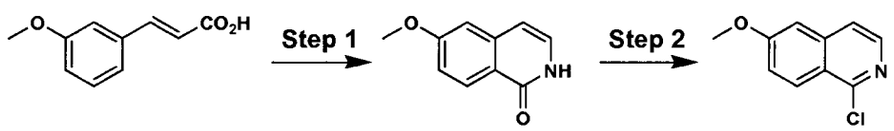
N-(4,6-dimethyl-2-pyridinyl)-D-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide

Example 1: Preparation of Compounds 1A and 1B



Compounds 1A and 1B

Scheme 1



Step 1:

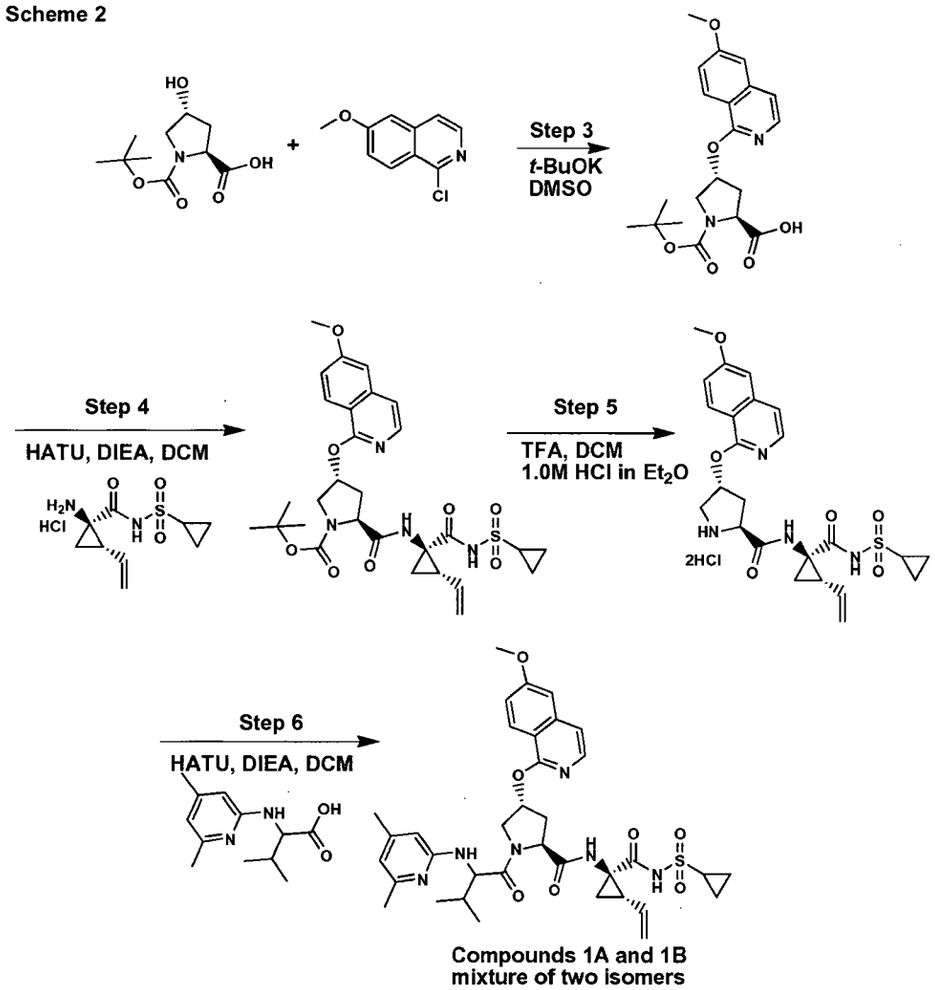
To a solution of 3-methoxycinnamic acid (11.0 g, 62 mmol) and triethylamine (12.5 g, 124 mmol) in acetone (80 mL) was added ethyl chloroformate (approximately 1.5 equivalents) dropwise at 0 °C. After stirring at this temperature for 1 hour, aqueous NaN_3 (6.40 g, 100 mmol in 35 mL H_2O) was added dropwise and the reaction mixture was stirred for 16 hours at ambient temperature. Water (100 mL) was added to the mixture and volatiles were removed *in vacuo*. The resulting slurry was extracted with toluene (3 x 50 mL) and the organic layers were combined, dried over $MgSO_4$, and filtered. The filtrate was added dropwise to a heated solution of diphenylmethane (50 mL) and tributylamine (30 mL) at 190 °C. The toluene was

removed by distillation during the addition. After complete addition, the reaction temperature was raised to 210 °C for 2 hours. Upon cooling, the precipitated product was collected by filtration, washed with hexane (2 x 50 mL), and dried to provide the desired product as a white solid (5.53 g, 51%) (Nicolas Briet *et al, Tetrahedron*, **2002**, 5761-5766). LC-MS, MS *m/z* 176 ($M^+ + H$).

Step 2:

6-Methoxy-*2H*-isoquinolin-1-one (5.0 g, 28.4 mmol) in $POCl_3$ (10 mL) was heated to gentle reflux for 3 hours and the mixture was then concentrated *in vacuo* (Nicolas Briet *et al, Tetrahedron*, **2002**, 5761-5766). The residue was poured into ice water (20 mL) and brought to pH = 10 by addition of 10.0M NaOH. The resulting mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (1:1 hexane-ethyl acetate) to provide 4.41 g (80%) of the desired product as a white solid. ^1H NMR (CD_3OD) δ ppm 3.98 (s, 3H), 7.34-7.38 (m, 2H), 7.69 (d, J = 5.5Hz, 1H), 8.10 (d, J = 6.0 Hz, 1H), 8.23 (d, J = 9.5 Hz, 1H); LC-MS, MS m/z 194 ($M^+ + H$).

Scheme 2



Step 3:

To a solution of *N*-Boc-4-(*R*)-hydroxy-L-proline (0.892 g, 3.89 mmol) in DMSO (40 mL) at ambient temperature was added solid potassium *tert*-butoxide (1.34 g, 12.0 mmol) in one portion. The suspension was stirred at room temperature for 30 minutes before being cooled to 10 °C. 1-Chloro-6-methoxy-isoquinoline (the product of Step 2, Example 1) (785 mg, 4.05 mmol) was added as a solid in one portion and the resulting mixture was stirred at ambient temperature for 12 hours. The mixture was quenched with ice cold 5% citric acid (aq) and was then extracted with ethyl acetate (100 mL). The aqueous phase was extracted with ethyl acetate once more. The combined organic layers were washed with 5% citric acid (aq) and brine respectively, dried over $MgSO_4$ and filtered. The filtrate was concentrated *in*

vacuo to dryness to provide the desired product as an off-white foam (1.49 g, 99% yield). This crude material was used in the next reaction step without further purification. ^{1}H NMR (CD_3OD) δ 1.42, 1.44 (rotamers, 9H), 2.38-2.43 (m, 1H), 2.66-2.72 (m, 1H), 3.80-3.87 (m, 2H), 3.92 (s, 3H), 4.44-4.52 (m, 1H), 5.73 (bs, 1H), 7.16-7.18 (m, 2H), 7.24-7.25 (m, 1H), 7.87-7.88 (m, 1H), 8.07 (d, J = 8.5 Hz, 1H); LC-MS, MS *m/z* 389 (M^+ + H).

Step 4:

To a mixture of the product of Step 3, Example 1 (1.49 g, 3.84 mmol), HATU (2.19 g, 5.76 mmol) and cyclopropanesulfonic acid (1-(*R*)-amino-2-(*S*)-vinyl-cyclopropanecarbonyl)-amide HCl salt (1.12 g, 4.22 mmol) in CH_2Cl_2 (50 mL) was added DIPEA (1.29 g, 11.5 mmol) at 0°C. After stirring at ambient temperature for 12 hours, the resulting solution was diluted with CH_2Cl_2 (50 mL) and washed with ice cold 5% citric acid (aq). The organic layer was washed with 5% citric acid (aq) and brine respectively, dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* to dryness. The residue was recrystallized from methanol to provide 1.60 g (70%) of the desired product as a white solid. ^{1}H NMR (CD_3OD) δ 1.05-1.08 (m, 2H), 1.16-1.20 (m, 1H), 1.24-1.27 (m, 1H), 1.42-1.45 (m, 10H), 1.88 (dd, J = 8.09, 5.34 Hz, 1H), 2.24-2.30 (m, 2H), 2.53-2.57 (m, 1H), 2.94-2.98 (m, 1H), 3.80 (d, J = 12.5 Hz, 1H), 3.86-3.89 (m, 1H), 3.93 (s, 3H), 4.40-4.42 (m, 1H), 5.13 (d, J = 10.5 Hz, 1H), 5.32 (d, J = 18.0 Hz, 1H), 5.72-5.81 (m, 2H), 7.17-7.20 (m, 2H), 7.26 (d, J = 6.0 Hz, 1H), 7.88 (d, J = 6.0 Hz, 1H), 8.07 (d, J = 9.0 Hz, 1H); LC-MS, MS *m/z* 601 (M^+ + H).

Step 5:

To an ice cold solution of the product of Step 4, Example 1 (1.50 g, 2.50 mmol) in CH_2Cl_2 (10 mL) was added TFA (10 mL). The resulting solution was allowed to warm to ambient temperature and was stirred for 2 hours. The solvent was removed *in vacuo*. The residue was triturated with 1M HCl in diethyl ether, collected by filtration, and the solid was washed with diethyl ether to provide the desired product as a hygroscopic white solid (1.43 g, 99.8%). ^{1}H NMR (CD_3OD) δ ppm 1.03-1.21 (m, 4H), 1.26-1.31 (m, 1H), 1.37-1.40 (m, 1H), 1.95-1.97 (m, 1H),

2.32-2.37 (m, 1H), 2.42-2.48 (m, 1H), 2.95-2.99 (m, 1H), 3.88 (d, J = 12.5 Hz, 2H), 3.98 (s, 3H), 4.40-4.42 (m. 1H), 5.16 (d, J = 10.5 Hz, 1H), 5.33 (d, J = 18.0 Hz, 1H), 5.62-5.69 (m, 1H), 5.97 (bs, 1H), 7.30-7.34 (m, 2H), 7.47 (d, J = 6.0 Hz, 1H), 7.90 (d, J = 6.5 Hz, 1H), 8.34 (d, J = 9.0 Hz, 1H), 9.14 (bs, 1H); LC-MS, MS *m/z* 501 (M^+ + H).

Step 6:

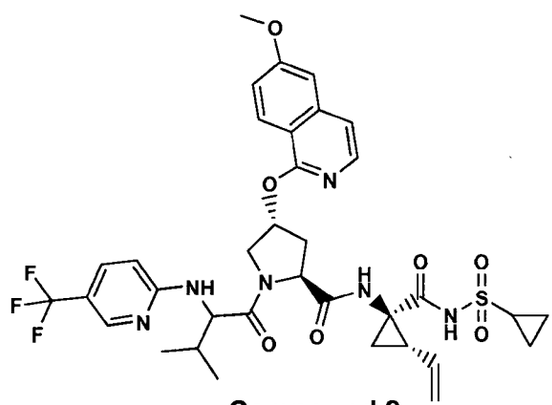
To a mixture of the product of Step 5, Example 1 (0.350 g, 0.610 mmol), HATU (0.302 g, 0.793 mmol), DIEA (0.277 g, 2.14 mmol) and dichloromethane (6 mL) was added (+/-)-2-(4,6-dimethylpyridin-2-ylamino)-3-methylbutanoic acid (0.135 g, 0.610 mmol, purchased from Specs, catalog # AP-836/41220382). The reaction was stirred at room temperature for 14 hours. Additional HATU (0.302 g, 0.793 mmol), DIEA (0.079 g, 0.61 mmol) and (+/-)-2-(4,6-dimethylpyridin-2-ylamino)-3-methylbutanoic acid (0.135 g, 0.610 mmol) were added and the resulting mixture was stirred for an additional 6 hours in an attempt to push the reaction further toward completion. The mixture was concentrated *in vacuo*, dissolved in ethyl acetate (75 mL), and washed with 1.0M aqueous HCl (3 x 10mL). The combined HCl washes were extracted with ethyl acetate (50 mL). The organic phases were combined and washed with 10% aqueous $NaHCO_3$ (2 x 10 mL) and with brine, and were then dried over $MgSO_4$, filtered and concentrated *in vacuo* to a dark brown residue. Purification by reverse phase preparative HPLC gave two products with identical *m/z* by LCMS. The first isomer to elute by reverse phase preparative HPLC was labeled Compound 1A (47.7 mg, 11.1%) and the second isomer to elute was labeled Compound 1B (16.9 mg, 3.9%).

Compound 1A: ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.01 (d, J = 6.71 Hz, 3H), 1.10 (d. J = 6.71 Hz, 3H), 1.12-1.17 (m, 2H), 1.26-1.30 (m, 2H), 1.47 (dd, J = 9.46, 5.49 Hz, 1H), 1.85 (dd, J = 8.09, 5.34 Hz, 1H), 2.17 (s, 3H), 2.31 (q, J = 8.85 Hz, 2H), 2.36-2.40 (m, 2H), 2.41 (s, 3H), 2.65 (dd, J = 13.73, 7.02 Hz, 1H), 2.97-3.03 (m, 1H), 3.95 (s, 3H), 4.16 (dd, J = 12.05, 3.51 Hz, 1H), 4.30 (d, J = 11.60 Hz, 1H), 4.49 (d, J = 7.02 Hz, 1H), 4.68 (dd, J = 10.22, 7.17 Hz, 1H), 5.17 (dd, J = 10.38, 1.53 Hz, 1H), 5.35 (dd, J = 17.24, 1.07 Hz, 1H), 5.77-5.86 (m, 1H), 5.99 (s, 1H), 6.59 (s, 1H), 6.65 (s, 1H), 7.11 (dd, J = 9.16, 2.44 Hz, 1H), 7.23 (d, J = 2.44 Hz, 1H), 7.30 (d, J = 5.80 Hz, 1H), 7.94 (d, J = 5.80 Hz, 1H), 7.98 (d, J = 9.16 Hz, 1H); LC-MS,

MS *m/z* 705 (M^+ + H).

Compound 1B: ^{1}H NMR (500 MHz, *MeOD*) δ ppm 1.02 (d, *J*=6.7 Hz, 3 H), 1.03 - 1.06 (m, *J*=2.1 Hz, 2 H), 1.07 (d, *J*=6.7 Hz, 3 H), 1.14 - 1.19 (m, 1 H), 1.20 - 1.25 (m, 1 H), 1.32 (dd, *J*=9.5, 5.2 Hz, 1 H), 1.81 (dd, *J*=8.1, 5.3 Hz, 1 H), 2.14 (q, *J*=8.9 Hz, 1 H), 2.25 - 2.39 (m, 2 H), 2.55 (dd, *J*=13.9, 6.9 Hz, 1 H), 2.88 - 2.94 (m, 1 H), 3.82 (s, 3 H), 4.12 (dd, *J*=11.7, 4.1 Hz, 1 H), 4.43 (dd, *J*=10.4, 7.0 Hz, 1 H), 4.55 (d, *J*=11.9 Hz, 1 H), 4.62 (d, *J*=9.2 Hz, 1 H), 5.03 (d, *J*=10.4 Hz, 1 H), 5.20 (d, *J*=17.1 Hz, 1 H), 5.65 - 5.74 (m, 1 H), 5.79 (t, *J*=3.5 Hz, 1 H), 6.99 (dd, *J*=9.2, 2.4 Hz, 1 H), 7.04 (d, *J*=2.1 Hz, 1 H), 7.11 (d, *J*=6.1 Hz, 1 H), 7.68 (t, *J*=7.6 Hz, 1 H), 7.73 (t, *J*=7.3 Hz, 1 H), 7.77 (d, *J*=6.1 Hz, 1 H), 7.79 (d, *J*=7.6 Hz, 1 H), 8.01 (d, *J*=7.6 Hz, 1 H), 8.07 (d, *J*=9.2 Hz, 1 H); LC-MS, MS *m/z* 705 (M^+ + H).

Example 2: Preparation of Compound 2: N-(5-(trifluoromethyl)-2-pyridinyl)valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide

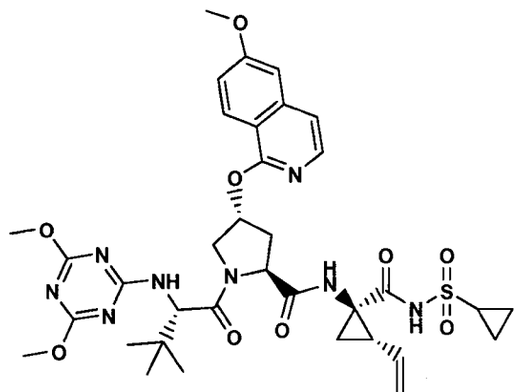


Compound 2

To a mixture of the product of Step 5, Example 1 (0.350 g, 0.610 mmol), HATU (0.464 g, 1.22 mmol), DIEA (0.316 g, 2.44 mmol) and dichloromethane (6 mL) was added N-[5-(trifluoromethyl)-pyridin-2-yl]valine (0.320 g, 1.22 mmol). The reaction was stirred at room temperature for 72 hours. The mixture was concentrated *in vacuo*, dissolved in ethyl acetate (50 mL), and washed with 1.0M aqueous HCl (3 x 5 mL). The HCl washes were combined and extracted with ethyl acetate (25 mL). The organic phases were combined and washed with 10% aqueous $NaHCO_3$ (2 x 5 mL) and with brine, and were then dried over $MgSO_4$, filtered and

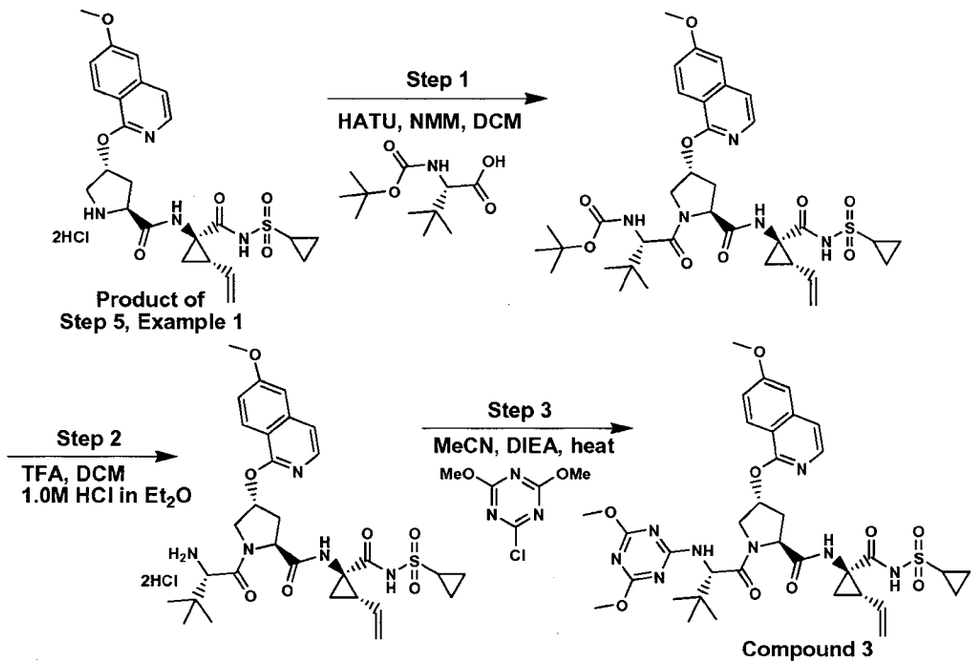
concentrated *in vacuo* to a residue. The crude material was passed through a plug of silica gel using 95:5 dichloromethane:methanol. Further purification by reverse phase preparative HPLC gave Compound 2 (0.174 g, 38.3%) as a white solid. Compound 2 was the major of two isomers that had formed in the reaction. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 0.68 (d, *J*=5.5 Hz, 1 H), 0.77 - 0.85 (m, 2 H), 0.93 (d, *J*=6.7 Hz, 3 H), 0.99 (d, *J*=6.4 Hz, 3 H), 1.14 (t, *J*=7.2 Hz, 3 H), 1.31 (dd, *J*=9.3, 5.0 Hz, 1 H), 1.74 - 1.81 (m, 1 H), 2.02 - 2.12 (m, 1 H), 2.28 - 2.41 (m, 1 H), 2.48 - 2.61 (m, 1 H), 3.83 (s, 2 H), 3.84 (s, 1 H), 3.99 - 4.03 (m, 1 H), 4.29 - 4.40 (m, 1 H), 4.50 (q, *J*=8.4 Hz, 1 H), 4.98 (d, *J*=9.2 Hz, 1 H), 5.17 (d, *J*=17.4 Hz, 1 H), 5.60 - 5.72 (m, 1 H), 5.76 (s, 1 H), 6.35 (d, *J*=8.9 Hz, 1 H), 6.95 (dd, *J*=9.2, 2.4 Hz, 1 H), 7.04 - 7.12 (m, 2 H), 7.15 - 7.23 (m, 2 H), 7.79 - 7.84 (m, 2 H); LC-MS, MS *m/z* 745 (M^+ + H).

Example 3: Preparation of Compound 3: N-(4,6-dimethoxy-1,3,5-triazin-2-yl)-3-methyl-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide



Compound 3

Scheme 1



Step 1:

A mixture of the product of Step 5, Example 1 (70.2 g, 122 mmol), Boc-*tert*-leucine (31.2 g, 135 mmol), NMM (63.1 g, 624 mmol) and HATU (60.5 g, 159 mmol) in dichloromethane (750 mL) was stirred at room temperature overnight. The mixture was concentrated *in vacuo* and to the residue was added ethyl acetate (3 L) and pH = 4 buffer (1 L). The mixture was shaken and the phases were separated. The organic phase was again washed with pH = 4 buffer (2 x 1 L) and with brine (300 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated to an orange foam. The crude solid was purified by silica gel chromatography (step elution with dichloromethane, followed by 10:1 dichloromethane:acetone, then with 7:1 dichloromethane:acetone). Iterative crystallizations from isopropanol of the concentrated material gave pure product as large colorless flakes (58.3 g, 67% yield). LC-MS, MS *m/z* 714 ($M^+ + H$).

Step 2:

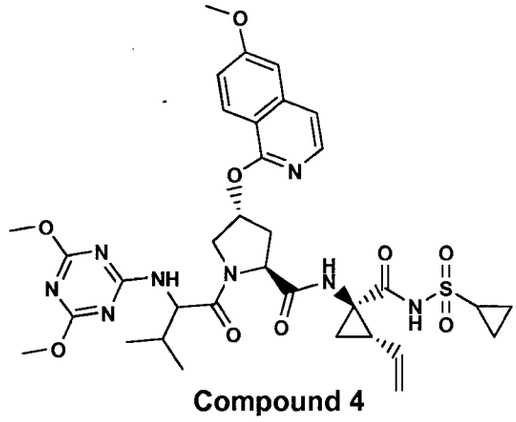
To a stirred solution of the product of Step 1, Example 3 (15.0 g, 21.0 mmol) in dry dichloromethane (200 mL) was added TFA (100 mL). The mixture was stirred

for 80 minutes and was then concentrated *in vacuo* to a residue. 1,2-Dichloroethane (200 mL) was added, and the mixture was again concentrated *in vacuo* to give a white foam. The material was dissolved in dry dichloromethane (50 mL) and diethyl ether (50 mL) was added. The rapidly stirred solution was then treated slowly with a mixture of 2.0M HCl in ether (150 mL) and dry diethyl ether (250 mL). The resulting suspension was stirred under nitrogen for 30 minutes, and was then filtered. The filtrant solid was rinsed with diethyl ether and allowed to air dry. The solid was dried in a vacuum oven at 40 °C overnight to yield a white free flowing powder product as the bis-HCl salt (13.9 g, 96.3% yield). LC-MS, MS *m/z* 614 (M^+ + H).

Step 3:

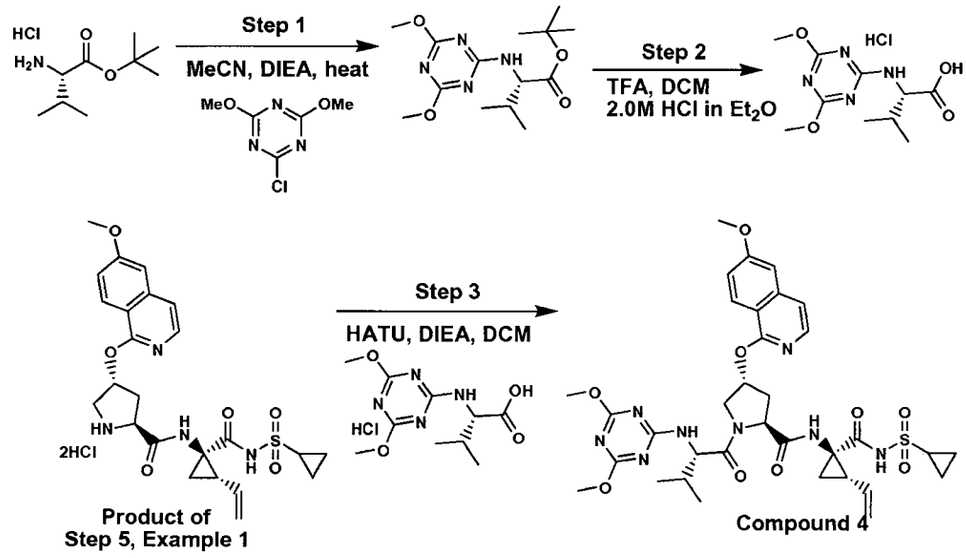
To a solution of the product of Step 2, Example 3 (0.253 g, 0.369 mmol) and DIEA (0.215 g, 1.66 mmol) in acetonitrile (4 mL) was added 2-chloro-4,6-dimethoxy-1,3,5-triazene (0.100 g, 0.553 mmol). The mixture was heated to 135 °C in a Chemglass pressure vessel for 2 hours. The mixture was concentrated *in vacuo*, and the residue was dissolved in ethyl acetate (50 mL) and washed with 1.0M HCl aqueous (2 x 5 mL) followed by 10% aqueous sodium carbonate and brine. The organic was dried over $MgSO_4$, filtered, and concentrated. Purification by silica gel flash chromatography (97:3 dichloromethane:methanol) gave pure Compound 3 (0.252 g, 91% yield) as a white solid. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 1.07 (s, 9 H), 1.09 - 1.14 (m, 2 H), 1.25 - 1.33 (m, 2 H), 1.48 (dd, *J*=9.5, 5.5 Hz, 1 H), 1.93 (dd, *J*=8.1, 5.3 Hz, 1 H), 2.24 - 2.39 (m, 2 H), 2.94 - 3.03 (m, 1 H), 3.55 (s, 3 H), 3.83 (s, 3 H), 3.95 (s, 3 H), 4.04 (dd, *J*=4.9, 3.1 Hz, 1 H), 4.08 (s, 2 H), 4.45 (d, *J*=11.9 Hz, 1 H), 4.67 (dd, *J*=10.4, 7.3 Hz, 1 H), 4.91 (s, 1 H), 5.16 (d, *J*=10.4 Hz, 1 H), 5.34 (d, *J*=17.1 Hz, 1 H), 5.75 - 5.84 (m, 1 H), 5.90 - 5.94 (m, 1 H), 7.03 (dd, *J*=9.2, 2.4 Hz, 1 H), 7.16 (d, *J*=2.1 Hz, 1 H), 7.26 (d, *J*=5.8 Hz, 1 H), 7.80 (d, *J*=8.9 Hz, 1 H), 7.89 (d, *J*=5.8 Hz, 1 H); LC-MS, MS *m/z* 753 (M^+ + H).

Example 4: Preparation of Compound 4: N-(4,6-dimethoxy-1,3,5-triazin-2-yl)valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide



Compound 4

Scheme 1



Step 1:

To a mixture of valine *tert*-butyl ester hydrochloride (0.367 g, 1.75 mmol) and DIEA (0.567 g, 4.38 mmol) in acetonitrile (5 mL) was added 2-chloro-4,6-dimethoxy-1,3,5-triazene (0.476 g, 2.63 mmol). The mixture was heated to 130 °C in a microwave reactor for 1 hours. Solvent was removed and the viscous brown residue was dissolved in ethyl acetate (75 mL) and the solution was washed with

1.0M aqueous HCl (2 x 10 mL). The aqueous extracts were combined and back-extracted with ethyl acetate (50 mL), and the organic phases were combined and washed with 10% aqueous sodium carbonate (15 mL) and then with brine. The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated to a brown oil which was purified by flash silica gel chromatography (97:3 dichloromethane:methanol) to give the product as a light brown viscous oil (0.521 g, 95% yield).

Step 2:

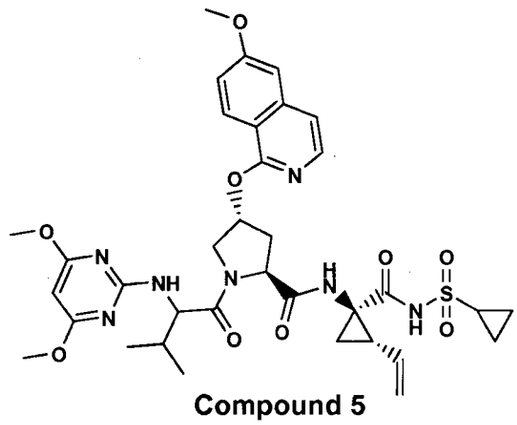
The product of Step 1, Example 4 (0.500 g, 1.60 mmol) was dissolved in dichloromethane (5 mL) and treated with TFA (5 mL). The mixture was stirred at room temperature for 3 hours and was then concentrated *in vacuo*. The residue was then dissolved in 1,2-dichloroethane (20 mL) and again concentrated *in vacuo*. The residue was then dissolved in dichloromethane (3 mL) and was added dropwise to a rapidly stirred solution of 2.0M HCl in ether (10 mL). No precipitatation occurred. The solution was concentrated *in vacuo* to give a slightly yellow solid which was dried *in vacuo*. Thus was obtained a yellow solid (0.45 g, 96% yield) which was subsequently used without further purification.

Step 3:

To a mixture of the product of Step 5, Example 1 (0.421 g, 0.734 mmol) and DIEA (0.428 g, 3.30 mmol) in dichloromethane (7 mL) was added the product of Step 2, Example 4 (0.215 g, 0.734 mmol) and HATU (0.335 g, 0.881 mmol). The mixture was stirred at room temperature for 80 minutes. Solvent was removed and the viscous brown residue was dissolved in ethyl acetate (50 mL) and the solution was washed with 1.0M aqueous HCl (2 x 10 mL). The aqueous extracts were combined and back-extracted with ethyl acetate (50 mL), and the organic phases were combined and washed with 10% aqueous sodium carbonate (15 mL) and then with brine. The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated to a brown solid which was purified by flash silica gel chromatography (97:3 dichloromethane:methanol) to give Compound 4 as a white solid (0.243 g, 45% yield). ^{1}H NMR (500 MHz, *MeOD*) δ ppm 0.71 (d, *J*=6.4 Hz, 3 H), 0.73 - 0.78 (m, 1 H), 0.79 - 0.88 (m, 1 H), 0.90 - 0.98 (m, 1 H), 1.01 - 1.07 (m, 1 H), 1.08 (d, *J*=6.7 Hz,

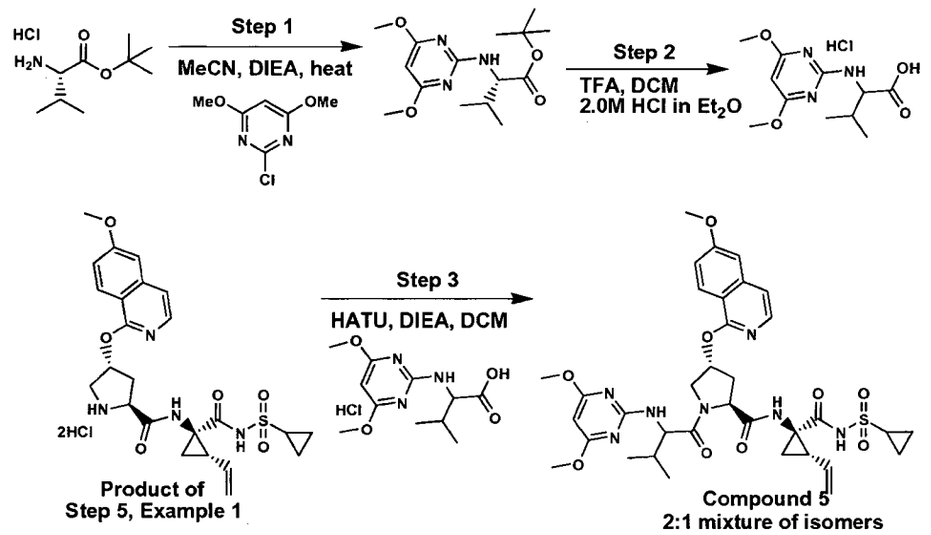
3 H), 1.23 (dd, *J*=9.0, 5.3 Hz, 1 H), 1.90 (q, *J*=8.5 Hz, 1 H), 1.99 - 2.06 (m, 1 H), 2.09 - 2.20 (m, 1 H), 2.22 - 2.33 (m, 1 H), 2.33 - 2.41 (m, 1 H), 2.47 (dd, *J*=13.4, 6.1 Hz, 1 H), 3.25 (s, 3 H), 3.45 (s, 2 H), 3.75 (s, 3 H), 4.11 (dd, *J*=11.7, 3.5 Hz, 1 H), 4.41 (d, *J*=12.2 Hz, 1 H), 4.52 (dd, *J*=11.9, 6.4 Hz, 1 H), 4.63 - 4.70 (m, 1 H), 4.85 (d, *J*=10.7 Hz, 1 H), 4.95 (d, *J*=17.4 Hz, 1 H), 5.81 (t, *J*=3.2 Hz, 1 H), 5.85 - 5.97 (m, 1 H), 6.48 (d, *J*=9.2 Hz, 1 H), 7.04 (s, 1 H), 7.18 (d, *J*=5.8 Hz, 1 H), 7.35 (d, *J*=8.9 Hz, 1 H), 7.80 (d, *J*=6.1 Hz, 1 H); LC-MS, MS *m/z* 739 ($M^+ + H$).

Example 5: Preparation of Compound 5: N-(4,6-dimethoxy-2-pyrimidinyl)valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide



Compound 5

Scheme 1



Step 1:

To a mixture of valine *tert*-butyl ester hydrochloride (1.55 g, 7.39 mmol) and DIEA (2.01 g, 15.5 mmol) in acetonitrile (37 mL) was added 2-chloro-4,6-dimethoxypyrimidine (1.55 g, 8.87 mmol). The mixture was heated to 130 °C in a Chemglass pressure vessel for 48 hours. Solvent was removed and the viscous brown residue was dissolved in ethyl acetate (100 mL) and the solution was washed with 1.0M aqueous HCl (2 x 25 mL). The aqueous extracts were combined and back-extracted with ethyl acetate (50 mL), and the organic phases were combined and washed with 10% aqueous sodium carbonate and then with brine. The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated to a brown oil which was purified by flash silica gel chromatography (step gradient 9:1 hexanes:ethyl acetate then 1:1 hexanes:ethyl acetate) to give the product as a brown viscous oil (1.02 g, 44% yield).

Step 2:

The product of Step 1, Example 5 (0.944 g, 3.03 mmol) was dissolved in dichloromethane (10 mL) and treated with TFA (10 mL). The mixture was stirred at room temperature for 4 hours and was then concentrated *in vacuo*. The residue was then dissolved in 1,2-dichloroethane (50 mL) and again concentrated *in vacuo*. The residue was then dissolved in dichloromethane (3 mL) and was added dropwise to a

rapidly stirred solution of 1.0M HCl in ether and hexanes (100 mL). No precipitate occurred. The solution was concentrated *in vacuo* to give a brown foamy solid which was subsequently used without further purification.

Step 3:

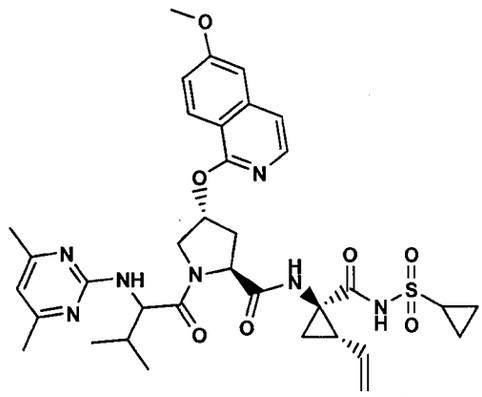
To a mixture of the product of Step 5, Example 1 (0.425 g, 0.741 mmol) and DIEA (0.432 g, 3.34 mmol) in dichloromethane (7 mL) was added the product of Step 2, Example 5 (0.259 g, 0.889 mmol) and HATU (0.366 g, 0.963 mmol). The mixture was stirred at room temperature for 16 hours. The solvent was removed and the viscous brown residue was dissolved in ethyl acetate (50 mL) and the solution was washed with 1.0M aqueous HCl (2 x 10 mL). The aqueous extracts were combined and extracted with ethyl acetate (30 mL), and the organic phases were combined and washed with 10% aqueous sodium carbonate (15 mL) and then with brine. The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated to a viscous brown oil which was passed through a plug of silica gel (95:5 dichloromethane:methanol). The product was further purified by reverse phase preparative HPLC to give white solid Compound 5 (0.243 g, 45% yield) as an apparent mixture of two isomers in a 2 to 1 ratio. The isomers were not separated. LC-MS, MS *m/z* 738 ($M^+ + H$).

Compound 6 Isomers:

N-(4,6-dimethyl-2-pyrimidinyl)-D-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide

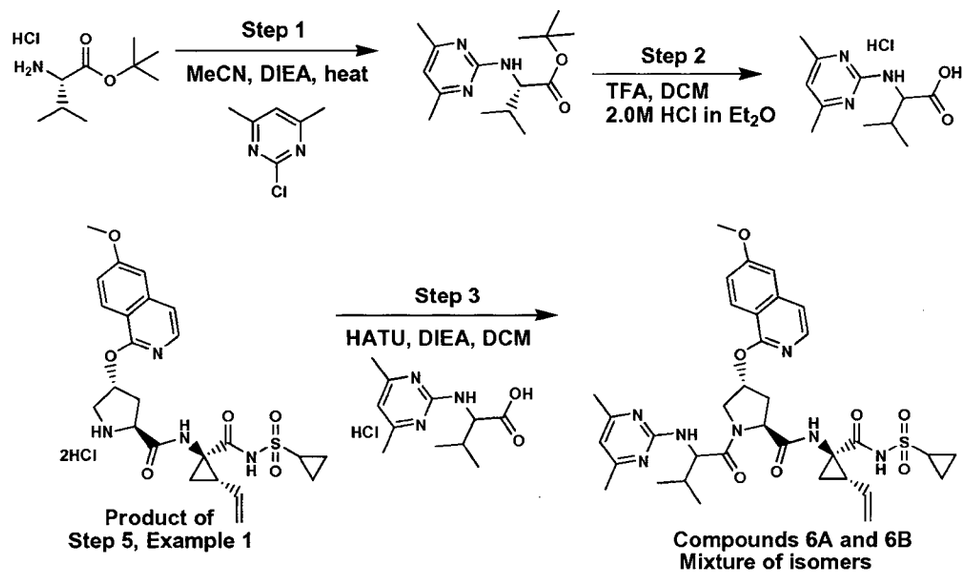
N-(4,6-dimethyl-2-pyrimidinyl)-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide

Example 6: Preparation of Compounds 6A and 6B



Compounds 6A and 6B

Scheme 1



Step 1:

To a mixture of valine *tert*-butyl ester hydrochloride (3.09 g, 14.7 mmol) and DIEA (4.01 g, 31.0 mmol) in acetonitrile (50 mL) was added 2-chloro-4,6-dimethylpyrimidine (2.31 g, 16.2 mmol). The mixture was heated to 135 °C in a Chemglass pressure vessel for 72 hours. The solvent was removed and the viscous brown residue was dissolved in ethyl acetate (150 mL) and the solution was washed with 1.0M aqueous HCl (2 x 50 mL). The aqueous extracts were combined and back-extracted with ethyl acetate (2 x 50 mL), and the organic phases were combined and washed with 10% aqueous sodium carbonate and then with brine. The organic

phase was dried over anhydrous $MgSO_4$, filtered and concentrated to a brown oil which was purified by flash silica gel chromatography (4:1 hexanes:ethyl acetate) to give the product which was used directly in the next step.

Step 2:

The product of Step 1, Example 6 (1.80 g, 6.44 mmol) was dissolved in dichloromethane (25 mL) and treated with TFA (25 mL). The mixture was stirred at room temperature for 3 hours and was then concentrated *in vacuo*. The residue was then dissolved in 1,2-dichloroethane (50 mL) and again concentrated *in vacuo*. The residue was then dissolved in ethyl acetate (50 mL) and extracted with aqueous 1N HCl (2 x 50). The combined acid extracts were concentrated *in vacuo* to give a yellow solid (1.23 g). LC-MS, MS *m/z* 224 ($M^+ + H$).

Step 3:

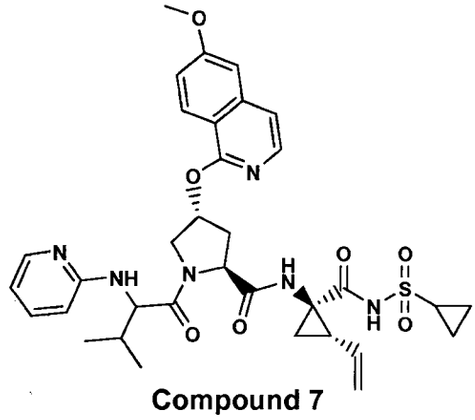
To a mixture of the product of Step 5, Example 1 (0.438 g, 0.764 mmol) and DIEA (0.495 g, 3.82 mmol) in dichloromethane (10 mL) was added the product of Step 2, Example 6 (0.218 g, 0.840 mmol) and HATU (0.378 g, 0.993 mmol). The mixture was stirred at room temperature for 15 hours. The solvent was removed and the viscous brown residue was dissolved in ethyl acetate (75 mL) and the solution was washed with 1.0M aqueous HCl (2 x 10 mL). The aqueous extracts were combined and extracted with ethyl acetate (50 mL), and the organic phases were combined and washed with 10% aqueous sodium carbonate (15 mL) and then with brine. The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated to a viscous brown oil which was purified by flash silica gel chromatography (gradient 97:3 dichloromethane:methanol then 95:5 dichloromethane:methanol). Two distinct compounds with identical *m/z* by LCMS were separated. The first product to elute was the minor compound and was labeled Compound 6A (light yellow solid, 0.0408 g, 7.6% yield). The major product eluted second from the column (yellow solid, 0.280 g) and was further purified by reverse phase preparative HPLC to give Compound 6B (0.040 g, 7.4 % yield) as a yellow solid bis-HCl salt.

Compound 6A: ^{1}H NMR (500 MHz, *MeOD*) δ ppm 0.85 (d, *J*=7.0 Hz, 3 H), 0.96 (d, *J*=6.7 Hz, 3 H), 1.00 (dd, *J*=12.8, 7.0 Hz, 1 H), 1.05 - 1.14 (m, 2 H), 1.23 - 1.29 (m, 1 H), 1.37 (dd, *J*=9.6, 5.3 Hz, 1 H), 1.87 (dd, *J*=8.1, 5.3 Hz, 1 H), 1.99 - 2.05

(m, 1 H), 2.25 (q, *J*=8.7 Hz, 1 H), 2.30 (d, *J*=6.4 Hz, 1 H), 2.36 - 2.47 (m, 5 H), 2.60 - 2.66 (m, 1 H), 2.83 - 2.85 (m, 1 H), 2.87 - 2.93 (m, 1 H), 3.96 (s, 3 H), 4.28 - 4.32 (m, 1 H), 4.37 - 4.42 (m, 1 H), 4.57 - 4.62 (m, 1 H), 4.72 (d, *J*=8.2 Hz, 1 H), 5.14 (dd, *J*=10.4, 1.5 Hz, 1 H), 5.33 (dd, *J*=17.1, 1.5 Hz, 1 H), 5.71 - 5.80 (m, 1 H), 5.95 (s, 1 H), 7.19 (dd, *J*=9.2, 2.4 Hz, 1 H), 7.24 (d, *J*=2.4 Hz, 1 H), 7.31 (d, *J*=6.1 Hz, 1 H), 7.94 (d, *J*=6.1 Hz, 1 H), 8.05 (d, *J*=9.2 Hz, 1 H); LC-MS, MS *m/z* 706 (M^+ + H).

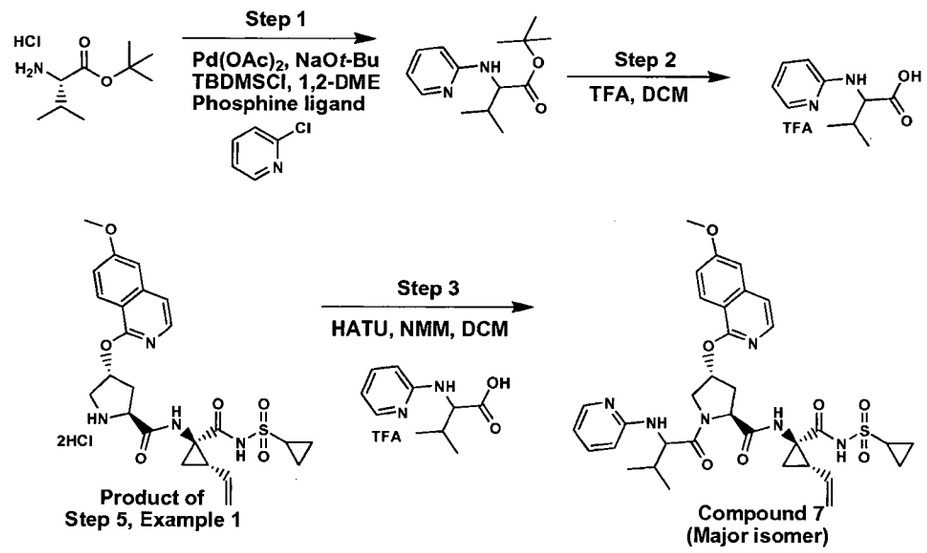
Compound 6B: ^{1}H NMR (500 MHz, *MeOD*) δ ppm 1.17 (d, *J*=6.7 Hz, 1 H), 1.28 (d, *J*=6.7 Hz, 1 H), 1.31 (d, *J*=6.7 Hz, 3 H), 1.39 (d, *J*=6.7 Hz, 3 H), 1.43 - 1.56 (m, 2 H), 1.69 (dd, *J*=9.5, 5.2 Hz, 1 H), 2.15 - 2.26 (m, 3 H), 2.50 - 2.56 (m, 1 H), 2.57 - 2.62 (m, 1 H), 2.63 - 2.72 (m, 3 H), 2.89 (dd, *J*=13.9, 6.6 Hz, 1 H), 3.20 - 3.27 (m, 1 H), 4.22 (s, 3 H), 4.48 (dd, *J*=12.2, 3.7 Hz, 1 H), 4.79 (d, *J*=11.9 Hz, 1 H), 4.85 - 4.92 (m, 1 H), 5.02 (d, *J*=7.9 Hz, 1 H), 5.40 (d, *J*=11.6 Hz, 1 H), 5.59 (d, *J*=16.8 Hz, 1 H), 6.00 - 6.09 (m, 1 H), 6.25 (t, *J*=3.2 Hz, 1 H), 6.94 (s, 1 H), 7.42 (dd, *J*=9.0, 2.3 Hz, 1 H), 7.54 (d, *J*=2.1 Hz, 1 H), 7.64 (d, *J*=6.1 Hz, 1 H), 8.19 (d, *J*=6.1 Hz, 1 H), 8.23 (d, *J*=9.2 Hz, 1 H); LC-MS, MS *m/z* 706 (M^+ + H).

Example 7: Preparation of Compound 7: N-2-pyridinylvalyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide



Compound 7

Scheme 1



Step 1:

To a mixture of 2-chloropyridine (0.205 g, 1.80 mmol) and sodium *tert*-butoxide (0.590 g, 6.13 mmol) in dry 1,2-dichloroethane (1 mL) was added a pre-mixed solution of $Pd(OAc)_2$ (0.0405 g, 0.180 mmol) and (*R*)-(-)-1-[(*S*)-(dicyclohexylphosphino)ferrocenyl] ethyl di-*tert*-butyl phosphine (0.100 g, 0.180 mmol, Strem Chemicals catalog # 26-0975, CAS # [158923-11-6]) in dry 1,2-dimethoxyethane (1 mL). The mixture was shaken, and was quickly treated with TBDMSCl (0.598 g, 3.97 mmol). The mixture was shaken briefly, and quickly added valine *tert*-butyl ester hydrochloride (0.454 g, 2.16 mmol) and shook again. A moderate exotherm resulted immediately. After 10 minutes stirring, the mixture was added to rapidly stirred pH = 7 buffer solution (50 mL). Added ethyl acetate (50 mL) and shook and separated the phases. The aqueous was saturated by addition of NaCl and was extracted again with ethyl acetate (2 x 50 mL). The organic extracts were combined and washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to a dark residue. The crude product was purified by flash silica gel chromatography (8:1 hexanes:ethyl acetate) to give a colorless liquid (0.365 g) which was determined to contain the desired product plus 0.6 equivalents of TBDMS byproduct. The material was carried on to the next step without further purification. Approximate yield was 61%. LC-MS, MS *m/z* 251 (M^+ + H).

Step 2:

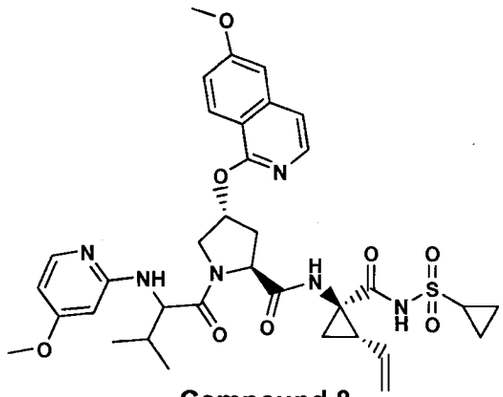
The product of Step 1, Example 7 (0.944g, 3.03 mmol) was dissolved in dichloromethane (10 mL) and treated with TFA (10 mL). The mixture was stirred at room temperature for 1.5 hours and was then concentrated *in vacuo*. The residue was then purified by reverse phase preparative HPLC, and then purified further by flash silica gel chromatography (gradient, 10:1 dichloromethane:methanol to 5:1 dichloromethane:methanol) to give a colorless waxy solid (0.126 g, 59.0% yield). LC-MS, MS *m/z* 195 ($M^+ + H$).

Step 3:

To a mixture of the product of Step 5, Example 1 (0.250 g, 0.436 mmol) and NMM (0.176 g, 1.74 mmol) in dichloromethane (2 mL) was added the product of Step 2, Example 7 (0.085 g, 0.44 mmol) and HATU (0.199 g, 0.523 mmol). The mixture was stirred at room temperature for 96 hours. The solvent was removed, the viscous brown residue was dissolved in ethyl acetate (50 mL), and the solution was washed with 1.0M aqueous HCl. The aqueous extracts were combined and extracted with ethyl acetate, and the organic phases were combined and washed with 10% aqueous sodium carbonate and then with brine. The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated to a residue which was purified by reverse phase preparative HPLC to give Compound 7 (0.243 g, 45% yield) as a white solid. Compound 7 was the major of two isomers formed in the reaction with identical MS *m/z* by LCMS. The minor isomer (more retained on the reverse phase preparative HPLC column than the major isomer) was not isolated. ^{1}H NMR (500 MHz, MeOD) δ ppm 0.99 (d, *J*=6.71 Hz, 3 H) 1.12 (d, *J*=6.41 Hz, 3 H) 1.14 - 1.19 (m, 2 H) 1.24 - 1.31 (m, 1 H) 1.31 - 1.37 (m, 1 H) 1.48 (dd, *J*=9.46, 5.49 Hz, 1 H) 1.95 (dd, *J*=8.09, 5.34 Hz, 1 H) 2.32 (q, *J*=8.85 Hz, 1 H) 2.42 (ddd, *J*=13.96, 10.15, 4.27 Hz, 1 H) 2.47 - 2.55 (m, 1 H) 2.68 (dd, *J*=13.73, 7.02 Hz, 1 H) 3.02 (ddd, *J*=12.59, 8.16, 4.88 Hz, 1 H) 3.37 (s, 1 H) 3.95 (s, 3 H) 4.22 (dd, 1 H) 4.31 (d, *J*=11.90 Hz, 1 H) 4.34 (d, *J*=8.54 Hz, 1 H) 4.70 (dd, *J*=10.22, 7.17 Hz, 1 H) 5.17 (d, *J*=10.38 Hz, 1 H) 5.36 (d, *J*=17.09 Hz, 1 H) 5.82 (ddd, *J*=17.24, 9.61, 9.46 Hz, 1 H) 5.97 (t, *J*=3.20 Hz, 1 H) 6.93 (t, *J*=6.71 Hz, 1 H) 7.02 (d, *J*=9.16 Hz, 1 H) 7.14 (dd, *J*=9.00, 2.29 Hz, 1 H) 7.23 (d, *J*=2.14 Hz, 1 H) 7.31 (d, *J*=6.10 Hz, 1 H) 7.83 (t, *J*=7.93 Hz, 1 H) 7.88 (d, *J*=6.41 Hz, 1 H) 7.93 (d, *J*=6.10 Hz, 1 H) 8.03 (d, *J*=9.16

Hz, 1 H); LC-MS, MS *m/z* 677 ($M^+ + H$).

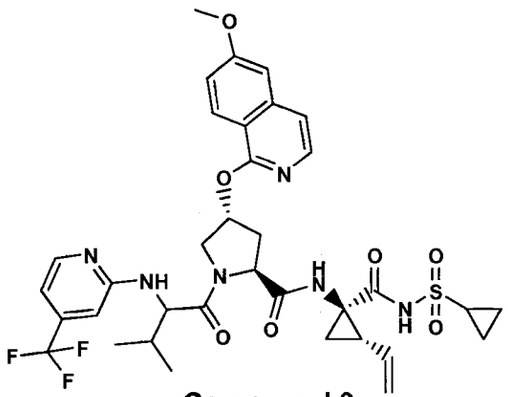
Example 8: Preparation of Compound 8: N-(4-methoxy-2-pyridinyl)valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide



Compound 8

Compound 8 was prepared by the same procedure as that described for the preparation of Compound 7, except 2-chloro-4-methoxypyridine (259 mg, 1.80 mmol) was used in Step 1 in place of the 2-chloropyridine, and 2.0M HCl in ether was added to the concentrated Step 1 product in dichloromethane to give the hydrochloride salt in Step 2. The scale of Steps 2 and 3 were also adjusted based on the yields of the previous steps. Compound 8 (0.0290 g, 11.6% yield) was obtained as an off-white powder bis-TFA salt from reverse phase preparative HPLC. This compound was a single isomer. ^{1}H NMR (500 MHz, MeOD) δ ppm 1.00 (d, *J*=6.71 Hz, 3 H) 1.11 (d, *J*=6.71 Hz, 3 H) 1.16 (dd, *J*=7.63, 2.75 Hz, 2 H) 1.22 - 1.42 (m, 4 H) 1.48 (dd, *J*=9.61, 5.34 Hz, 1 H) 1.93 - 1.97 (m, 1 H) 2.32 (q, *J*=8.85 Hz, 1 H) 2.36 - 2.50 (m, 2 H) 2.67 (dd, *J*=13.43, 7.02 Hz, 1 H) 2.89 (s, 1 H) 3.01 (ddd, *J*=12.82, 8.09, 4.73 Hz, 1 H) 3.17 - 3.27 (m, 1 H) 3.84 (s, 3 H) 3.95 (s, 3 H) 3.98 - 4.08 (m, 1 H) 4.20 (dd, 1 H) 4.26 - 4.33 (m, 2 H) 4.70 (dd, *J*=10.38, 7.02 Hz, 1 H) 5.17 (dd, *J*=10.53, 1.37 Hz, 1 H) 5.36 (dd, *J*=17.09, 1.22 Hz, 1 H) 5.77 - 5.87 (m, *J*=17.17, 9.58, 9.58 Hz, 1 H) 5.97 (t, *J*=3.36 Hz, 1 H) 6.32 (d, *J*=2.44 Hz, 1 H) 6.55 (dd, *J*=7.32, 2.14 Hz, 1 H) 7.14 (dd, *J*=9.16, 2.44 Hz, 1 H) 7.22 (d, *J*=2.44 Hz, 1 H) 7.30 (d, *J*=5.80 Hz, 1 H) 7.72 (d, *J*=7.32 Hz, 1 H) 7.93 (d, *J*=5.80 Hz, 1 H) 8.01 (d, *J*=9.16 Hz, 1 H); LC-MS, MS *m/z* 707 ($M^+ + H$).

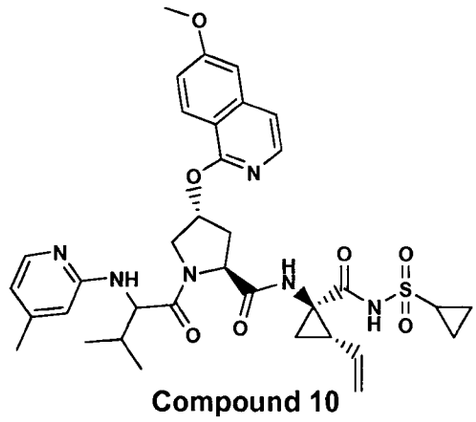
Example 9: Preparation of Compound 9: N-(4-(trifluoromethyl)-2-pyridinyl)valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide



Compound 9

Compound 9 was prepared by the same procedure as that described for the preparation of Compound 7, except 2-chloro-4-trifluoromethyl pyridine (0.328 g, 1.80 mmol) was used in Step 1 in place of the 2-chloropyridine, and 2.0M HCl in ether was added to the concentrated Step 1 product in dichloromethane to give the hydrochloride salt in Step 2. The scale of Steps 2 and 3 were also adjusted based on the yields of the previous steps. Compound 9 (0.0630 g, 12.6% yield) was obtained as a deep blue turquoise solid bis-TFA salt from reverse phase preparative HPLC. This compound was a single isomer. ^{1}H NMR (500 MHz, MeOD) δ ppm 1.04 (d, *J*=6.41 Hz, 3 H) 1.08 (d, *J*=6.41 Hz, 3 H) 1.10 - 1.16 (m, 2 H) 1.18 - 1.38 (m, 3 H) 1.45 (dd, *J*=9.46, 5.19 Hz, 1 H) 1.93 (dd, *J*=7.93, 5.49 Hz, 1 H) 2.18 - 2.24 (m, 1 H) 2.29 (q, *J*=8.95 Hz, 1 H) 2.33 - 2.42 (m, 1 H) 2.58 (dd, *J*=12.97, 6.56 Hz, 1 H) 2.89 (s, 1 H) 2.96 - 3.05 (m, 1 H) 3.85 - 3.93 (m, 1 H) 3.96 (s, 3 H) 4.10 (dd, *J*=11.60, 2.75 Hz, 1 H) 4.49 (d, *J*=9.77 Hz, 1 H) 4.57 (dd, *J*=10.68, 6.71 Hz, 1 H) 4.92 (d, *J*=11.90 Hz, 1 H) 5.16 (d, *J*=10.38 Hz, 1 H) 5.34 (d, *J*=17.40 Hz, 1 H) 5.75 - 5.86 (m, 1 H) 5.94 (s, 1 H) 6.20 (d, *J*=4.58 Hz, 1 H) 6.69 (s, 1 H) 7.05 (dd, *J*=9.00, 2.29 Hz, 2 H) 7.25 (d, *J*=2.14 Hz, 1 H) 7.86 (d, *J*=9.16 Hz, 1 H) 7.96 (d, *J*=5.80 Hz, 1 H); LC-MS, MS *m/z* 745 (M^+ + H).

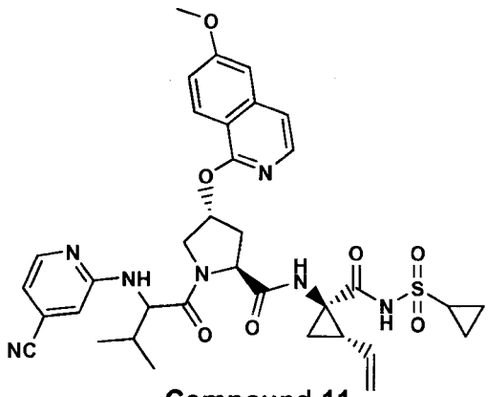
Example 10: Preparation of Compound 10: N-(4-methyl-2-pyridinyl)valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide



Compound 10

Compound 10 was prepared by the same procedure as that described for the preparation of Compound 7, except 2-bromo-4-methyl pyridine (0.310 g, 1.80 mmol) was used in Step 1 in place of the 2-chloropyridine, and 2.0M HCl in ether was added to the concentrated Step 1 product in dichloromethane to give the hydrochloride salt in Step 2. The scale of Steps 2 and 3 were also adjusted based on the yields of the previous steps. Compound 10 (0.0110 g, 8.9% yield) was obtained as an off-white powder bis-TFA salt from reverse phase preparative HPLC. This compound was a single isomer. ^{1}H NMR (500 MHz, MeOD) δ ppm 0.98 (d, *J*=6.41 Hz, 3 H) 1.11 (d, *J*=6.71 Hz, 3 H) 1.14 - 1.19 (m, 2 H) 1.23 - 1.38 (m, 4 H) 1.48 (dd, *J*=9.46, 5.49 Hz, 1 H) 1.95 (dd, *J*=7.93, 5.49 Hz, 1 H) 2.30 (s, 3 H) 2.31 - 2.36 (m, 1 H) 2.37 - 2.52 (m, 2 H) 2.67 (dd, *J*=14.04, 7.02 Hz, 1 H) 2.89 (s, 1 H) 2.98 - 3.05 (m, 1 H) 3.95 (s, 3 H) 3.96 (d, *J*=1.83 Hz, 1 H) 4.21 (dd, 1 H) 4.26 - 4.33 (m, 2 H) 4.69 (dd, *J*=10.22, 7.17 Hz, 1 H) 5.18 (d, *J*=10.38 Hz, 1 H) 5.36 (d, *J*=17.09 Hz, 1 H) 5.77 - 5.87 (m, *J*=17.17, 9.58, 9.58 Hz, 1 H) 5.97 (s, 1 H) 6.78 (d, *J*=6.41 Hz, 1 H) 6.81 (s, 1 H) 7.13 (dd, *J*=9.00, 2.29 Hz, 1 H) 7.22 (d, *J*=2.14 Hz, 1 H) 7.30 (d, *J*=6.10 Hz, 1 H) 7.72 (d, *J*=6.41 Hz, 1 H) 7.93 (d, *J*=6.10 Hz, 1 H) 8.01 (d, *J*=9.16 Hz, 1 H); LC-MS, MS *m/z* 691 (M^+ + H).

Example 11: Preparation of Compound 11: N-(4-cyano-2-pyridinyl)valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide



Compound 11

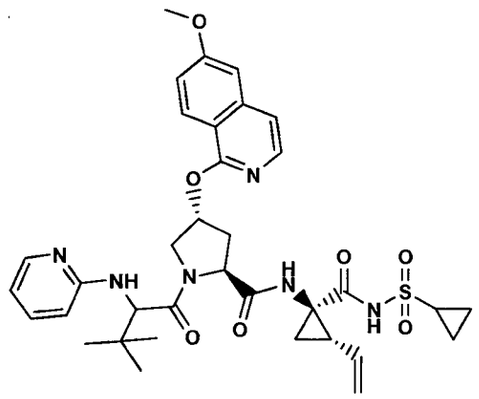
Compound 11 was prepared by the same procedure as that described for the preparation of Compound 7, except 2-chloro-4-cyano pyridine (0.328 mg, 1.80 mmol) was used in Step 1 in place of the 2-chloropyridine, and 2.0M HCl in ether was added to the concentrated Step 1 product in dichloromethane to give the hydrochloride salt in Step 2. The scale of Steps 2 and 3 were also adjusted based on the yields of the previous steps. Compound 11 (0.0210 g, 6.0% yield) was obtained as a purple solid bis-TFA salt from reverse phase preparative HPLC. This material was an inseparable mixture of two isomers in a ratio of approximately 2 to 1. LC-MS, MS *m/z* 702 ($M^+ + H$).

Compound 12 Isomers:

3-methyl-N-2-pyridinyl-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide

3-methyl-N-2-pyridinyl-D-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide

Example 12: Preparation of Compounds 12A and 12B



Compounds 12A and 12B

Compounds 12A and 12B were prepared by the same procedure as that described for the preparation of Compound 7, except *tert*-leucine *tert*-butyl ester hydrochloride (0.486 g, 2.16 mmol) was used in Step 1 in place of the valine *tert*-butyl ester hydrochloride, and 2.0M HCl in ether was added to the concentrated Step 1 product in dichloromethane to give the hydrochloride salt in Step 2. The scale of Steps 2 and 3 were also adjusted based on the yields of the previous steps. Purification of the crude product of Step 3 by reverse phase preparative HPLC gave two compounds in good purity with identical MS *m/z*. Compound 12A (0.0772 g, 20.9% yield) was the first of two isomers formed in the reaction to elute from reverse phase preparative HPLC and was obtained as a beige glassy solid bis-TFA salt. Compound 12B (0.0204 g, 5.5% yield) was the second of two isomers formed in the reaction to elute from reverse phase preparative HPLC and was obtained as a beige solid bis-TFA salt.

Compound 12A: ^{1}H NMR (500 MHz, MeOD) δ ppm 1.09 - 1.14 (m, 2 H) 1.15 (s, 9 H) 1.28 (d, *J*=3.05 Hz, 2 H) 1.47 (dd, *J*=9.00, 5.04 Hz, 1 H) 1.91 - 1.97 (m, 1 H) 2.25 - 2.38 (m, 2 H) 2.66 (dd, *J*=13.28, 6.56 Hz, 1 H) 2.95 - 3.03 (m, 1 H) 3.95 (s, 3 H) 4.14 (d, *J*=11.60 Hz, 1 H) 4.39 (d, *J*=12.51 Hz, 1 H) 4.54 (s, 1 H) 4.65 - 4.71 (m, 1 H) 5.17 (d, *J*=10.68 Hz, 1 H) 5.34 (d, *J*=17.09 Hz, 1 H) 5.74 - 5.84 (m, 1 H) 5.94 (s, 1 H) 6.78 (t, *J*=6.71 Hz, 1 H) 6.96 (d, *J*=9.16 Hz, 1 H) 7.07 (d, *J*=9.16 Hz, 1 H) 7.22 (s, 1 H) 7.30 (d, *J*=6.10 Hz, 1 H) 7.57 (t, *J*=8.09 Hz, 1 H) 7.75 (d, *J*=6.10 Hz, 1 H) 7.92 (d, *J*=9.46 Hz, 1 H) 7.94 (d, *J*=6.10 Hz, 1 H); LC-MS, MS *m/z* 691 (M^+ + H).

Compound 12B: ^{1}H NMR (500 MHz, MeOD) δ ppm 0.91 (s, 9 H) 1.02 - 1.17

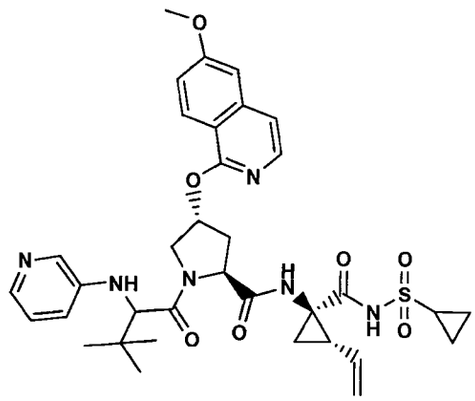
(m, 3 H) 1.20 - 1.31 (m, 2 H) 1.32 - 1.38 (m, 1 H) 1.40 - 1.46 (m, 1 H) 1.90 - 1.96 (m, 1 H) 2.30 - 2.37 (m, 1 H) 2.39 - 2.47 (m, 1 H) 2.69 (dd, *J*=15.11, 8.09 Hz, 1 H) 2.89 (s, 1 H) 2.91 - 2.99 (m, 1 H) 3.97 (s, 3 H) 4.21 (dd, *J*=12.05, 2.90 Hz, 1 H) 4.44 (d, *J*=12.21 Hz, 1 H) 4.66 (s, 1 H) 4.68 - 4.73 (m, 1 H) 5.18 (d, *J*=10.38 Hz, 1 H) 5.38 (d, *J*=17.09 Hz, 1 H) 5.77 - 5.86 (m, 1 H) 5.95 (s, 1 H) 6.99 (t, *J*=6.56 Hz, 1 H) 7.21 (d, *J*=9.16 Hz, 1 H) 7.24 - 7.29 (m, 2 H) 7.32 (d, *J*=6.41 Hz, 1 H) 7.95 (d, *J*=6.10 Hz, 1 H) 7.97 - 8.02 (m, 1 H) 8.05 (d, *J*=8.85 Hz, 1 H); LC-MS, MS *m/z* 691 (M^+ + H).

Compound 13 Isomers:

3-methyl-N-3-pyridinyl-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide and

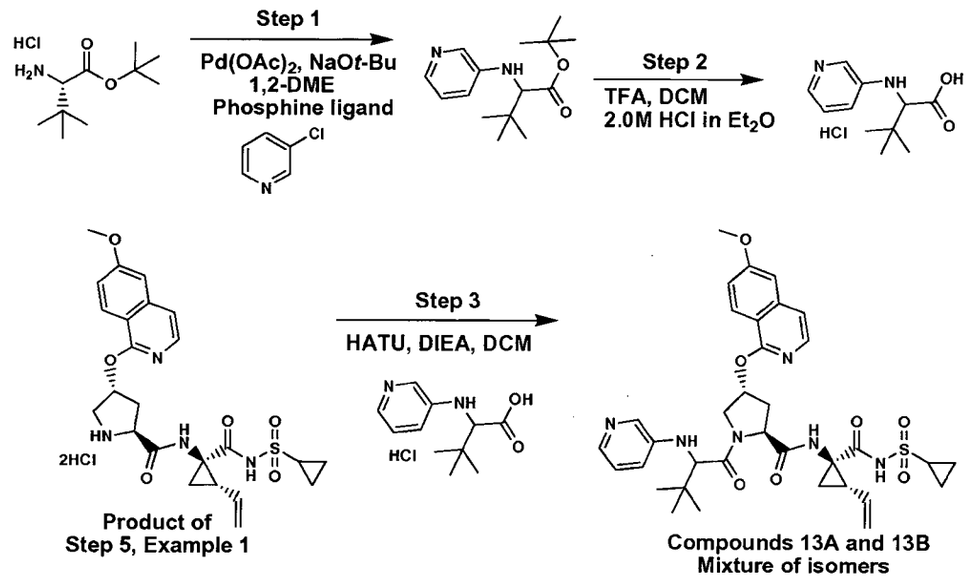
3-methyl-N-3-pyridinyl-D-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide

Example 13: Preparation of Compounds 13A and 13B



Compounds 13A and 13B

Scheme 1



Step 1:

To a mixture of 3-chloropyridine (0.410 g, 3.61 mmol) and sodium *tert*-butoxide (1.18 g, 12.3 mmol) in dry 1,2-dichloroethane (5 mL) was added a pre-mixed solution of $Pd(OAc)_2$ (0.0405 g, 0.180 mmol) and (*R*)-(-)-1-[(*S*)-(dicyclohexylphosphino) ferrocenyl] ethyl di-*tert*-butyl phosphine (0.100 g, 0.180 mmol, Strem Chemicals catalog # 26-0975, CAS # [158923-11-6]) in dry 1,2-dimethoxyethane (2 mL). The mixture was shaken briefly, treated quickly with *tert*-leucine *tert*-butyl ester hydrochloride (0.970 g, 4.33 mmol) and shaken again. The mixture was heated to 100 °C for 20 hours, added to a rapidly stirred mixture of pH = 7 buffer solution (100 mL) and 1.0M aqueous HCl (12 mL), treated with ethyl acetate, and shaken. The phases were allowed to separate and the organic extract was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to a deep orange residue. The crude product was purified by flash silica gel chromatography (linear gradient 100% hexanes to 1:1 hexanes:ethyl acetate) to give a flesh colored solid (0.583 g, 61.1% yield). LC-MS, MS *m/z* 265 ($M^+ + H$).

Step 2:

The product of Step 1, Example 13 (0.200g, 0.756 mmol) was dissolved in dichloromethane (5 mL) and treated with TFA (5 mL). The mixture was stirred at

room temperature for 5 hours and was then concentrated *in vacuo*. The residue was then dissolved in 1,2-dichloroethane (15 mL) and again concentrated *in vacuo*. The residue was then dissolved in dichloromethane (3 mL) and was added dropwise to rapidly stirred 2.0M HCl in ether (40 mL). The resulting beige precipitate was isolated by filtration and allowed to air dry. Beige powder (0.160 g, 86.4% yield). LC-MS, MS *m/z* 209 (M^+ + H).

Step 3:

To a mixture of the product of Step 5, Example 1 (0.242 g, 0.422 mmol) and NMM (0.203 g, 2.01 mmol) in dichloromethane (2 mL) was added the product of Step 2, Example 13 (0.098 g, 0.40 mmol) and HATU (0.242 g, 0.422 mmol). The mixture was stirred at room temperature for 18 hours. The solvent was removed *in vacuo* and the viscous brown residue was directly purified by reverse phase preparative HPLC to give two compounds in good purity with identical MS *m/z*. Compound 13A (0.154 g, 41.6% yield) was the first of the two isomers to elute from the reverse phase preparative HPLC column and was obtained as an off-white solid bis-TFA salt. Compound 13B (0.118 g, 31.9% yield) was the second of the two isomers to elute from the reverse phase preparative HPLC column and was obtained as a beige powder bis-TFA salt.

Compound 13A: ^{1}H NMR (500 MHz, MeOD) δ ppm 1.06 - 1.18 (m, 12 H) 1.24 - 1.36 (m, 2 H) 1.42 - 1.48 (m, 1 H) 1.93 (t, *J*=6.71 Hz, 1 H) 2.23 - 2.33 (m, 2 H) 2.61 (dd, *J*=13.73, 7.02 Hz, 1 H) 2.96 - 3.05 (m, 1 H) 3.96 (s, 3 H) 3.98 - 4.04 (m, 1 H) 4.23 (s, 1 H) 4.38 (d, *J*=12.21 Hz, 1 H) 4.66 (t, *J*=8.70 Hz, 1 H) 5.17 (dd, *J*=10.53, 0.76 Hz, 1 H) 5.34 (d, *J*=17.09 Hz, 1 H) 5.74 - 5.83 (m, 1 H) 5.89 (s, 1 H) 7.08 (dd, *J*=9.16, 0.92 Hz, 1 H) 7.22 (s, 1 H) 7.23 - 7.28 (m, 1 H) 7.30 (d, *J*=6.10 Hz, 1 H) 7.57 (d, *J*=8.85 Hz, 1 H) 7.80 (d, *J*=5.49 Hz, 1 H) 7.86 (d, *J*=9.16 Hz, 1 H) 7.94 (d, *J*=6.10 Hz, 1 H) 8.09 (s, 1 H) 9.26 (s, 1 H); LC-MS, MS *m/z* 691 (M^+ + H).

Compound 13B: ^{1}H NMR (500 MHz, MeOD) δ ppm 0.94 (s, 9 H) 1.10 (d, *J*=7.32 Hz, 2 H) 1.17 - 1.35 (m, 2 H) 1.41 (dd, *J*=9.46, 5.19 Hz, 1 H) 1.87 - 1.94 (m, 1 H) 2.31 (q, *J*=8.65 Hz, 1 H) 2.35 - 2.43 (m, 1 H) 2.59 - 2.69 (m, 1 H) 2.92 - 3.01 (m, 1 H) 3.97 (s, 3 H) 4.12 (d, *J*=11.90 Hz, 1 H) 4.38 (s, 1 H) 4.49 (d, *J*=11.90 Hz, 1 H) 4.67 (t, *J*=8.85 Hz, 1 H) 5.17 (d, *J*=10.38 Hz, 1 H) 5.36 (d, *J*=17.09 Hz, 1 H) 5.75 - 5.87 (m, 1 H) 5.94 (s, 1 H) 7.20 (d, *J*=8.85 Hz, 1 H) 7.25 (s, 1 H) 7.31 (d, *J*=5.80

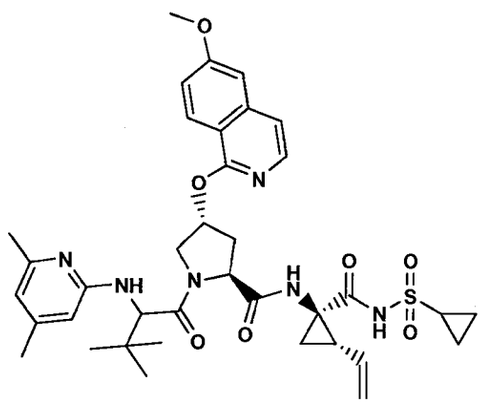
Hz, 1 H) 7.71 - 7.78 (m, 1 H) 7.89 - 7.99 (m, 3 H) 8.04 (d, *J*=8.85 Hz, 1 H) 8.22 (s, 1 H) 9.57 (s, 1 H); LC-MS, MS *m/z* 691 (M^+ + H).

Compound 14 Isomers:

N-(4,6-dimethyl-2-pyridinyl)-3-methyl-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide and

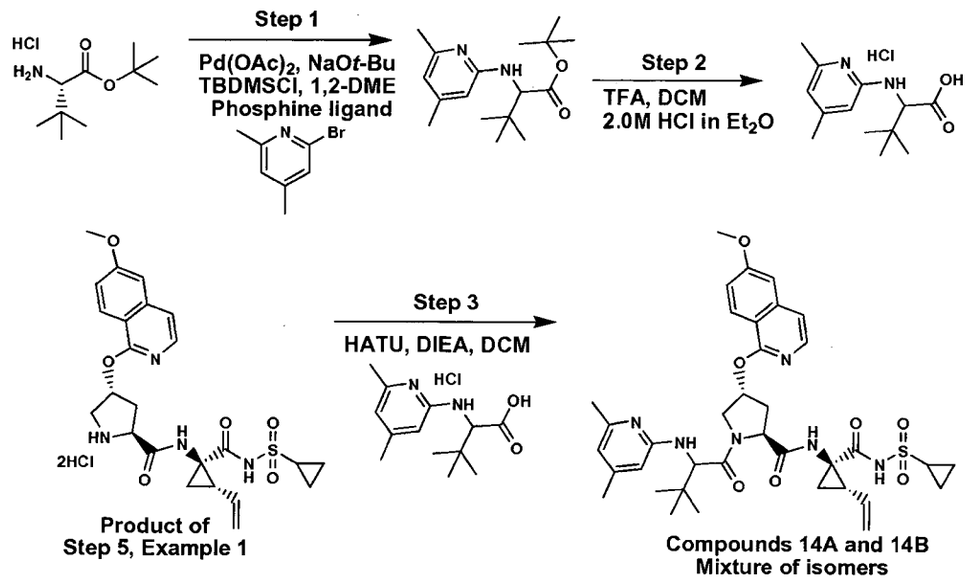
N-(4,6-dimethyl-2-pyridinyl)-3-methyl-D-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide

Example 14: Preparation of Compounds 14A and 14B



Compounds 14A and 14B

Scheme 1



Step 1:

2-Bromo-4,6-dimethylpyridine (0.839 g, 4.51 mmol), sodium *tert*-butoxide (1.47 g, 15.3 mmol), *tert*-leucine *tert*-butyl ester hydrochloride (1.21 g, 5.41 mmol) and TBDMSCl (1.5 g, 9.9 mmol) were combined and treated with 1,2-dimethoxyethane (6 mL). The mixture was shaken and a pre-mixed solution of $Pd(OAc)_2$ (0.202 g, 0.902 mmol) and (*R*)-(-)-1-[(*S*)-(dicyclohexylphosphino) ferrocenyl] ethyl di-*tert*-butyl phosphine (0.500 g, 0.902 mmol, Strem Chemicals catalog # 26-0975, CAS # [158923-11-6]) in dry 1,2-dimethoxyethane (2 mL) was immediately added. A moderate exotherm resulted and the mixture became deep brown in color. After 10 minutes, the mixture was orange in color. The mixture was stirred at room temperature for 72 hours. The mixture was then added to a rapidly stirred mixture of pH = 7 buffer solution (75 mL) and 1.0M aqueous HCl (15 mL). Ethyl acetate (40 mL) was added and the mixture was shaken and separated the phases. The aqueous phase was extracted with ethyl acetate (2 x 50 mL). The organic extracts were combined and washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to a brown residue. The crude product was purified by flash silica gel chromatography (linear gradient 100% hexanes to 10:1 hexanes:ethyl acetate) to give a yellow oil (0.786 g) which was determined to contain the desired product plus 1.9 equivalents of TBDMS byproduct. The material was

carried on to the next step without further purification. LC-MS, MS *m/z* 293 (M^+ + H).

Step 2:

The product of Step 1, Example 14 (0.750 g) was dissolved in dichloromethane (10 mL) and treated with TFA (10 mL). The mixture was stirred at room temperature for 7 hours and was then concentrated *in vacuo*. The residue was then dissolved in 1,2-dichloroethane (15 mL) and again concentrated *in vacuo*. The residue was then dissolved in dichloromethane (3 mL) and was added dropwise to rapidly stirred 2M HCl in diethyl ether (40 mL). No precipitation occurred. Iterative precipitations of the crude material from dichloromethane using hexanes and ethyl acetate as the countersolvents eventually yielded a yellow powder (0.286 g, 23% yield over 2 steps). LC-MS, MS *m/z* 237 (M^+ + H).

Step 3:

To a mixture of the product of Step 5, Example 1 (0.189 g, 0.330 mmol) and NMM (0.167 g, 1.65 mmol) in dichloromethane (2 mL) was added the product of Step 2, Example 14 (0.090 g, 0.33 mmol) and HATU (0.151 g, 0.396 mmol). The mixture was stirred at room temperature for 18 hours. Additional product of Step 2, Example 14 (0.049 g, 0.18 mmol), HATU (0.082 g, 0.216 mmol) and NMM (0.0381 g, 0.377 mmol) were added to the mixture, and the solution was stirred at 40 °C overnight. The solvent was removed *in vacuo* and the residue was directly purified by reverse phase preparative HPLC to give two separate compounds with identical MS *m/z*. Compound 14A (0.118 g, 37.8% yield) was the first of the two isomers to elute from the reverse phase preparative HPLC column and was obtained as an off-white powder bis-TFA salt. Compound 14B (0.044 g, 14.1% yield) was the second of the two isomers to elute from the reverse phase preparative HPLC column and was obtained as a beige powder bis-TFA salt.

Compound 14A: ^{1}H NMR (500 MHz, MeOD) δ ppm 1.07 - 1.11 (m, 2 H) 1.13 (s, 9 H) 1.25 - 1.30 (m, 2 H) 1.46 (dd, *J*=9.46, 5.49 Hz, 1 H) 2.25 - 2.37 (m, 2 H) 2.38 (s, 3 H) 2.65 (dd, *J*=13.58, 7.78 Hz, 1 H) 2.94 - 3.03 (m, 1 H) 3.95 (s, 3 H) 4.09 (dd, *J*=12.21, 2.75 Hz, 1 H) 4.36 (d, *J*=12.21 Hz, 1 H) 4.48 (s, 1 H) 4.69 - 4.75 (m, 1 H) 5.17 (d, *J*=10.38 Hz, 1 H) 5.35 (d, *J*=17.40 Hz, 1 H) 5.72 - 5.83 (m, 1 H) 5.96 (s,

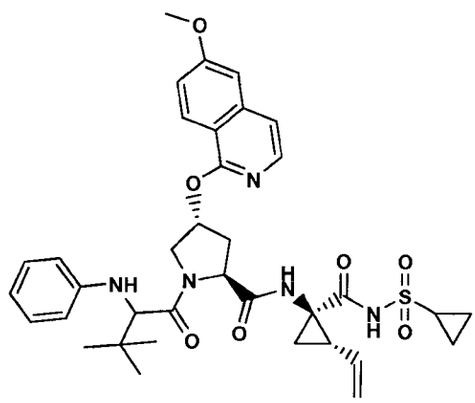
1 H) 6.53 (s, 1 H) 6.60 (s, 1 H) 7.02 - 7.07 (m, 1 H) 7.19 - 7.22 (m, 1 H) 7.30 (d, *J*=6.10 Hz, 1 H) 7.87 (d, *J*=9.16 Hz, 1 H) 7.94 - 7.97 (m, 1 H); LC-MS, MS *m/z* 719 (M^++H).

Compound 14B: ^{1}H NMR (500 MHz, MeOD) δ ppm 0.92 (s, 9 H) 1.05 - 1.10 (m, 2 H) 1.13 - 1.19 (m, 1 H) 1.21 - 1.26 (m, 1 H) 1.41 (dd, *J*=9.46, 5.19 Hz, 1 H) 1.89 - 1.94 (m, 1 H) 2.32 (q, *J*=8.75 Hz, 1 H) 2.40 - 2.44 (m, 1 H) 2.45 (s, 3 H) 2.48 (s, 3 H) 2.65 - 2.71 (m, 1 H) 2.90 - 2.96 (m, 1 H) 3.96 (d, *J*=1.83 Hz, 1 H) 3.97 (d, *J*=1.53 Hz, 3 H) 4.20 (dd, *J*=12.36, 2.90 Hz, 1 H) 4.51 (d, *J*=12.51 Hz, 1 H) 4.62 (s, 1 H) 4.69 (t, *J*=8.39 Hz, 1 H) 5.17 (d, *J*=10.07 Hz, 1 H) 5.36 (d, *J*=17.40 Hz, 1 H) 5.75 - 5.83 (m, 1 H) 5.97 (s, 1 H) 6.71 (s, 1 H) 6.88 (s, 1 H) 7.19 - 7.23 (m, 1 H) 7.25 (d, *J*=2.14 Hz, 1 H) 7.32 (d, *J*=5.80 Hz, 1 H) 7.95 (dd, *J*=5.95, 1.68 Hz, 1 H) 8.05 (d, *J*=9.16 Hz, 1 H); LC-MS, MS *m/z* 719 (M^+ + H).

Compound 15 Isomers:

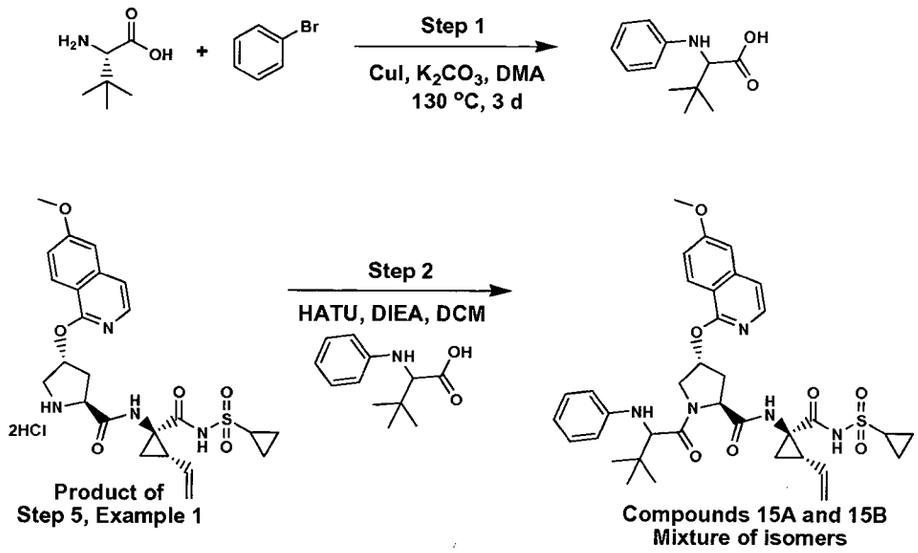
3-methyl-N-phenyl-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide and 3-methyl-N-phenyl-D-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide

Example 15: Preparation of Compounds 15A and 15B



Compounds 15A and 15B

Scheme 1



Step 1:

L-*tert*-Leucine (0.840 g, 6.40 mmol), K_2CO_3 (1.33 g, 9.60 mmol) and CuI (0.122 g, 0.64 mmol) were combined in a 35 mL Chemglass pressure vessel. Bromobenzene (1.01 g, 6.4 mmol) and DMA (8 mL) were added, the vessel headspace was with nitrogen, the vessel was sealed, and the mixture was heated to 90 °C overnight. Additional DMA (8 mL) was added to facilitate stirring and the mix was heated to 130 °C overnight. With only a small amount of product formation as determined by LCMS, the mixture was charged with an excess of CuI (approximately 1 g), the reaction was resealed and heated to 130 °C for 2 days. The mixture was cooled to room temperature and treated with 1.0M aqueous HCl until pH = 5 was achieved, then pH = 7 buffer (50 mL) and ethyl acetate (50 mL) were added and the mixture was shaken and phases were separated. The aqueous phase was extracted with ethyl acetate (2 x 50 mL), and the organics were combined and washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to a solid residue. Purification by silica gel flash chromatography (20:1 dichloromethane:methanol) gave a waxy flesh-colored solid (0.286 g) which contained approximately 1.2 equivalents of entrained DMA by ^{1}H NMR. LC-MS, MS *m/z* 208 (M^+ + H).

Step 2:

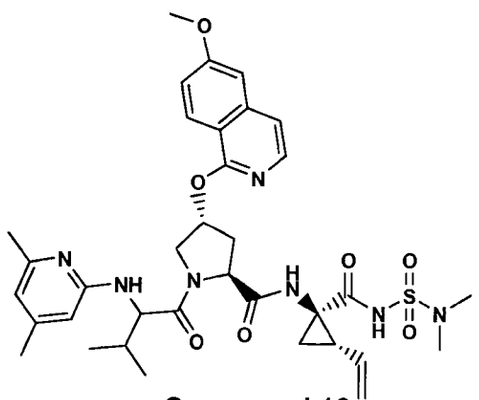
To a mixture of the product of Step 5, Example 1 (0.200 g, 0.349 mmol) and NMM (0.141 g, 1.40 mmol) in dichloromethane (2 mL) was added the product of Step 1, Example 15 (0.108 g, 0.35 mmol, 67% pure) and HATU (0.160 g, 0.418 mmol). The mixture was stirred at room temperature for 18 hours. The solvent was removed *in vacuo* and to the residue was added ethyl acetate (30 mL) and water (30 mL). Not all solids dissolved. The mixture was transferred to a 250 mL round bottom flask with 1:1 dichloromethane:methanol solvent, and the mixture was concentrated *in vacuo* until the organic solvents were removed, leaving the aqueous phase and undissolved solids. It was determined by LCMS that a crude purification had occurred where the aqueous phase held mostly water soluble byproducts with little product, and the solid consisted mostly of product. The solid was filtered from the liquid to give a white powder (0.225 g). Further purification of the white powder by reverse phase preparative HPLC gave two separate compounds with identical MS *m/z*. Compound 15A (0.124 g, 38.8% yield) was the first of the two isomers to elute from the reverse phase preparative HPLC column and was obtained as a brown powder bis-TFA salt. Compound 15B (0.0633 g, 19.8% yield) was the second of the two isomers to elute from the reverse phase preparative HPLC column and was obtained as a brown powder bis-TFA salt.

Compound 15A: ^{1}H NMR (500 MHz, MeOD) δ ppm 1.09 - 1.15 (m, 2 H) 1.19 (s, 9 H) 1.27 - 1.33 (m, *J*=2.44 Hz, 2 H) 1.43 - 1.48 (m, 1 H) 1.89 - 1.94 (m, 1 H) 2.21 - 2.30 (m, 1 H) 2.57 (dd, *J*=13.58, 7.17 Hz, 1 H) 2.96 - 3.03 (m, 1 H) 3.99 (d, *J*=1.83 Hz, 3 H) 4.02 - 4.08 (m, 1 H) 4.14 (s, 1 H) 4.28 (d, *J*=12.21 Hz, 1 H) 4.44 - 4.51 (m, 1 H) 5.16 (d, *J*=10.38 Hz, 1 H) 5.32 (d, *J*=17.09 Hz, 1 H) 5.73 - 5.83 (m, 2 H) 6.41 (t, *J*=7.17 Hz, 1 H) 6.69 - 6.73 (m, 2 H) 6.76 (t, *J*=7.02 Hz, 2 H) 7.10 (d, *J*=9.16 Hz, 1 H) 7.26 (s, 1 H) 7.30 - 7.34 (m, 1 H) 7.73 (dd, *J*=9.00, 1.37 Hz, 1 H) 7.92 (dd, *J*=5.80, 1.83 Hz, 1 H); LC-MS, MS *m/z* 690 (M^++H).

Compound 15B: ^{1}H NMR (500 MHz, DMSO-D6) δ ppm 0.87 (s, 9 H) 0.94 - 1.00 (m, 1 H) 1.00 - 1.05 (m, *J*=6.41 Hz, 2 H) 1.10 - 1.19 (m, 1 H) 1.28 (dd, *J*=9.31, 5.04 Hz, 1 H) 1.72 (dd, *J*=7.63, 5.19 Hz, 1 H) 2.05 - 2.13 (m, 1 H) 2.21 - 2.28 (m, 1 H) 2.40 - 2.48 (m, 1 H) 2.81 - 2.88 (m, 1 H) 3.91 (d, *J*=1.83 Hz, 3 H) 3.94 - 4.00 (m, 1 H) 4.19 (s, 1 H) 4.41 (d, *J*=11.90 Hz, 1 H) 4.43 - 4.49 (m, 1 H) 5.12 (d, *J*=10.07 Hz, 1 H) 5.27 (d, *J*=17.09 Hz, 1 H) 5.58 - 5.71 (m, 1 H) 5.87 (s, 1 H) 6.55 (t, *J*=7.17

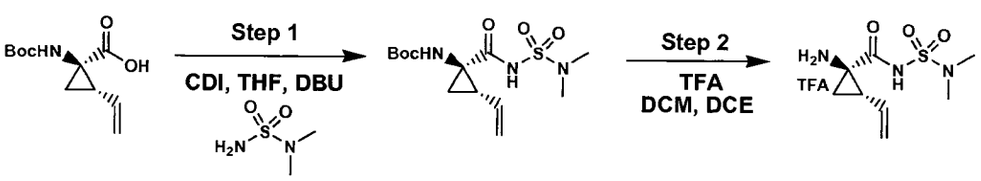
Hz, 1 H) 6.74 (d, *J*=7.63 Hz, 2 H) 7.03 - 7.10 (m, 2 H) 7.22 - 7.27 (m, 1 H) 7.31 - 7.37 (m, 2 H) 7.88 (d, *J*=9.16 Hz, 1 H) 7.97 (dd, *J*=5.80, 2.14 Hz, 1 H) 9.18 (s, 1 H) 10.74 (s, 1 H); LC-MS, MS *m/z* 690 (M^+ + H).

Example 16: Preparation of Compound 16: N-(4,6-dimethyl-2-pyridinyl)valyl-(4R)-N-((1R,2S)-1-((dimethylsulfamoyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide



Compound 16

Scheme 1



Step 1:

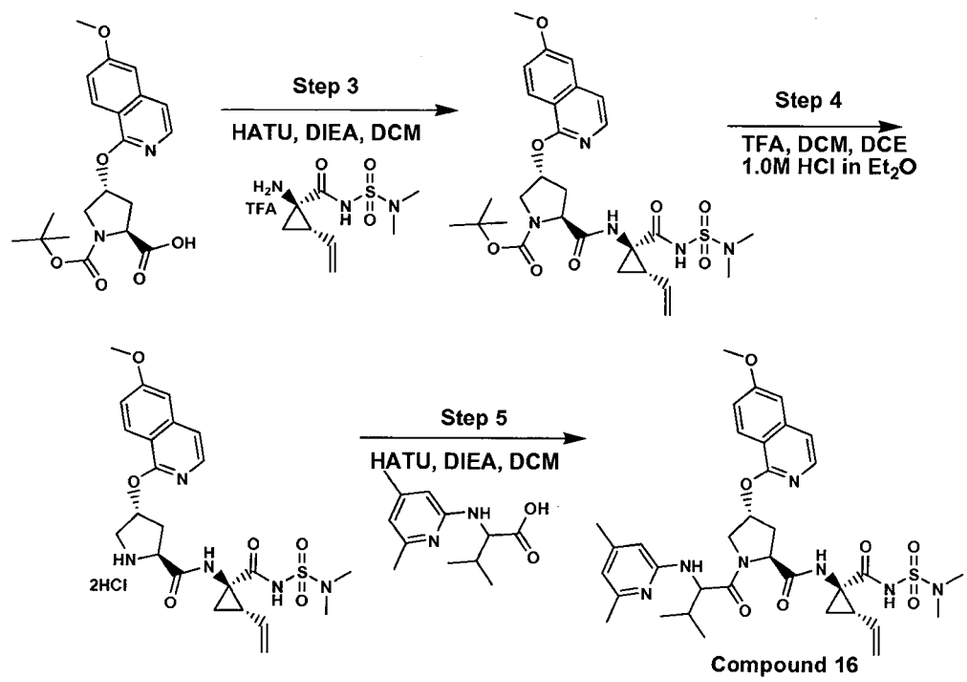
To a solution of *N*-Boc-vinylcyclopropane carboxylic acid (1.83 g, 8.05 mmol) and THF (32 mL) was added 1,1'-carbonyldiimidazole (1.44 g, 8.86 mmol). After stirring at room temperature for 3 hours, the reaction mixture was treated with *N,N*-dimethylsulfamide (1.0 g, 8.05 mmol) followed by DBU (2.45 g, 16.1 mmol) and was stirred at room temperature for an additional 15 hours. The reaction was then diluted with ethyl acetate (50 mL) and washed with 1.0M aqueous HCl (2 x 25 mL). The aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic portion was washed with H_2O (25 mL) and brine, dried over $MgSO_4$, filtered,

and concentrated to a light yellow solid (2.6 g, 97% yield) which was used without further purification. LC-MS, MS *m/z* 356 (M^+ + Na).

Step 2:

To a solution of the product of Step 2, Example 16, (1.42 g, 4.26 mmol) in 1:1 dichloromethane:1,2-dichloroethane (20 mL) was added TFA (10 mL). After stirring at room temperature for 0.5 hours, the solvent and excess TFA were removed and the residue was redissolved in 1,2-dichloroethane (20 mL) and concentrated again to give a yellow solid (1.46g, 99% yield). LC-MS, MS *m/z* 234 (M^++ H).

Scheme 2



Step 3:

The product of Step 3, Example 16, was prepared in 91% yield from the product of Step 2, Example 16, by the same procedure as described for the preparation of the product of Step 4, Example 1.

Step 4:

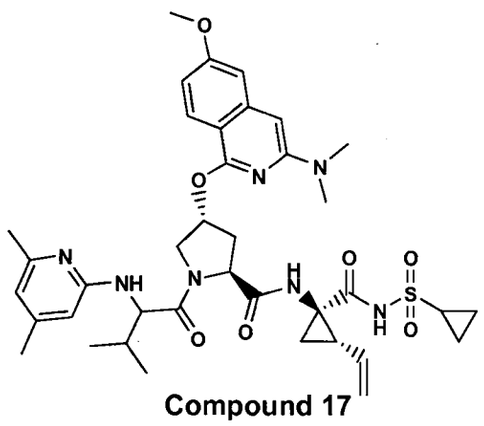
The product of Step 4, Example 16, was prepared in 95% yield from the

product of Step 3, Example 16, by the same procedure as described for the preparation of the product of Step 5, Example 1. LC-MS, MS *m/z* 504 (M^++ H).

Step 5:

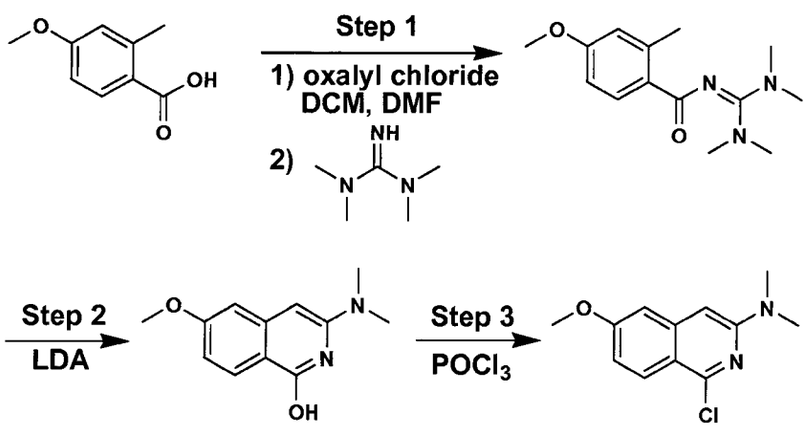
To a mixture of the product of Step 4, Example 16 (0.200 g, 0.347 mmol) and DIEA (0.180 g, 1.39 mmol) in dichloromethane (4 mL) was added 2-(4,6-dimethylpyridine-2-ylamino)-3-methylbutanoic acid (0.092 g, 0.416 mmol) and HATU (0.198 g, 0.520 mmol). The mixture was stirred at room temperature for 8 hours. The reaction was incomplete by LCMS. Additional 2-(4,6-dimethylpyridine-2-ylamino)-3-methylbutanoic acid (0.039 g, 0.174 mmol) and HATU (0.066 g, 0.174 mmol) were added and the mixture was stirred at room temperature for another 16 hours. The reaction was still incomplete by LCMS. Again, additional 2-(4,6-dimethylpyridine-2-ylamino)-3-methylbutanoic acid (0.039 g, 0.174 mmol) and HATU (0.066 g, 0.174 mmol) were added and the mixture was stirred at room temperature for another 16 hours. The solvent was removed and the residue was dissolved in ethyl acetate (50 mL) and the solution was washed with 1.0M aqueous HCl (2 x 5 mL). The aqueous extracts were combined and back-extracted with ethyl acetate (50 mL), and the organic phases were combined and washed with 10% aqueous sodium carbonate and then with brine. The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated to a residue which was purified by reverse phase preparative HPLC to give Compound 16 (the major of two isomers formed) as a yellow solid bis-HCl salt (0.060 g, 22.1% yield). ^{1}H NMR (500 MHz, *MeOD*) δ ppm 1.01 (d, *J*=6.7 Hz, 3 H), 1.10 (d, *J*=6.7 Hz, 3 H), 1.43 (dd, *J*=9.5, 5.2 Hz, 1 H), 1.88 - 1.95 (m, 1 H), 2.20 (s, 3 H), 2.23 - 2.32 (m, 1 H), 2.39 (s, 1 H), 2.43 (s, 3 H), 2.69 (dd, *J*=13.7, 7.0 Hz, 1 H), 2.77 - 2.80 (m, 1 H), 2.87 - 2.90 (m, 1 H), 2.93 (s, 6 H), 3.97 (s, 3 H), 4.18 (dd, *J*=12.2, 3.4 Hz, 1 H), 4.38 (d, *J*=12.2 Hz, 1 H), 4.57 (d, *J*=6.7 Hz, 1 H), 4.70 (dd, *J*=10.1, 7.0 Hz, 1 H), 5.18 (dd, *J*=10.4, 1.8 Hz, 1 H), 5.35 (d, *J*=17.1 Hz, 1 H), 5.72 - 5.83 (m, 1 H), 5.98 (d, *J*=2.7 Hz, 1 H), 6.60 (s, 1 H), 6.69 (s, 1 H), 7.17 (dd, *J*=9.2, 2.4 Hz, 1 H), 7.28 (d, *J*=2.4 Hz, 1 H), 7.39 (d, *J*=6.1 Hz, 1 H), 7.94 (d, *J*=6.1 Hz, 1 H), 8.05 (d, *J*=9.2 Hz, 1 H); LC-MS, MS *m/z* 708 (M^+ + H).

Example 17: Preparation of Compound 17: N-(4,6-dimethyl-2-pyridinyl)valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((3-(dimethylamino)-6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide



Compound 17

Scheme 1



Step 1:

A solution of 4-methoxy-2-methylbenzoic acid (10.2 g, 61.4 mmol) in dichloromethane (200 mL) was treated slowly with oxalyl chloride. A drop of DMF was added and the reaction was stirred at room temperature for 12 hours. The mixture was then treated with 1,1,3,3-tetramethylguanidine (14.9 g, 128.9 mmol) and stirred at room temperature for 4 hours. The mixture was washed with 5% aqueous citric acid (2 x 100 mL). The aqueous phase was back-extracted with

dichloromethane (2 x 100 mL), and the organic phases were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated to provide a minimal amount of desired product. The aqueous phase was made basic by addition of 10.0M aqueous NaOH until pH = 13 was achieved and was then extracted with dichloromethane (4 x 200 mL). The organic phases were combined, dried over anhydrous $MgSO_4$, filtered and concentrated. The resulting oil was combined with the earlier obtained product and the mixture was treated with diethyl ether to give a white precipitate which was removed by filtration. The filtrate was concentrated to give the desired product (11.3 g, 70% yield) as a viscous yellow oil. ^{1}H NMR (CD_3OD) δ 2.54 (s, 3H), 3.97 (s, 6H), 3.79 (s, 3H), 6.60 (d, J = 9.2 Hz, 1H), 6.75 (s, 1H), 7.65 (d, J = 8.9 Hz, 1H). LC-MS, MS *m/z* 264 (M^+ + H).

Step 2:

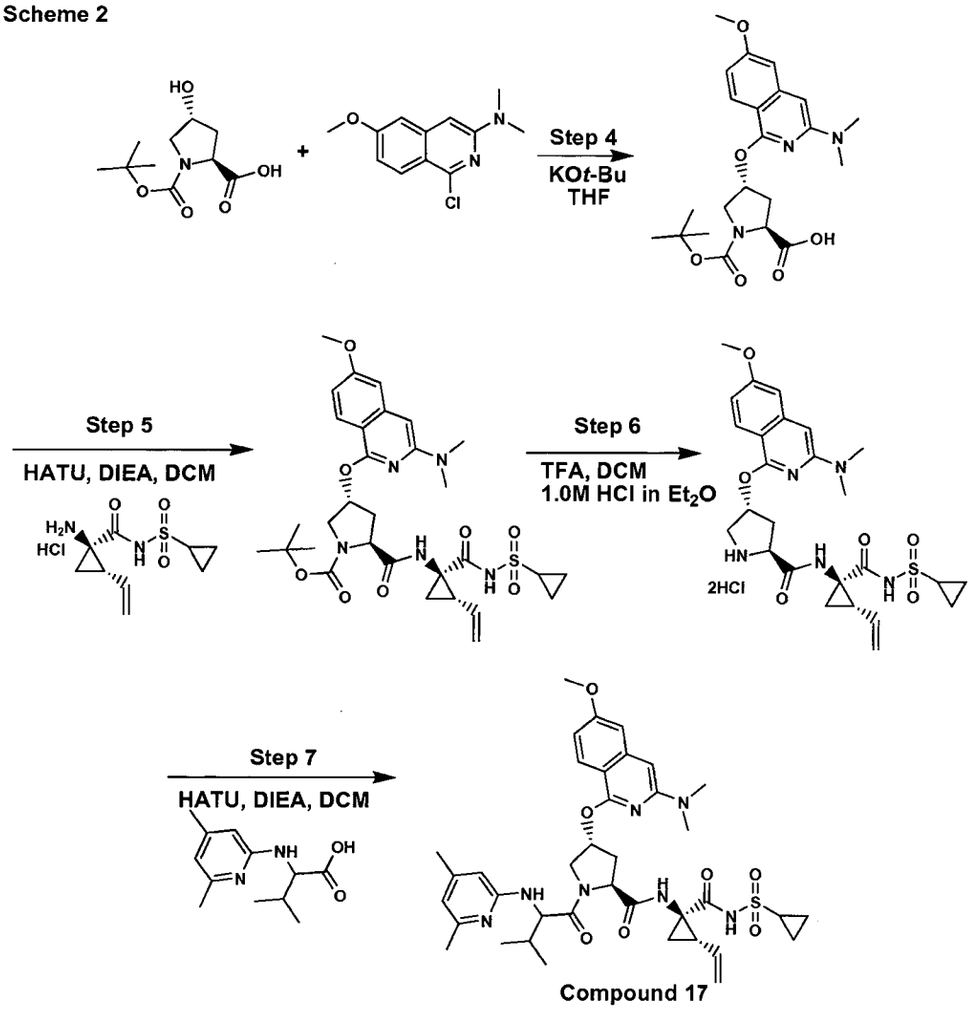
A solution of the product of Step 1, Example 17 (0.461 g, 1.78 mmol) in THF (5 mL) at 0 °C was treated with LDA solution (1.8M in THF/hexanes, 1.2 mL, 2.14 mmol). The reaction was stirred at room temperature for 5 hours and was then treated with additional LDA (1 mL) and stirred at room temperature for 14 hours. The mixture was quenched with saturated ammonium chloride (10 mL) and extracted with ethyl acetate (3 x 25 mL). The organic phases were combined, dried over anhydrous $MgSO_4$, filtered and concentrated. The concentrate was dissolved in minimal dichloromethane and diethyl ether was added. The resulting precipitate was collected by filtration to provide the desired product (0.312 g, 80% yield) as a brown solid. ^{1}H NMR (CD_3OD) δ 2.94 (s, 6H), 3.86 (s, 3H), 5.71 (s, 1H), 6.75 (dd, J = 8.9, 2.4 Hz, 1H), 6.83 (d, J = 2.4 Hz, 1H). 7.97 (d, J = 9.2 Hz, 1H). LC-MS, MS *m/z* 219 (M^+ + H).

Step 3:

The product of Step 2, Example 17 (10.0 g, 45.8 mmol) was treated with $POCl_3$ (43 mL) and the mixture was heated to 110 °C for 5 hours in a Chemglass pressure vessel. Upon cooling to room temperature, the resulting cake was dissolved in dichloromethane (200 mL) and the solution was quenched by slow addition of saturated aqueous sodium bicarbonate. Vigorous gas evolution ensued. When gas

evolution ceased, the mixture was shaken in a separatory funnel and the phases were separated. The aqueous phase was extracted with dichloromethane (3 x 200 mL). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. Diethyl ether was added to the residue to effect the precipitation of a black solid which was collected by filtration and washed with ether. Thus was obtained the desired product (5.72 g, 53.0% yield). LC-MS, MS *m/z* 237 ($M^+ + H$).

Scheme 2



Step 4:

To a solution of Boc-Hyp-OH (5.60 g, 24.2 mmol) in THF (100 mL) was added potassium *tert*-butoxide (1.0M in THF, 53.2 mL, 53.2 mmol). The mixture

turned brown and became a gel which broke with vigorous stirring. After 15 minutes, the product of Step 3, Example 17 (5.72 g, 24.2 mmol) was added in portions. The mixture was heated to 70 °C for 48 hours. The mixture was quenched by addition of 1.0M HCl and was then extracted with ethyl acetate. The aqueous phase was extracted with ethyl acetate once more. The organic phases were combined and washed with brine, dried over $MgSO_4$, and filtered. The filtrate was evaporated *in vacuo* to dryness to give the desired product. LC-MS, MS *m/z* 430 (M -H).

Step 5:

A mixture of the product of Step 4, Example 17 (8.90 g, 20.6 mmol), DIEA (8.01 g, 61.9 mmol), and cyclopropanesulfonic acid (1-(*R*)-amino-2-(*S*)-vinyl-cyclopropanecarbonyl)-amide HCl salt (6.60 g, 24.8 mmol) in dichloromethane (150 mL) was treated with HATU (10.2 g, 26.8 mmol), and the resulting brown solution was stirred at room temperature for 18 hours. The solvent was removed in vacuo, and the residue was taken up in ethyl acetate (200 mL) and washed with water (100 mL). The phases were separated and the aqueous phase was back-extracted with ethyl acetate (3 x 100 mL). The combined organic phase was washed with 0.10 M aqueous HCl (100 mL), then with 10% aqueous sodium carbonate (50 mL) and finally with brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated to give a dark brown foamy solid. The product was purified by flash silica gel chromatography (95:5 dichloromethane:methanol) to give a brown solid (12.9 g, 97% yield). LC-MS, MS *m/z* 642 (M-H).

Step 6:

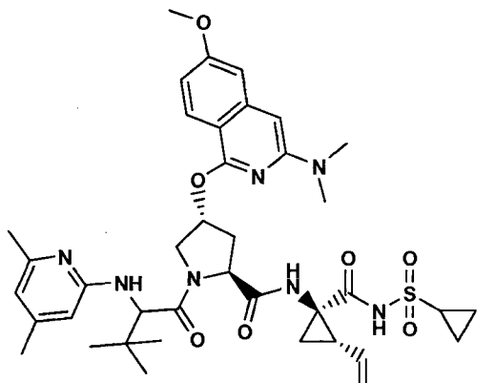
To a solution of the product of Step 5, Example 17 (12.7 g, 19.6 mmol) in 1:1 dichloromethane:1,2-dichloroethane (100 mL) was added TFA (50 mL). The mixture was stirred at room temperature for 30 minutes and was then concentrated *in vacuo*. The residue was redissolved in 1,2-dichloroethane (100 mL) and again concentrated *in vacuo*. The residue was then dissolved in dichloromethane (50 mL) and was added dropwise to vigorously stirred 1.0M HCl in diethyl ether (500 mL). The resulting light brown solid precipitate was isolated by filtration and washed with 1.0M HCl in diethyl ether to give a brown powder (10.2 g, 85.0% yield). LC-MS, MS *m/z* 544

($M^+ + H$).

Step 7:

The product of Step 6, Example 17 (0.258 g, 0.419 mmol), 2-(4,6-dimethylpyridin-2-ylamino)-3-methyl butanoic acid (0.111 g, 0.503 mmol), DIEA (0.217 g, 1.68 mmol) and HATU (0.239 g, 0.629 mmol) were combined in dichloromethane (4 mL) and the mixture was stirred for 8 hours at room temperature. Additional 2-(4,6-dimethylpyridin-2-ylamino)-3-methylbutanoic acid (0.0465 g, 0.210 mmol) and HATU (0.080 g, 0.21 mmol) were added and the mixture was stirred at room temperature for an additional 14 hours. Solvent was removed and the residue was redissolved in ethyl acetate (50 mL) and washed with 1.0M aqueous HCl (2 x 5 mL). The aqueous extracts were combined and back-extracted with ethyl acetate (50 mL), and the organic phases were combined and washed with 10% aqueous sodium carbonate and then with brine. The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated to a residue which was purified by reverse phase preparative HPLC to give Compound 17 (0.037 g, 10.8% yield) as a brown powder bis-HCl salt. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 1.02 (d, *J*=6.7 Hz, 3 H), 1.10 (d, *J*=6.4 Hz, 3 H), 1.12 - 1.18 (m, 3 H), 1.22 - 1.30 (m, 2 H), 1.35 (t, *J*=7.3 Hz, 1 H), 1.46 (dd, *J*=9.6, 5.3 Hz, 1 H), 1.95 (dd, *J*=7.9, 5.5 Hz, 1 H), 2.22 (s, 3 H), 2.28 - 2.36 (m, 2 H), 2.41 (s, 3 H), 2.52 (d, *J*=14.6 Hz, 1 H), 2.66 (dd, *J*=13.7, 7.3 Hz, 1 H), 2.96 - 3.03 (m, 2 H), 3.21 (s, 6 H), 3.91 (s, 3 H), 4.01 - 4.06 (m, 1 H), 4.18 (dd, *J*=11.9, 3.4 Hz, 1 H), 4.31 (d, *J*=11.9 Hz, 1 H), 4.56 (d, *J*=7.0 Hz, 1 H), 4.68 (dd, *J*=9.9, 7.2 Hz, 1 H), 5.14 - 5.19 (m, 1 H), 5.35 (d, *J*=17.1 Hz, 1 H), 5.75 - 5.85 (m, 1 H), 6.01 (s, 1 H), 6.60 (s, 1 H), 6.69 (s, 1 H), 6.83 (d, *J*=8.9 Hz, 1 H), 7.05 (s, 1 H), 7.81 (d, *J*=9.2 Hz, 1 H); LC-MS, MS *m/z* 748 ($M^+ + H$).

Example 18: Preparation of Compound 18: N-(4,6-dimethyl-2-pyridinyl)-3-methylvalyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((3-(dimethylamino)-6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide



Compound 18

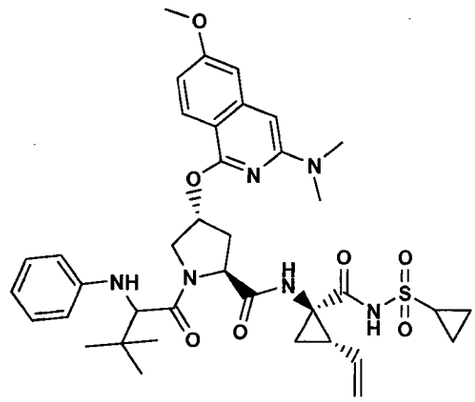
Compound 18 was prepared by the same method as described in Step 3, Example 14, except the product of Step 6, Example 17 (0.203 g, 0.330 mmol) was used in place of the product of Step 5, Example 1. Two products with identical LCMS *m/z* were formed in the reaction, but only the single isomer Compound 18 was isolated in reasonable purity. Compound 18 was the first of the two isomers to elute by reverse phase preparative HPLC and was obtained as a brown powder bis-TFA salt (0.102 g, 40.6% yield). ^{1}H NMR (500 MHz, MeOD) δ ppm 1.08 - 1.11 (m, *J*=3.05 Hz, 2 H) 1.13 (s, 9 H) 1.15 - 1.19 (m, *J*=1.83 Hz, 2 H) 1.25 - 1.30 (m, 2 H) 1.43 - 1.48 (m, 1 H) 1.92 - 1.97 (m, 1 H) 2.06 (s, 3 H) 2.26 - 2.35 (m, 2 H) 2.37 (s, 3 H) 2.61 - 2.67 (m, 1 H) 2.96 - 3.03 (m, 2 H) 3.13 (d, *J*=1.83 Hz, 6 H) 3.88 (d, *J*=1.83 Hz, 3 H) 4.06 (dd, *J*=12.21, 2.75 Hz, 1 H) 4.28 (d, *J*=12.51 Hz, 1 H) 4.47 (s, 1 H) 4.71 (t, *J*=8.70 Hz, 1 H) 5.17 (d, *J*=10.38 Hz, 1 H) 5.35 (d, *J*=17.09 Hz, 1 H) 5.73 - 5.82 (m, 1 H) 5.99 (s, 1 H) 6.52 (s, 1 H) 6.54 - 6.58 (m, 1 H) 6.61 (s, 1 H) 6.87 (t, *J*=1.98 Hz, 1 H) 7.56 (dd, *J*=9.00, 1.98 Hz, 1 H); LC-MS, MS *m/z* 762 (M^+ + H).

Compound 19 Isomers:

3-methyl-N-phenyl-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((3-(dimethylamino)-6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide and

3-methyl-N-phenyl-D-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((3-(dimethylamino)-6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide

Example 19: Preparation of Compounds 19A and 19B



Compounds 19A and 19B

The product of Step 6, Example 17 (0.203 g, 0.330 mmol), NMM (0.134 g, 1.32 mmol), HATU (0.151 g, 0.396 mmol) and the product of Step 1, Example 15 (0.102 g, 0.330 mmol) were combined in dichloromethane (2 mL) and stirred for 72 hours. Two products with identical LCMS *m/z* were formed in the reaction. The mixture was concentrated and purified by reverse phase preparative HPLC. Compound 19A was the first of the two isomers to elute by reverse phase preparative HPLC and was obtained as a brown powder bis-TFA salt (0.0806 g, 33.3% yield). Compound 19B was the second of the two isomers to elute by reverse phase preparative HPLC and was obtained as a brown powder bis-TFA salt (0.0573 g, 23.7% yield).

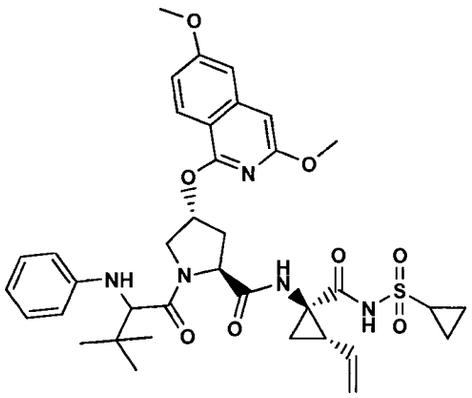
Compound 19A: LC-MS, MS *m/z* 733 (M^++H).

Compound 19B: LC-MS, MS *m/z* 733 (M^+ + H).

Compound 20 Isomers:

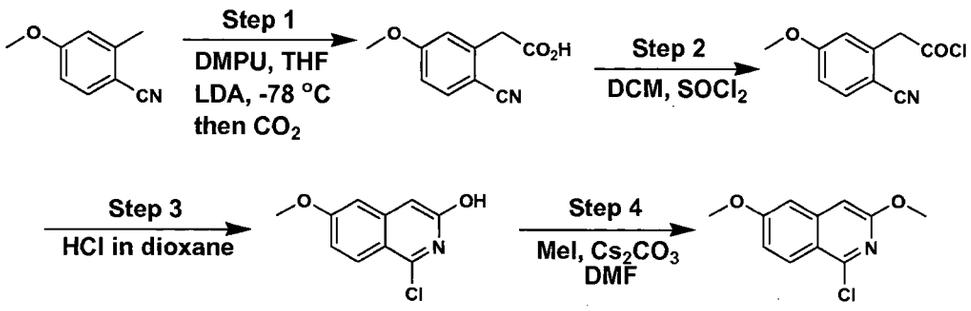
3-methyl-N-phenyl-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((3,6-dimethoxy-1-isoquinolinyl)oxy)-L-prolinamide and 3-methyl-N-phenyl-D-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((3,6-dimethoxy-1-isoquinolinyl)oxy)-L-prolinamide

Example 20: Preparation of Compounds 20A and 20B



Compounds 20A and 20B

Scheme 1



Step 1:

To a solution of 1, 3-dimethyl-3, 4, 5, 6-tetrahydro-2(*1H*)-pyrimidinone (DMPU, 7.02 g, 55 mmol) in THF (100 mL) was added LDA (2.0M in THF, 27.5 mL, 55 mmol) dropwise at -78 °C. The resulting orange solution was kept at this temperature for 10 minutes with stirring and then 4-methoxy-2-methylbezonitrile (7.36 g, 50 mmol in 5 mL THF) was added dropwise. The resulting dark orange solution was kept at this temperature for 30 minutes with stirring. CO_2 gas was then bubbled into this solution at -78 °C until it became colorless. The final solution was kept at this temperature for an additional 30 minutes with stirring before being purged with N_2 for 5 minutes. The mixture was quenched with H_2O (80 mL) at -78 °C, then allowed to warm up to room temperature. 10.0M NaOH (aq, 20 mL, 200 mmol) was added, resulting in a homogeneous solution which was extracted with diethyl ether (100 mL). The aqueous layer was acidified by concentrated HCl to pH = 2, and the resulting precipitate was collected by filtration. The cake was washed with H_2O thoroughly and dried *in vacuo* overnight to furnish the desired product

(7.90 g 83.0% yield) as a white fakes. ^{1}H NMR (300 MHz, CD_3OD) δ ppm 3.83 (s, 2H), 3.86 (s, 3H), 6.99 (m, 2H), 7.64 (d, J = 8.42 Hz, 1H).

Step 2:

A slurry of 2-(2-cyano-5-methoxyphenyl)acetic acid in dichloromethane (40 mL) and thionyl chloride (40 mL) was stirred at room temperature overnight. The volatiles were removed, and the residue was triturated with dichloromethane (50 mL) and filtered. The filtrate was concentrated *in vacuo* to yield the desired product as a brownish viscous oil (6.80 g, 97% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 3.86 (m, 3H), 4.35 (s, 2H), 6.92 (m, 2H), 7.63 (d, J = 8.78 Hz, 1H).

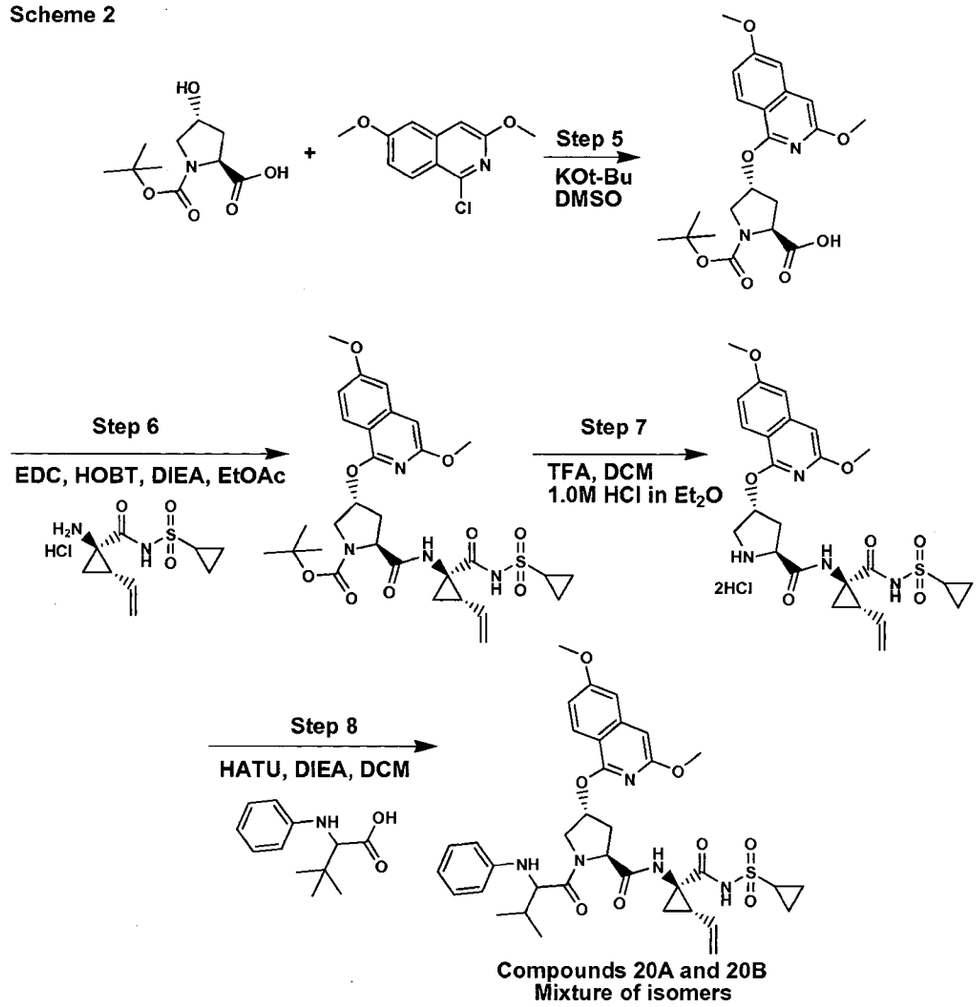
Step 3:

A solution of 2-(2-cyano-5-methoxyphenyl)acetyl chloride (6.40 g, 30.6 mmol) in 4.0M HCl in 1,4-dioxane (100 mL) was heated in a sealed vessel at 60 °C with stirring overnight. After cooling to room temperature, the mixture was filtered and the cake was washed with ethyl acetate thoroughly and dried *in vacuo* to provide the desired product as a fine pale yellow powder (6.14 g, 96% yield). ^{1}H NMR (500 MHz, CD_3OD) δ ppm 3.98 (s, 3H), 6.94 (s, 1H), 7.14 (m, 2H), 8.10 (d, J = 9.16 Hz, 1H); LC-MS MS *m/z* 210 (M^++ H).

Step 4:

A slurry of 1-chloro-6-methoxyisoquinolin-3-ol (0.209 g, 1.0 mmol), Cs_2CO_3 (0.715 g, 2.2 mmmol), and CH_3I (0.284 g, 2.0 mmol) in DMF (2.5 mL) was heated to 85 °C in a sealed tube for 3 hours. Upon cooling to room temperature, the upper layer of brownish solution was decanted into iced 5% citric acid. The mixture was extracted with ethyl acetate (20 mL). The organic layer was washed with 5% citric acid, 1.0M NaOH (aq), and brine sequentially, dried over $MgSO_4$, and filtered. The filtrate was concentrated and the residue was purified by flash column silica gel chromatography. Elution with dichloromethane furnished the desired product as an off-white solid (0.152 g, 68.0% yield). LC-MS MS *m/z* 224 (M^++ H).

Scheme 2



Step 5:

The product of Step 5, Example 20 was obtained by the same procedure as described for the preparation of the product of Step 3, Example 1, except the product of Step 4, Example 20 (1.25 g, 5.60 mmol) was used as starting material instead of the product of Step 2 Example 1. The crude product was purified by silica gel flash chromatography (step gradient 3:1 hexanes:acetone, followed by 2:1 and then 1:1 of the same) to give an off-white foam (2.34 g, 91.6% yield). LC-MS MS *m/z* 419 (M^++ H).

Step 6:

To a 0 °C solution of the product of Step 5, Example 20 (1.94 g, 5.68 mmol)

in ethyl acetate (150 mL) was added cyclopropanesulfonic acid (1-(*R*)-amino-2-(*S*)-vinyl-cyclopropanecarbonyl)-amide HCl salt (2.29 g, 5.68 mmol) in one portion. The mixture was stirred for 15 minutes, and then DIPEA (1.91 g, 17.0 mmol) was added dropwise and the suspension was stirred for 5 minutes. The mixture was then treated with EDC (1.41 g, 7.38 mmol) and HOBT (0.767 g, 5.68 mmol) and was stirred overnight. The mixture was poured into ice cold 5 % aqueous citric acid and the resulting mixture was shaken and the phases were separated. The organic phase was washed with 5 % aqueous citric acid, 5 % aqueous sodium citrate, and finally with brine. The organic was dried over $MgSO_4$, filtered and concentrated. Purification by flash column silica gel chromatography (1:1 hexanes:acetone) gave the product as a white foam (2.50 g, 79% yield). LC-MS MS *m/z* 631 (M^++ H).

Step 7:

The product of Step 6, Example 20 (3.20 g, 5.08 mmol) was dissolved in dichloromethane (20 mL) and the solution was treated with TFA (20 mL) at room temperature for 1 hours. Solvent was removed *in vacuo*, and the residue was combined with 1.0M HCl in ether and stirred overnight. The resulting solid was isolated by filtration, rinsed with ether and dried *in vacuo* to give an off-white solid (2.97 g, 95.0% yield). LC-MS MS *m/z* 531 (M^++ H).

Step 8:

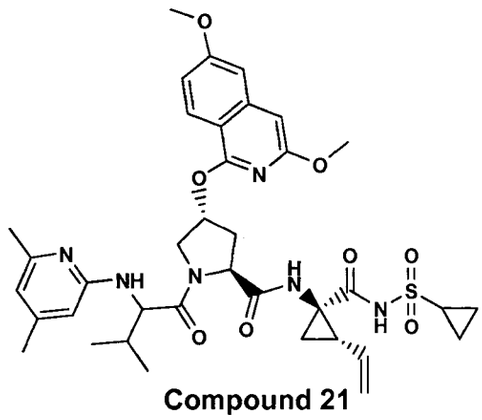
Compounds 20A and 20B were prepared by the same procedure as described for the preparation of Compounds 19A and 19B, except the product of Step 7, Example 20 (0.100 g, 0.166 mmol) was used in place of the product of Step 6, Example 17. Compound 20A was the first of the two isomers to elute by reverse phase preparative HPLC and was obtained as a beige powder bis-TFA salt (0.0564 g, 35.9% yield). Compound 20B was the second of the two isomers to elute by reverse phase preparative HPLC and was obtained as a beige powder bis-TFA salt (0.0367 g, 23.4% yield).

Compound 20A: LC-MS, MS *m/z* 720 (M^++H).

Compound 20B: ^{1}H NMR (500 MHz, MeOD) δ ppm 0.98 (s, 9 H) 1.00 - 1.09 (m, 2 H) 1.14 - 1.21 (m, 1 H) 1.28 - 1.41 (m, 3 H) 1.88 (dd, *J*=8.09, 5.34 Hz, 1 H) 2.25 (q, *J*=9.05 Hz, 1 H) 2.31 - 2.39 (m, 1 H) 2.60 (dd, *J*=13.73, 7.02 Hz, 1 H) 2.79 -

2.87 (m, 1 H) 3.92 (s, 3 H) 3.98 (d, *J*=1.53 Hz, 3 H) 4.08 (dd, *J*=12.21, 3.36 Hz, 1 H) 4.20 (s, 1 H) 4.45 (d, *J*=11.90 Hz, 1 H) 4.54 - 4.60 (m, 1 H) 5.15 (d, *J*=10.38 Hz, 1 H) 5.34 (d, *J*=17.09 Hz, 1 H) 5.76 - 5.86 (m, 1 H) 5.91 (s, 1 H) 6.57 - 6.63 (m, 2 H) 6.77 (d, *J*=8.54 Hz, 2 H) 6.93 (dd, *J*=9.16, 2.44 Hz, 1 H) 7.05 - 7.13 (m, 3 H) 7.87 (d, *J*=9.16 Hz, 1 H) 9.33 (s, 1 H); LC-MS, MS *m/z* 720 (M^+ + H).

Example 21: Preparation of Compound 21: N-(4,6-dimethyl-2-pyridinyl)valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((3,6-dimethoxy-1-isoquinolinyl)oxy)-L-prolinamide



Compound 21

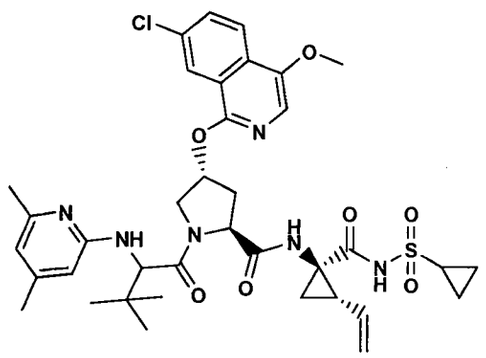
Compound 21 was prepared by the same procedure as described in Step 7, Example 17, except the product of Step 7, Example 20 (0.253 g, 0.419 mmol) was used in place of the product of Step 6, Example 17. Compound 21 (0.052 g, 15.3 % yield) was obtained as a brown powder bis-HCl salt. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 1.01 (d, *J*=6.7 Hz, 1 H), 1.10 (d, *J*=6.7 Hz, 3 H), 1.12 - 1.16 (m, 2 H), 1.23 - 1.29 (m, 2 H), 1.30 - 1.37 (m, 1 H), 1.43 - 1.49 (m, 1 H), 1.91 - 1.97 (m, 1 H), 2.19 (s, 3 H), 2.26 - 2.34 (m, 1 H), 2.40 (s, 3 H), 2.62 - 2.70 (m, 1 H), 2.89 (s, 1 H), 2.95 - 3.03 (m, 1 H), 3.16 - 3.22 (m, 1 H), 3.92 (s, 3 H), 3.99 (s, 3 H), 4.17 (dd, *J*=12.1, 3.5 Hz, 1 H), 4.23 - 4.29 (m, 1 H), 4.50 (d, *J*=7.0 Hz, 1 H), 4.64 - 4.70 (m, 1 H), 5.17 (d, *J*=10.4 Hz, 1 H), 5.35 (d, *J*=17.1 Hz, 1 H), 5.75 - 5.86 (m, 1 H), 5.98 (d, *J*=2.1 Hz, 1 H), 6.60 (d, *J*=8.2 Hz, 1 H), 6.66 (s, 1 H), 6.87 (dd, *J*=9.2, 2.4 Hz, 1 H), 7.06 (t, *J*=2.1 Hz, 1 H), 7.83 (d, *J*=9.2 Hz, 1 H); LC-MS, MS *m/z* 748 (M^+ + H).

Compound 22 Isomers:

N-(4,6-dimethyl-2-pyridinyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and

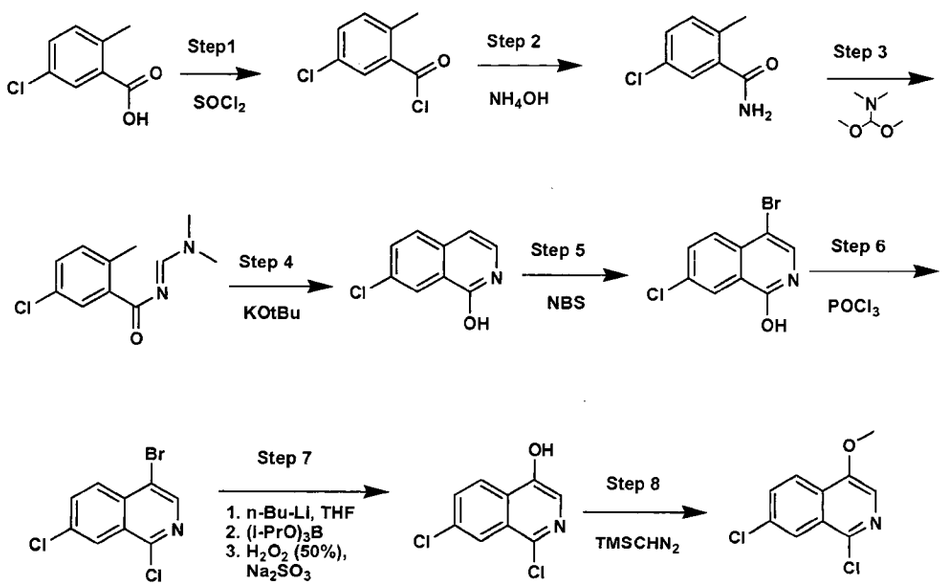
N-(4,6-dimethyl-2-pyridinyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 22: Preparation of Compounds 22A and 22B:



Compounds 22A and 22B

Scheme 1 of Example 22



Step 1:

A slurry of 3-chloro-6-methylbezoic acid (17.0 g, 0.10 mol) in thionyl chloride (23.5 ml, 0.30 mol) was heated slowly to a gentle reflux and maintained at this temperature for 2h. The reaction mixture was then cooled to RT and the excess thionyl chloride removed in vacuo. The residue was taken up in DCM (50 ml), and the solvent then removed in vacuo. (It should be noted that this process was repeated several times to ensure removal of residual thionyl chloride and HCl). The resulting product was then dissolved in THF (80 ml) which was used directly in the next reaction as described below.

Step 2:

To a solution of 30% ammonia (58 ml) in water (240 ml), cooled by salt-ice bath (-10 °C), was added dropwise a THF solution of the product of Step 1 above. After the addition was complete, the resulting reaction mixture (slurry) was stirred at -10 °C for 1 hr. The reaction mixture was then warmed to room temperature and decanted. The remaining solid in the reaction vessel was then triturated with water (50 ml). This process of trituration and decanting was then repeated. The remaining solid was then filtered and the filter cake washed with water. The solid was then dried in vacuo overnight to yield 13.8 g (82%) of desired product as a white crystalline material. ^{1}H NMR (DMSO-D_6) δ ppm 2.33 (s, 3H), 7.24-7.27 (m, 1H), 7.35-7.38 (m , 2H), 7.44 (b, 1H), 7.80 (b, 1H); ^{13}C NMR (100 MHz, DMSO-D_6) δ ppm 18.87, 126.64, 128.86, 129.81, 132.31, 134.19, 138.65, 169.41; LC-MS, MS *m/z* 170.

Step 3:

A mixture of the product of Step 2 (11.5 g, 68 mmol), DMF-acetal (10.9 ml, 82 mmol), and THF (150 ml) was heated to reflux and maintained at this temperature for 2 hr. The reaction mixture was then cooled to room temperature and the volatiles were removed in vacuo. The resulting residue was recrystallized from hexane (150 ml) to yield 14.7 g (96%) of the desired product as white needles.
^{1}H NMR (DMSO-D_6) δ 2.49-2.51 (m, 3H), 3.09 (s, 3H), 3.20 (s, 3H), 7.24, 7.27 (d, J=13.5 Hz, 1H), 7.37-7.41 (dd, J1=14 Hz, J2=4.5 Hz, 1H), 7.91, 7.92 (d, J=4.0 Hz, 1H), 8.55 (s, 1H); ^{13}C NMR (100 MHz, DMSO-D_6) δ ppm 20.69, 35.09, 40.91,

129.50, 129.72, 132.98, 136.86,138.87, 160.60, 177.04; LC-MS, MS *m/z* 225.

Step 4:

A mixture of the product of Step 3 and KOtBu (14.7 g, 131 mmol) in THF (300 ml) was heated to reflux and maintained at this temperature for 2 hr (reaction mixture became a dark solution upon heating). The volume of the reaction mixture was then reduced by distilling off approximately 100 ml of solvent. The resulting solution was then carefully poured into water (1 L) and the resulting mixture was acidified with 1M HCl to a resulting pH of 4. The mixture was then filtered, and the collected solid was washed thoroughly with water, then dried in vacuo overnight to yield 7.0 g (60%) of the desired product as a off-white powder.
^{1}H NMR (400 Hz, CD_3OD) δ ppm 6.66 (d, J=7.05 Hz, 1 H), 7.18 (d, J=7.05 Hz, 1 H), 7.66 (s, 1 H) 7.67 (d, J=2.01 Hz, 1 H), 8.24 (d, J=2.27 Hz, 1 H); ^{13}C NMR (100 MHz, DMSO-D_6) δ ppm 104.05, 125.62, 127.21, 128.54, 129.52, 130.77, 132.43, 136.55, 160.72; LC-MS, MS *m/z* 180.

Step 5:

A slurry of the product of Step 4 and NBS (39.747 g, 223.3 mmol) in MeCN (500 mL, anhydrous) was slowly heated to a gentle reflux over a period of approximately 2 h and maintained at a gentle reflux for 1.5 h (This reaction can be monitored by LC/MS). The reaction mixture was then slowly cooled to room temperature over a period of 3 h and the observed solid was removed by simple filtration. The collected solid was washed with MeCN (100 mL x 3) to provide 47 g of the desired product. This material was used in the next step without further purification.
^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.46(s, 1H), 7.81 (dd, J=8.40, 2.00 Hz, 1 H), 7.88 (d, J=8.8 Hz, 1 H), 8.27(d, J=2.00 Hz, 1 H); ^{13}C NMR (100 MHz, DMSO-D_6) δ ppm 96.68, 126.34, 127.58, 127.71, 130.73, 132.20, 133.47, 134.46, 159.88; LC-MS, MS *m/z* 258.

Step 6:

A heterogeneous solution of the product of Step 5 (47 g, 182 mmol) in $POCl_3$ (200 mL, 2.15 mol) slowly heated to reflux over a period of 1 h. The reaction mixture

was maintained at reflux for 4 h. The reaction mixture was then cooled to room temperature and concentrated in vacuo to remove excess $POCl_3$. The resulting residue was then taken-up into 600 mL of CH_2Cl_2, cooled to at -35 °C, then neutralized carefully with 1 N NaOH (400 mL) until the mixture was slightly basic (pH = 8). The resulting organic layer was separated, washed with water, dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was crystallized from EtOAc (approximately 50 mL) to give 32 g of desired product. The collected solid was washed with 10% EtOAc/Hexanes (3 x 50 ml).

The mother liquid was concentrated and purified by Biotage (elution with 16% EtOAc in hexanes) to give 4 g of the desired product as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.80 (dd, J=8.81, 2.01 Hz, 1 H), 8.14 (d, J=9.06 Hz, 1 H), 8.34 (d, J=1.76 Hz, 1 H), 8.48 (s, 1 H); ^{13}C NMR (100 MHz, DMSO-D_6) δ ppm 118.39, 125.06, 127.59, 128.71, 133.89, 134.14, 134.93, 143.18, 148.98; LC-MS, MS *m/z* 275.

Step 7:

To a slurry of the product of Step 6 (22.16 g, 80 mmol) in THF (500 ml) at -78 °C was added 100 ml of 1.6 M n-BuLi (in hexanes, 160 mmol) dropwise via cannula over 15 min (maintaining the internal temperature < -65 °C). The resulting solution was stirred for 0.5 h, after such time, $(i\text{-}PrO)_3B$ (37 ml, 160 mmol) was added dropwise via syringe over 10 min (maintaining the internal temperature < -65 °C). The resulting reaction mixture was stirred for 0.5 h. After checking the reaction by LC/MS for completion, 80 ml of 30% H_2O_2 (776 mmol) was added dropwise via addition funnel over 10 min (the internal temperature rose to -60 °C during addition), followed by addition of 80 ml of 1 N NaOH (80 mmol). The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature and stirred at room temperature for additional 1 h. After conforming the completion of the reaction by LC/MS, the reaction mixture was then cooled to -40 °C, and a solution of 100 g of Na_2SO_3 (0.793 moles) in 400 ml of water was added dropwise via addition funnel as a means to quench excess H_2O_2 over 30 min (maintaining the internal temperature 5-10 °C). The resulting slurry was then neutralized with 6 N HCl (approximately 50 ml) at 0□C till pH ~ 6, then diluted with 500 ml of EtOAc and decanted to a 2 L separatory funnel. To the remaining solid in the reaction vessel

was added 500 mL of water and 300 ml of EtOAc, then neutralized with 6 N HCl (approximately 20 ml). The combined organic layers were washed with brine (300 ml x 3), then water (200 ml x 3), dried over $MgSO_4$ and concentrated to give a crude product which was triturated with 50 ml of EtOAc. The solid was collected by filtration, rinsed with EtOAc (3 x 25 ml) and dried to give desired product (2 runs: 12.0 g, 70% and 13.8 g, 81%). The filtrates were combined, concentrated and purified by Biotage eluted with 35% EtOAc in hexanes to give 2.1 g of product. Overall, 44.4 g of bromide gave 27.9 g (81%) of 4-OH product.

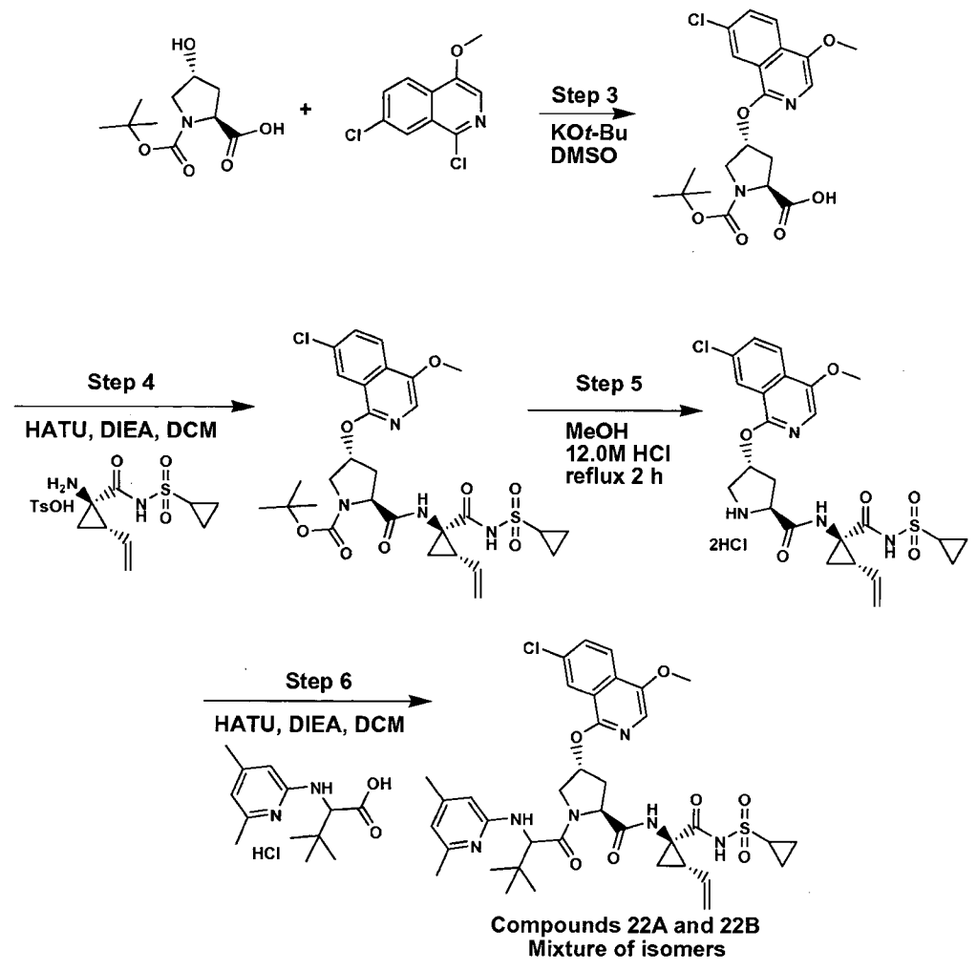
^{1}H NMR (400 MHz, CD_3OD) δ ppm 4.05 (s, 3 H), 7.4 (s, 1 H), 7.76 (dd, J=8.8, 2, Hz, 1 H), 8.16 (d, J=2 Hz, 1 H), 8.23 (d, J=8.8 Hz, 1 H); ^{13}C NMR (100 MHz, DMSO-D_6) δ ppm 123.78, 124.66, 125.62, 127.03, 127.71, 130.72, 133.80, 137.63; 148.88; LC-MS, MS *m/z* 213.

Step 8:

To a slurry of the product of Step 7 (16 g, 75.5 mmol) in MeOH-MeCN (30 mL/300 mL) at 0 0C was added dropwise 60 ml of 2 M solution of $TMSCHN_2$ in hexanes (120 mmol). The reaction mixture was allowed to warm to room temperature, then stirred for 14 h. The solution was then concentrated and the resulting solid was recrystallized from EtOAc (about 50 mL) to give 8.1 g of the desired product which was washed with 25% EtOAc in hexances; 20 x3 times. The mother liquid was concentrated and purified by Biotage (elution with 16 % EtOAc in hexanes) to provide 3.2 g of the desired product as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.05 (s, 3 H), 7.67 (dd, J=9.06, 2.01 Hz, 1 H), 7.80 (s, 1 H), 8.16 (d, J=8.81 Hz, 1 H), 8.23 (d, J=2.01 Hz, 1 H); ^{13}C NMR (100 MHz, DMSO-D_6) δ ppm 56.68, 122.70, 123.99, 124.14, 126.67, 127.83, 131.43, 134.10, 139.75, 149.94; LC-MS, MS *m/z* 229.

Scheme 2 of Example 22



Step 3:

The product of Step 2, Example 22 (0.452 g, 1.98 mmol), Boc-HYP-OH (0.508 g, 2.20 mmol), and potassium *tert*-butoxide (0.672 g, 6.0 mmol) in DMSO (20 mL) was stirred at room temperature for 4 hours. The mixture was quenched with water and neutralized with 1.0M aqueous HCl. The mixture was extracted with ethyl acetate and the organic was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to give a crude solid (0.844 g, quantitative) which was used in the next step without further purification.

Step 4:

The product of Step 3, Example 22 (0.422 g, 1.00 mmol) was dissolved in

dichloromethane (10 mL) and DIEA (2 mL). To the solution were added cyclopropanesulfonic acid (1-(*R*)-amino-2-(*S*)-vinyl-cyclopropanecarbonyl)-amide p-toluenesulfonic acid salt (0.402 g, 1.00 mmol) and HATU (0.600 g, 1.58 mmol) and the mixture was stirred for 6 hours and concentrated. Purification by flash column silica gel chromatography (1:1 hexane:acetone) gave solid desired product (0.600 g, 94.5% yield). LC-MS, MS *m/z* 636 (M^+ + H).

Step 5:

The product of Step 4, Example 22 (6.34 g, 9.98 mmol) dissolved in methanol (50 mL) was treated with 12M HCl (3 mL) and the mixture was heated to reflux for 2 hours and concentrated. The crude material was used directly in the next step.

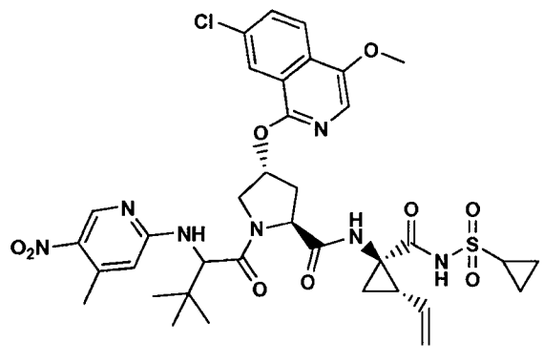
Step 6:

A solution of the product of Step 5, Example 22 (0.480 g, 0.790 mmol), DIEA (1 mL) and the product of Step 2, Example 14 (0.240 g, 0.880 mmol) in DMF (5 mL) was sparged with nitrogen. The mixture was cooled to 0 °C, treated with HATU (0.456 g, 1.12 mmol) and stirred at room temperature for 5 hours. The reaction was then heated to 46 °C for 25 hours. The mixture was concentrated, and the residue was purified by reverse phase preparative HPLC to give two separate products with identical MS *m/z* as observed by LCMS. Compound 22A (0.045 g, 7.6% yield) was the first of the two isomers to elute by reverse phase preparative HPLC. Compound 22B (0.050 g, 8.4% yield) was the second of the two isomers to elute by reverse phase preparative HPLC.

Compound 22A: LC-MS, MS *m/z* 754 (M^++H).

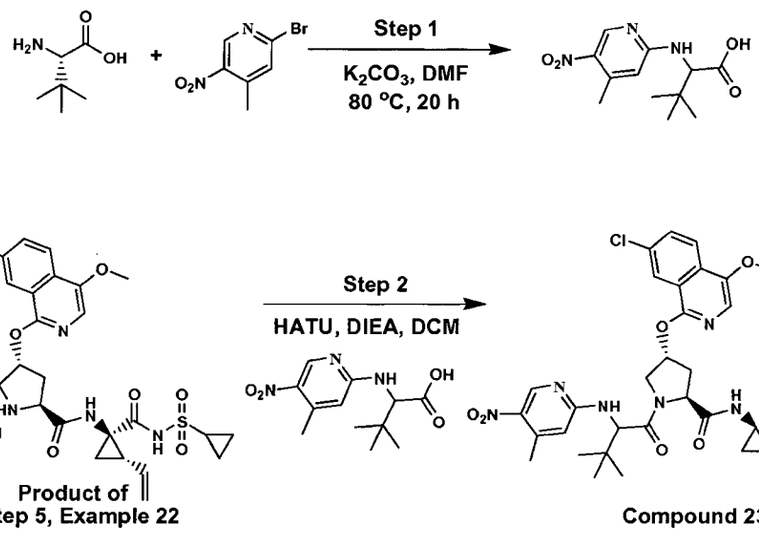
Compound 22B: LC-MS, MS *m/z* 754 (M^+ + H).

Example 23: Preparation of Compound 23: 3-methyl-N-(4-methyl-5-nitro-2-pyridinyl)valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide



Compound 23

Scheme 1



Step 1:

A mixture of 2-bromo-5-nitro-4-picoline (2.00 g, 9.22 mmol), L-tert-leucine (1.27 g, 9.68 mmol) and potassium carbonate (3.18 g, 23.0 mmol) in anhydrous DMF (50 mL) was heated to 80 °C for 20 h. The mixture was concentrated *in vacuo* to a residue (approx 25 mL), then DCM (200 mL) and water (100 mL) were added and the resulting mixture was shaken and the two phases were separated. The aqueous phase was extracted with DCM (3 x 100 mL), and the organic extracts were combined and dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to a deep red solid. Purification by reverse phase preparative HPLC afforded a

yellow solid (0.66 g, 27% yield). LC-MS, MS *m/z* 268 ($M^+ + H$).

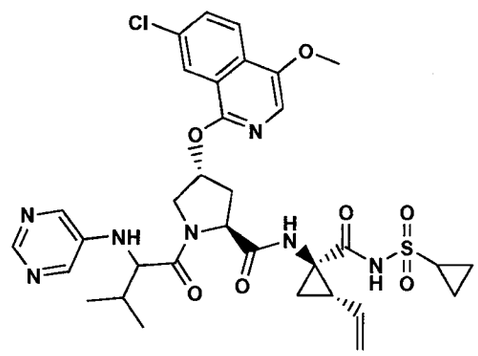
Step 2:

The product of Step 1, Example 23, (0.145 g, 0.543 mmol) was combined with the product of Step 5, Example 22, (0.300 g, 0.493 mmol) and HATU (0.281 g, 0.740 mmol) in DCM (4 mL). To the mixture was added N-methylmorpholine (0.250 g, 2.47 mmol), and the resulting mixture was agitated at room temperature overnight, then at 60 °C for 3 d. Additional product of Step 1, Example 23 (0.145 g, 0.543 mmol) and HATU (0.281 g, 0.740 mmol) were added, and the mixture was stirred at rt overnight. Purification by reverse phase preparative HPLC gave compound 23 as an orange/brown solid bis-TFA salt (0.097 g, 19.4% yield). ^1H NMR (500 MHz, CD_3OD) δ ppm 1.10 (s, 9 H) 1.11 - 1.15 (m, 2 H) 1.23 - 1.32 (m, 2 H) 1.43 - 1.50 (m, 1 H) 1.93 (dd, *J*=8.24, 5.49 Hz, 1 H) 2.24 - 2.32 (m, 2 H) 2.33 (s, 3 H) 2.60 (dd, *J*=13.58, 6.87 Hz, 1 H) 2.96 - 3.03 (m, 1 H) 3.99 - 4.03 (m, 1 H) 4.05 (s, 3 H) 4.65 (dd, *J*=10.68, 7.02 Hz, 1 H) 4.78 - 4.83 (m, 1 H) 4.90 (s, 1 H) 5.16 (dd, *J*=10.38, 1.53 Hz, 1 H) 5.31 - 5.37 (m, 1 H) 5.78 (ddd, *J*=17.17, 10.15, 9.00 Hz, 1 H) 5.87 (t, *J*=3.05 Hz, 1 H) 6.29 (s, 1 H) 7.57 - 7.64 (m, 2 H) 7.71 (s, 1 H) 7.76 (d, *J*=2.14 Hz, 1 H) 8.03 (d, *J*=8.85 Hz, 1 H) 9.22 (s, 1 H); LC-MS, MS *m/z* 785 ($M^+ + H$).

Compound 24 Isomers:

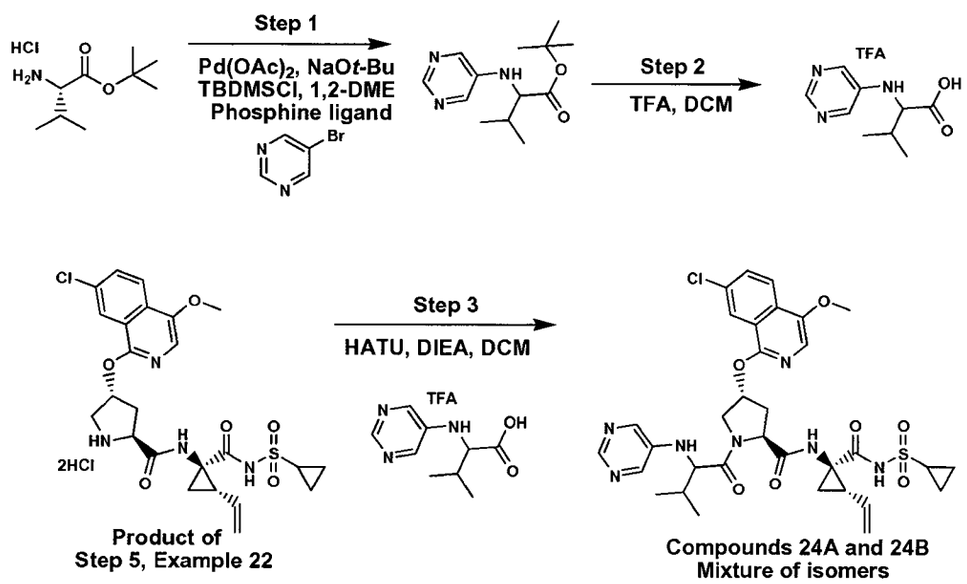
N-5-pyrimidinyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and N-5-pyrimidinyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 24: Preparation of Compounds 24A and 24B



Compounds 24A and 24B

Scheme 1



Step 1:

5-Bromopyrimidine (1.15 g, 7.21 mmol) and sodium *tert*-butoxide (2.36 g, 24.5 mmol), were combined with anhydrous 1,2-dimethoxyethane (15 mL) in a 75 mL Chemglass pressure vessel. The mixture was shaken, and a pre-mixed solution of $Pd(OAc)_2$ (0.0405 g, 0.180 mmol) and (*R*)-(-)-1-[(*S*)-(dicyclohexylphosphino) ferrocenyl] ethyl di-*tert*-butyl phosphine (0.100 g, 0.180 mmol, Strem Chemicals catalog # 26-0975, CAS # [158923-11-6]) in dry 1,2-dimethoxyethane (2 mL) was immediately added. *L*-valine *tert*-butyl ester hydrochloride (1.18 g, 5.62 mmol) was then quickly added to the resulting mixture. The pressure vessel was sealed and the mixture was stirred at 110 °C for 20 hours. The crude product was passed through a

plug of silica gel (elution 100% DCM then 100% EtOAc) to remove baseline contaminants. Solvent was removed *in vacuo*, and the 300 mg of recovered crude material was purified by flash silica gel chromatography (gradient 4:1 hexanes:EtOAc to 1:1 hexanes:EtOAc) to give a yellow solid (0.200 g, 14.2% yield). ^{1}H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.03 (t, *J*=6.87 Hz, 6 H) 1.45 (s, 9 H) 2.11 - 2.19 (m, 1 H) 3.75 (dd, *J*=9.16, 5.19 Hz, 1 H) 4.24 (d, *J*=9.16 Hz, 1 H) 8.13 (s, 2 H) 8.60 (s, 1 H); LC-MS, MS *m/z* 252 (M^+ + H).

Step 2:

The product of Step 1, Example 24, (0.200 g) was dissolved in dichloromethane (10 mL) and treated with TFA (10 mL). The mixture was stirred at room temperature for 3 h and was then concentrated *in vacuo*. The residue was then dissolved in 1,2-dichloroethane (15 mL) and again concentrated *in vacuo*. The dark green residue was then purified by reverse phase preparative HPLC to yield a dark green glassy solid as the HCl salt (0.091 g, 49% yield). ^{1}H NMR (500 MHz, DMSO-D_6) δ ppm 0.99 (dd, *J*=9.16, 7.02 Hz, 6 H) 2.14 (td, *J*=13.28, 6.71 Hz, 1 H) 3.90 (d, *J*=5.80 Hz, 1 H) 6.32 (s, 1 H) 8.22 (s, 2 H) 8.44 (s, 1 H); LC-MS, MS *m/z* 196 (M^+ + H).

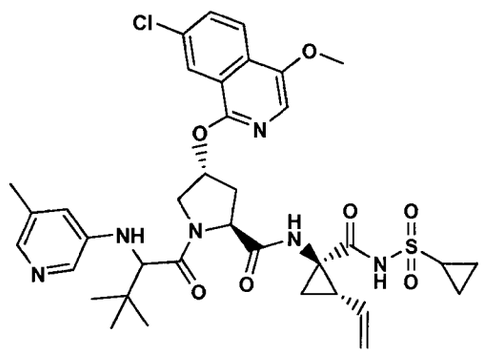
Step 3:

A mixture of the product of Step 2, Example 24, (0.084 g, 0.362 mmol), the product of Step 5, Example 22, (0.200 g, 0.329 mmol) and HATU (0.188 g, 0.493 mmol) suspended in DCM (4 mL) was treated with NMM (0.167 g, 1.65 mmol). The mixture was stirred at room temperature for 3 hours. The solvent was removed under a nitrogen stream and the crude mixture was purified by reverse phase preparative HPLC to give two separate compounds with identical MS *m/z*. Compound 24A (0.0902 g, 29.2% yield) was the first of the two isomers to elute from the reverse phase preparative HPLC column and was obtained as a beige powder bis-TFA salt. Compound 24B (0.0957 g, 30.9% yield) was the second of the two isomers to elute from the reverse phase preparative HPLC column and was obtained as a beige powder bis-TFA salt.

Compound 24A: ^{1}H NMR (300 MHz, CD_3OD) δ ppm 0.91 (dd, *J*=6.95, 3.29 Hz, 2 H) 1.04 (d, *J*=6.59 Hz, 3 H) 1.09 (d, *J*=6.59 Hz, 3 H) 1.19 - 1.38 (m, 8 H) 1.43 (dd, *J*=9.51, 5.12 Hz, 1 H) 1.91 (dd, *J*=8.23, 5.31 Hz, 1 H) 2.03 (s, 1 H) 2.19 - 2.38 (m, 3 H) 2.57 (dd, *J*=13.54, 7.32 Hz, 1 H) 2.94 - 3.06 (m, 1 H) 4.03 (s, 3 H) 4.06 - 4.21 (m, 2 H) 4.34 (d, *J*=12.08 Hz, 1 H) 4.57 (dd, *J*=10.25, 6.95 Hz, 1 H) 5.14 (dd, *J*=10.61, 1.10 Hz, 1 H) 5.32 (dd, *J*=17.20, 1.46 Hz, 1 H) 5.72 - 5.87 (m, 1 H) 5.89 (s, 1 H) 7.56 (s, 1 H) 7.70 (dd, *J*=8.78, 2.20 Hz, 1 H) 7.99 (d, *J*=2.20 Hz, 1 H) 8.07 - 8.16 (m, 3 H) 8.29 (s, 1 H); LC-MS, MS *m/z* 713 (M^+ + H).

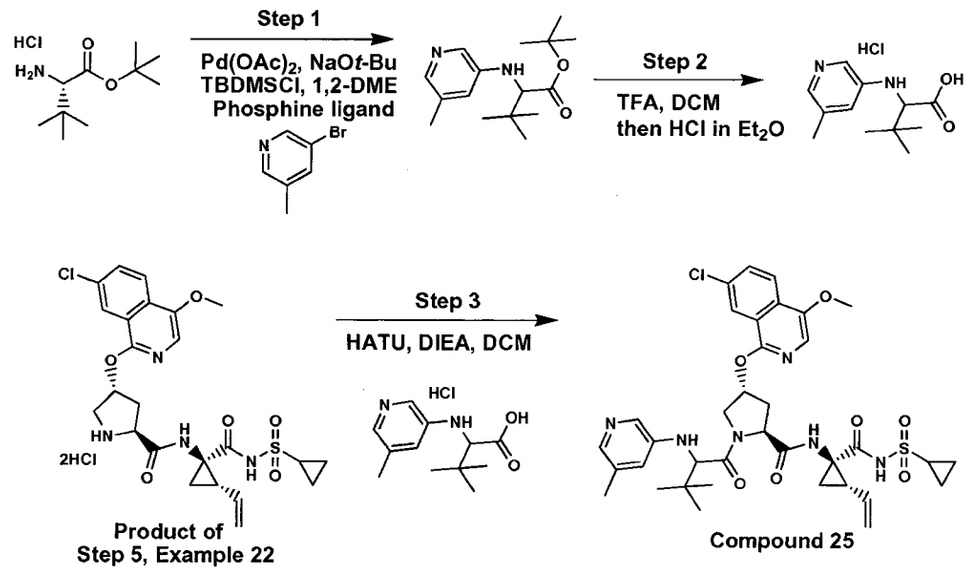
Compound 24B: ^{1}H NMR (300 MHz, CD_3OD) δ ppm 0.91 (d, *J*=6.95 Hz, 3 H) 0.95 (d, *J*=6.59 Hz, 3 H) 0.98 - 1.13 (m, 3 H) 1.20 - 1.31 (m, 2 H) 1.40 (dd, *J*=9.51, 5.12 Hz, 1 H) 1.90 (dd, *J*=8.23, 5.31 Hz, 1 H) 1.98 - 2.07 (m, 1 H) 2.22 - 2.41 (m, 2 H) 2.57 - 2.66 (m, 1 H) 2.82 - 2.93 (m, *J*=7.82, 7.82, 5.12, 4.85 Hz, 1 H) 4.04 (s, 3 H) 4.05 - 4.16 (m, 1 H) 4.23 (d, *J*=6.95 Hz, 1 H) 4.41 (d, *J*=12.08 Hz, 1 H) 4.62 (dd, *J*=9.70, 7.14 Hz, 1 H) 5.15 (dd, *J*=10.43, 1.65 Hz, 1 H) 5.34 (dd, *J*=17.20, 1.46 Hz, 1 H) 5.78 (ddd, *J*=17.20, 10.25, 8.78 Hz, 1 H) 5.87 (s, 1 H) 7.61 (s, 1 H) 7.73 (dd, *J*=8.97, 2.01 Hz, 1 H) 7.96 (d, *J*=1.83 Hz, 1 H) 8.13 (d, *J*=9.15 Hz, 1 H) 8.21 (s, 2 H) 8.33 (s, 1 H); LC-MS, MS *m/z* 713 (M^+ + H).

Example 25: Preparation of Compound 25: 3-methyl-N-(5-methyl-3-pyridinyl)valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide



Compound 25

Scheme 1



Step 1:

5-Bromo-3-picoline (1.00 g, 5.81 mmol), sodium *tert*-butoxide (1.90 g, 19.8 mmol) and *tert*-leucine *tert*-butyl ester hydrochloride (1.665 g, 6.98 mmol) were combined in anhydrous 1,2-dimethoxyethane (20 mL) in a 75 mL Chemglass pressure vessel. The mixture was stirred briefly, and a pre-mixed solution of $Pd(OAc)_2$ (0.0652 g, 0.291 mmol) and (*R*)-(-)-1-[(*S*)-(dicyclohexylphosphino) ferrocenyl] ethyl di-*tert*-butyl phosphine (0.161 g, 0.291 mmol, Strem Chemicals catalog # 26-0975, CAS # [158923-11-6]) in dry 1,2-dimethoxyethane (2 mL) was immediately added. The pressure vessel was sealed and the mixture was stirred at 100 °C for 20 hours. The mixture was poured into a rapidly stirred mixture of pH = 7 buffer (200 mL), 1.0M aqueous HCl (25 mL) and ethyl acetate (100 mL). The phases were separated and the aqueous was extracted with ethyl acetate (2 x 50 mL). The organic phases were combined, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to a residue. The crude material was purified by flash silica gel chromatography (gradient hexanes to 1:1 hexanes:EtOAc) to give a red oil (0.852 g, 52.6 % yield). 1H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.06 (s, 9 H) 1.40 (s, 9 H) 2.23 (s, 3 H) 3.63 (d, *J*=10.38 Hz, 1 H) 4.11 (dd, *J*=8.55, 1.22 Hz, 1 H) 6.74 (s, 1 H) 7.81 (s, 1 H) 7.89 (d, *J*=2.75 Hz, 1 H); LC-MS, MS *m/z* 279 (M^+ + H).

Step 2:

The product of Step 1, Example 25, (0.809 g, 2.91 mmol) was dissolved in dichloromethane (20 mL) and treated with TFA (20 mL). The mixture was stirred at room temperature for 20 h and was then concentrated *in vacuo*. The residue was then dissolved in 1,2-dichloroethane (15 mL) and again concentrated *in vacuo* to give a brown oil. The residue was then dissolved in minimum DCM and added dropwise to a rapidly stirred mixture of 2.0M HCl in ether (30 mL), diethyl ether (30 mL) and 1,2-DCE (50 mL). The mixture was stirred for 10 min and was then concentrated *in vacuo*. The resulting brown foamy solid was then taken up in 1.0M aqueous HCl and the solution was concentrated in vacuo to give a glassy yellow solid (0.600 g, 80 % yield). 1H NMR (500 MHz, DMSO-D_6) δ ppm 1.05 (s, 9 H) 2.35 (s, 3 H) 4.02 (d, *J*=9.77 Hz, 1 H) 7.03 (d, *J*=9.77 Hz, 1 H) 7.68 (s, 1 H) 7.95 (s, 1 H) 8.13 (s, 1 H) LC-MS, MS *m/z* 223 (M^+ + H).

Step 3:

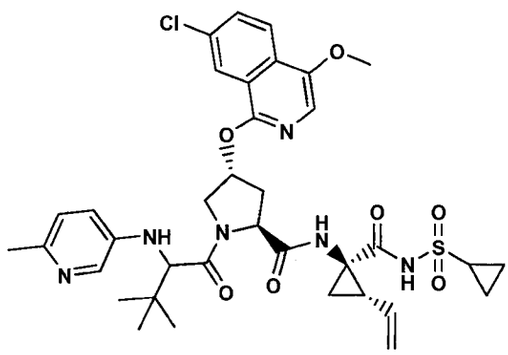
A mixture of the product of Step 2, Example 25 (0.094 g, 0.362 mmol), the product of Step 5, Example 22, (0.200 g, 0.329 mmol) and HATU (0.188 g, 0.493 mmol) suspended in DCM (2 mL) was treated with NMM (0.167 g, 1.65 mmol). The mixture was stirred at room temperature for 20 hours. The solvent was removed *in vacuo* and the crude mixture was purified by reverse phase preparative HPLC to give compound 25 (0.1421 g, 44.7% yield) as a white powder bis-TFA salt. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.07 - 1.21 (m, 11 H) 1.23 - 1.34 (m, 2 H) 1.45 (dd, *J*=9.46, 5.19 Hz, 1 H) 1.93 (dd, *J*=8.09, 5.65 Hz, 1 H) 2.14 (s, 3 H) 2.22 - 2.32 (m, 2 H) 2.59 (dd, *J*=13.73, 7.32 Hz, 1 H) 2.96 - 3.05 (m, 1 H) 4.01 (dd, *J*=12.21, 3.05 Hz, 1 H) 4.04 (s, 3 H) 4.26 (s, 1 H) 4.33 (d, *J*=12.21 Hz, 1 H) 4.66 (dd, *J*=10.22, 7.48 Hz, 1 H) 5.16 (d, *J*=10.38 Hz, 1 H) 5.34 (d, *J*=17.40 Hz, 1 H) 5.72 - 5.83 (m, 1 H) 5.89 (s, 1 H) 7.48 (s, 1 H) 7.59 (s, 1 H) 7.67 - 7.72 (m, 2 H) 7.81 (d, *J*=2.14 Hz, 1 H) 7.96 (d, *J*=1.83 Hz, 1 H) 8.11 (d, *J*=8.85 Hz, 1 H) 9.27 (s, 1 H); LC-MS, MS *m/z* 740 (M^+ + H).

Compound 26 Isomers:

3-methyl-N-(6-methyl-3-pyridinyl)-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and

3-methyl-N-(6-methyl-3-pyridinyl)-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 26: Preparation of Compounds 26A and 26B



Compounds 26A and 26B

Compounds 26A and 26B were prepared by a similar procedure as that described for the preparation of compound 25, except 5-bromo-2-methylpyridine was used in place of 5-bromo-3-picoline in Step 1, and the reaction scales were altered for Steps 2 and 3. Two isomeric compounds were isolated from Step 3: the first isomer to elute from a preparative HPLC column was compound 26A (0.111 g) isolated as a slightly off-white solid bis-TFA salt, and the second isomer to elute from the preparative HPLC column was compound 26B (0.0944 g) isolated as a slightly yellow solid bis TFA salt. The combined yield for both compounds 26A and 26B was 12.2% over three steps.

Product of Step 1, Example 26: Flesh-colored waxy solid; ^{1}H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.06 (s, 9 H) 1.40 (s, 9 H) 2.42 (s, 3 H) 3.59 (d, *J*=10.38 Hz, 1 H) 4.02 (d, *J*=10.38 Hz, 1 H) 6.87 (dd, 1 H) 6.93 (d, 1 H) 7.99 (d, *J*=2.75 Hz, 1 H); LC-MS, MS *m/z* 279 (M^+ + H).

Product of Step 2, Example 26: Yellow solid; 1H NMR (500 MHz, DMSO-D_6) δ ppm 1.05 (s, 9 H) 2.52 (s, 3 H) 3.98 (d, *J*=9.16 Hz, 1 H) 6.84 (d, *J*=9.77 Hz, 1

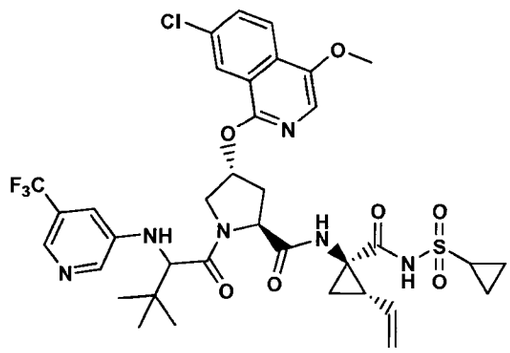
H) 7.59 (d, *J*=9.16 Hz, 1 H) 7.81 (dd, *J*=9.00, 2.59 Hz, 1 H) 8.05 (d, *J*=2.75 Hz, 1 H); LC-MS, MS *m/z* 223 ($M^+ + H$).

Compound 26A: ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.07 - 1.18 (m, 11 H) 1.25 - 1.32 (m, 2 H) 1.45 (dd, *J*=9.46, 5.49 Hz, 1 H) 1.93 (dd, *J*=7.93, 5.49 Hz, 1 H) 2.22 - 2.31 (m, 4 H) 2.46 (s, 3 H) 2.60 (dd, *J*=13.43, 6.71 Hz, 1 H) 2.96 - 3.04 (m, 1 H) 4.00 (dd, *J*=12.36, 2.90 Hz, 1 H) 4.05 (s, 3 H) 4.23 (s, 1 H) 4.37 (d, *J*=12.21 Hz, 1 H) 4.65 (dd, *J*=10.07, 7.32 Hz, 1 H) 5.14 - 5.19 (m, 1 H) 5.34 (d, *J*=17.09 Hz, 1 H) 5.77 (ddd, *J*=17.17, 10.15, 9.00 Hz, 1 H) 5.88 (s, 1 H) 7.05 (d, *J*=8.85 Hz, 1 H) 7.53 (dd, *J*=8.85, 2.75 Hz, 1 H) 7.62 (s, 1 H) 7.73 (dd, *J*=8.85, 2.14 Hz, 1 H) 7.84 (d, *J*=1.83 Hz, 1 H) 7.93 (d, *J*=2.75 Hz, 1 H) 8.14 (d, *J*=8.85 Hz, 1 H) 9.25 (s, 1 H); LC-MS, MS *m/z* 740 ($M^+ + H$).

Compound 26B: ^{1}H NMR (500 MHz, CD_3OD) δ ppm 0.97 (s, 9 H) 1.07 - 1.14 (m, 2 H) 1.18 - 1.24 (m, 1 H) 1.28 - 1.34 (m, 1 H) 1.41 (dd, *J*=9.46, 5.49 Hz, 1 H) 1.90 (dd, *J*=8.09, 5.34 Hz, 1 H) 2.30 (q, *J*=8.75 Hz, 1 H) 2.37 (ddd, *J*=13.89, 9.92, 4.27 Hz, 1 H) 2.58 (s, 3 H) 2.65 (dd, *J*=13.89, 7.48 Hz, 1 H) 2.93 - 3.00 (m, 1 H) 4.04 (s, 3 H) 4.09 (dd, *J*=12.21, 3.36 Hz, 1 H) 4.34 (s, 1 H) 4.50 (d, *J*=11.90 Hz, 1 H) 4.65 (dd, *J*=9.46, 7.32 Hz, 1 H) 5.16 (d, *J*=10.07 Hz, 1 H) 5.36 (d, *J*=17.40 Hz, 1 H) 5.75 - 5.86 (m, 1 H) 5.89 (s, 1 H) 7.57 (d, *J*=9.16 Hz, 1 H) 7.62 (s, 1 H) 7.75 (dd, *J*=8.85, 2.14 Hz, 1 H) 7.85 (dd, *J*=9.00, 2.90 Hz, 1 H) 8.05 (dd, *J*=4.12, 2.59 Hz, 2 H) 8.15 (d, *J*=9.16 Hz, 1 H) 9.56 (s, 1 H); LC-MS, MS *m/z* 740 ($M^+ + H$).

Compound 27 Isomers:
3-methyl-N-(5-(trifluoromethyl)-3-pyridinyl)-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and
3-methyl-N-(5-(trifluoromethyl)-3-pyridinyl)-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 27: Preparation of Compounds 27A and 27B



Compounds 27A and 27B

Compounds 27A and 27B were prepared by a similar procedure as that described for the preparation of compound 25, except 3-bromo-5-trifluoromethylpyridine was used in place of 5-bromo-3-picoline in Step 1, and the reaction scales were different. Also, the product from Step 2 was not isolated as the HCl salt but was instead carried on to Step 3 directly as a TFA salt. Two isomeric compounds were isolated from Step 3: the first isomer to elute from a preparative HPLC column was compound 27A (0.128 g) isolated as a slightly off-white solid bis-TFA salt, and the second isomer to elute from the preparative HPLC column was compound 27B (0.0564 g) isolated as a slightly off-white solid bis TFA salt. The combined yield for both compounds 27A and 27B was 17.9% over three steps.

Product of Step 1, Example 27: Orange waxy solid; ^{1}H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.08 (s, 9 H) 1.43 (s, 9 H) 3.66 (d, *J*=10.07 Hz, 1 H) 4.45 (d, *J*=10.07 Hz, 1 H) 7.06 (s, 1 H) 8.22 (s, 1 H) 8.24 (d, *J*=2.75 Hz, 1 H); LC-MS, MS *m/z* 333 (M^+ + H).

Product of Step 2, Example 27: Brown glassy solid; ^{1}H NMR (500 MHz, DMSO-D_6) δ ppm 1.06 (s, 9 H) 3.90 (s, 1 H) 3.92 (s, 1 H) 6.56 (s, 1 H) 7.42 (s, 1 H) 8.16 (s, 1 H) 8.40 (s, 1 H); LC-MS, MS *m/z* 277 (M^+ + H).

Compound 27A: ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.10 - 1.13 (m, 2 H) 1.15 (s, 9 H) 1.27 - 1.31 (m, 2 H) 1.45 (dd, *J*=9.46, 5.49 Hz, 1 H) 1.92 (dd, *J*=7.93, 5.49 Hz, 1 H) 2.23 - 2.32 (m, 2 H) 2.57 (dd, *J*=13.58, 7.17 Hz, 1 H) 2.91 (d, *J*=14.04 Hz, 1 H) 2.97 - 3.03 (m, 1 H) 4.02 (s, 3 H) 4.11 (dd, *J*=12.21, 3.36 Hz, 1 H) 4.29 - 4.35 (m, 2 H) 4.60 (dd, *J*=10.22, 7.17 Hz, 1 H) 5.15 (dd, *J*=10.38, 1.53 Hz, 1 H) 5.33 (d, *J*=17.09 Hz, 1 H) 5.73 - 5.83 (m, 1 H) 5.87 (s, 1 H) 7.54 (s, 1 H) 7.55 (s, 1 H)

7.66 (dd, *J*=8.85, 2.14 Hz, 1 H) 7.82 (d, *J*=1.83 Hz, 1 H) 8.04 (s, 1 H) 8.08 (d, *J*=8.85 Hz, 1 H) 8.23 (s, 1 H) 9.23 (s, 1 H); LC-MS, MS *m/z* 794 ($M^+ + H$).

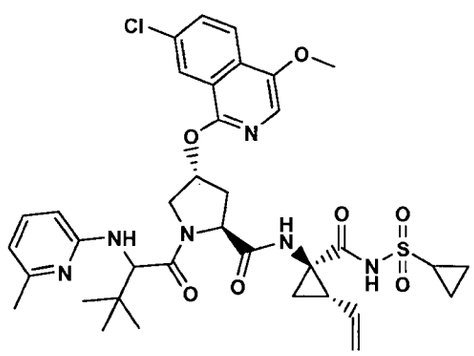
Compound 27B: ^{1}H NMR (500 MHz, CD_3OD) δ ppm 0.97 (s, 9 H) 1.04 - 1.12 (m, 2 H) 1.21 - 1.28 (m, 2 H) 1.40 (dd, *J*=9.46, 5.19 Hz, 1 H) 1.91 (dd, *J*=8.09, 5.34 Hz, 1 H) 2.30 (q, *J*=8.65 Hz, 1 H) 2.38 (ddd, *J*=13.81, 9.84, 4.12 Hz, 1 H) 2.65 (dd, *J*=13.89, 7.17 Hz, 1 H) 2.87 - 2.98 (m, 1 H) 4.04 (s, 3 H) 4.09 (dd, *J*=12.21, 3.36 Hz, 1 H) 4.46 (s, 1 H) 4.55 (d, *J*=12.21 Hz, 1 H) 4.65 (dd, *J*=9.46, 7.32 Hz, 1 H) 5.16 (d, *J*=10.38 Hz, 1 H) 5.36 (d, *J*=17.40 Hz, 1 H) 5.76 - 5.85 (m, 1 H) 5.89 (s, 1 H) 7.63 (s, 1 H) 7.75 (dd, *J*=8.85, 2.14 Hz, 1 H) 7.78 (s, 1 H) 8.05 (d, *J*=1.83 Hz, 1 H) 8.15 (d, *J*=9.16 Hz, 1 H) 8.19 (s, 1 H) 8.37 (s, 1 H) 9.56 (s, 1 H); LC-MS, MS *m/z* 794 ($M^+ + H$).

Compound 28 Isomers:

3-methyl-N-(6-methyl-2-pyridinyl)-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and

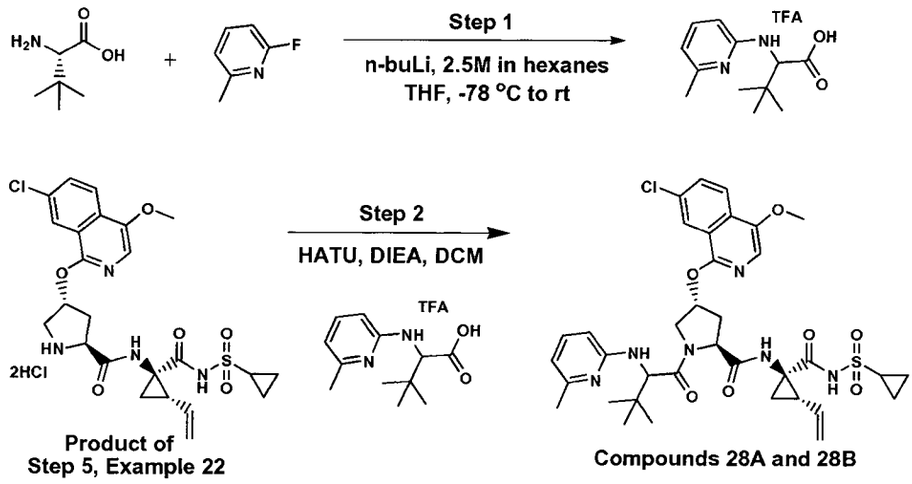
3-methyl-N-(6-methyl-2-pyridinyl)-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 28: Preparation of Compounds 28A and 28B



Compounds 28A and 28B

Scheme 1



Step 1:

L-tert-leucine (0.734 g, 5.60 mmol) was suspended with stirring in dry THF (10 mL). The suspension was cooled to -78 °C, and n-buLi, 2.5M in hexanes (4.48 mL, 11.2 mmol) was added dropwise. The yellow mixture was stirred at -78 °C for 30 min, then the cold bath was removed and the suspension was allowed to warm to rt for 25 min. The mixture was again cooled to -78 °C, and 2-fluoro-6-methylpyridine (0.311 g, 2.80 mmol) was added dropwise. The color changed from yellow to deep orange and finally brown over time. The cold bath was removed and the mixture was stirred at rt overnight. The crude mixture was poured into rapidly stirred saturated aqueous ammonium chloride solution (100 mL) and EtOAc (50 mL) was added. The phases were separated, and the aqueous phase was extracted with EtOAc (2 x 50 mL). The aqueous phase had to be saturated with NaCl and extracted with DCM (4 x 100 mL) to remove the product. The organics were combined and concentrated *in* vacuo to a residue. Purification of the residue by reverse phase preparative HPLC gave the product as a sticky yellow oil (0.279 g, 44.8% yield) TFA salt. ^{1}H NMR (300 MHz, CHLOROFORM-D) δ ppm 1.02 (s, 9 H) 2.49 (s, 3 H) 3.94 (s, 1 H) 3.96 - 4.16 (m, 1 H) 6.54 (d, *J*=7.32 Hz, 1 H) 6.70 (d, *J*=8.78 Hz, 1 H) 7.63 - 7.73 (m, 1 H); LC-MS, MS *m/z* 223 (M^+ + H).

Step 2:

A mixture of the product of Step 1, Example 28, (0.111 g, 0.329 mmol), the product of Step 5, Example 22, (0.200 g, 0.329 mmol) and HATU (0.163 g, 0.428 mmol) suspended in DCM (2 mL) was treated with NMM (0.167 g, 1.65 mmol). The mixture was stirred at room temperature for 20 hours. The solvent was removed by concentrating under a stream of nitrogen, and the crude mixture was purified by reverse phase preparative HPLC. Compound 28A (0.0916 g, 28.8% yield) was the first of two isomers to elute from the preparative HPLC column and was isolated as as an off-white powder bis-TFA salt. Compound 28B (0.0353 g, 11.1% yield) was the second of two isomers to elute from the preparative HPLC column and was also isolated as as an off-white powder bis-TFA salt.

Compound 28A: ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.09 - 1.14 (m, 2 H) 1.15 (s, 9 H) 1.25 - 1.30 (m, 2 H) 1.46 (dd, *J*=9.46, 5.49 Hz, 1 H) 1.94 (dd, *J*=8.24, 5.49 Hz, 1 H) 2.25 - 2.37 (m, 2 H) 2.45 (s, 3 H) 2.66 (dd, *J*=13.89, 7.17 Hz, 1 H) 2.99 (ddd, *J*=12.82, 8.09, 4.73 Hz, 1 H) 4.05 (s, 3 H) 4.09 (dd, *J*=12.21, 3.36 Hz, 1 H) 4.40 (d, *J*=11.90 Hz, 1 H) 4.53 (s, 1 H) 4.69 (dd, *J*=10.07, 7.32 Hz, 1 H) 5.17 (dd, *J*=10.38, 1.53 Hz, 1 H) 5.34 (dd, *J*=17.24, 1.37 Hz, 1 H) 5.77 (ddd, *J*=17.17, 10.15, 9.00 Hz, 1 H) 5.92 (s, 1 H) 6.67 (d, *J*=7.32 Hz, 1 H) 6.77 (d, *J*=8.85 Hz, 1 H) 7.43 (dd, *J*=9.00, 7.48 Hz, 1 H) 7.64 (s, 1 H) 7.71 (dd, *J*=8.85, 2.14 Hz, 1 H) 7.90 (d, *J*=1.83 Hz, 1 H) 8.13 (d, *J*=8.85 Hz, 1 H); LC-MS, MS *m/z* 740 (M^+ + H).

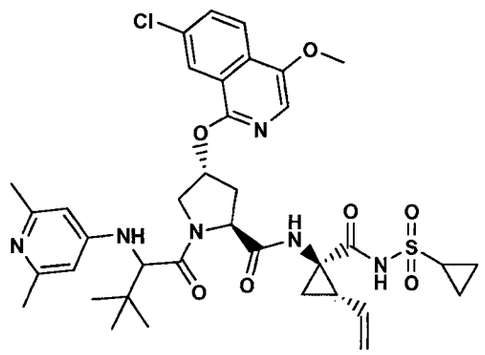
Compound 28B: ^{1}H NMR (500 MHz, CD_3OD) δ ppm 0.97 (s, 9 H) 1.03 - 1.12 (m, 2 H) 1.13 - 1.20 (m, 1 H) 1.22 - 1.29 (m, 1 H) 1.41 (dd, *J*=9.46, 5.19 Hz, 1 H) 1.91 (dd, *J*=8.24, 5.19 Hz, 1 H) 2.31 (q, *J*=8.75 Hz, 1 H) 2.43 (ddd, *J*=13.96, 9.54, 4.27 Hz, 1 H) 2.54 (s, 3 H) 2.69 (dd, *J*=14.04, 7.32 Hz, 1 H) 2.86 - 2.96 (m, 2 H) 4.04 (s, 3 H) 4.20 (dd, *J*=12.21, 3.36 Hz, 1 H) 4.50 (d, *J*=11.90 Hz, 1 H) 4.65 - 4.71 (m, 2 H) 5.13 - 5.19 (m, 1 H) 5.36 (dd, *J*=17.24, 1.37 Hz, 1 H) 5.79 (ddd, *J*=17.24, 10.22, 8.85 Hz, 1 H) 5.92 (s, 1 H) 6.84 (d, *J*=7.32 Hz, 1 H) 7.06 (d, *J*=8.85 Hz, 1 H) 7.63 (s, 1 H) 7.76 (dd, *J*=9.16, 2.14 Hz, 1 H) 7.96 (dd, *J*=8.85, 7.32 Hz, 1 H) 8.06 (d, *J*=2.14 Hz, 1 H) 8.16 (d, *J*=8.85 Hz, 1 H) 9.56 (s, 1 H); LC-MS, MS *m/z* 740 (M^+ + H).

Compound 29 Isomers:

N-(2,6-dimethyl-4-pyridinyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and

N-(2,6-dimethyl-4-pyridinyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 29: Preparation of Compounds 29A and 29B



Compounds 29A and 29B

Compounds 29A and 29B were prepared by a similar procedure as that described for the preparation of compound 25, except 4-bromo-2,6-dimethylpyridine 1.06 hydrobromide (0.980 g, 3.61 mmol) was used in place of 5-bromo-3-picoline in Step 1, and the reaction scales were different. Also, the product from Step 2 was not isolated as the HCl salt but was instead carried on to Step 3 directly as a TFA salt. Two isomeric compounds were isolated from Step 3: the first isomer to elute from a preparative HPLC column was compound 29A (0.127 g) isolated as a white solid bis-TFA salt, and the second isomer to elute from the preparative HPLC column was compound 29B (0.103 g) isolated as a white solid bis TFA salt. The combined yield for both compounds 29A and 29B was 47.8% over three steps.

Product of Step 1, Example 29: Light brown waxy solid; ^{1}H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.04 (s, 9 H) 1.43 (s, 9 H) 2.37 (s, 6 H) 3.71 (d, *J*=9.77 Hz, 1 H) 4.46 (d, *J*=9.77 Hz, 1 H) 6.20 (s, 2 H); LC-MS, MS *m/z* 293 (M^+ + H).

Product of Step 2, Example 29: Brown glassy solid; ^{1}H NMR (500 MHz, DMSO-D_6) δ ppm 1.03 (s, 9 H) 2.38 (s, 3 H) 2.42 (s, 3 H) 4.17 (d, *J*=9.77 Hz, 1 H) 6.79 (s, 1 H) 6.88 (s, 1 H) 8.23 (d, *J*=9.77 Hz, 1 H) 13.11 (s, 1 H); LC-MS, MS *m/z* 237 (M^+ + H).

Compound 29A: ^{1}H NMR (500 MHz, CD_3OD) δ ppm 0.99 (s, 1 H) 1.05 (s, 9 H) 1.07 - 1.13 (m, 2 H) 1.21 - 1.27 (m, 2 H) 1.42 (dd, *J*=9.61, 5.34 Hz, 1 H) 1.46 (s, 1 H) 1.90 (dd, *J*=8.09, 5.34 Hz, 1 H) 2.12 (s, 3 H) 2.21 - 2.29 (m, 2 H) 2.31 (s, 3 H) 2.60 (dd, *J*=13.89, 7.48 Hz, 1 H) 2.92 - 3.00 (m, 1 H) 4.01 (s, 3 H) 4.24 (d, *J*=11.60 Hz, 1 H) 4.35 (d, *J*=9.77 Hz, 1 H) 4.66 (dd, *J*=10.07, 7.32 Hz, 1 H) 5.13 (dd, *J*=10.38, 1.53 Hz, 1 H) 5.31 (dd, *J*=17.09, 1.22 Hz, 1 H) 5.74 (ddd, *J*=17.17, 10.15, 9.00 Hz, 1 H) 5.87 (s, 1 H) 6.49 (d, *J*=13.12 Hz, 2 H) 7.58 (s, 1 H) 7.66 (dd, *J*=8.85, 2.14 Hz, 1 H) 7.80 (d, *J*=1.83 Hz, 1 H) 7.92 (d, *J*=9.77 Hz, 1 H) 8.07 (d, *J*=8.85 Hz, 1 H) 9.22 (s, 1 H); LC-MS, MS *m/z* 754 (M^+ + H).

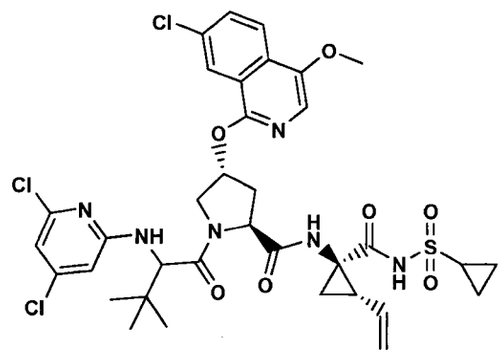
Compound 29B: ^{1}H NMR (500 MHz, CD_3OD) δ ppm 0.92 (s, 9 H) 1.03 - 1.11 (m, 2 H) 1.19 - 1.26 (m, 2 H) 1.39 (dd, *J*=9.46, 5.49 Hz, 1 H) 1.88 (dd, *J*=8.24, 5.19 Hz, 1 H) 2.28 (q, *J*=8.95 Hz, 1 H) 2.36 (ddd, *J*=14.04, 9.77, 4.27 Hz, 1 H) 2.44 (br s, 6 H) 2.63 (dd, *J*=14.04, 7.32 Hz, 1 H) 2.93 (ddd, *J*=12.74, 8.01, 4.58 Hz, 1 H) 4.01 (s, 3 H) 4.06 (dd, *J*=12.21, 3.36 Hz, 1 H) 4.47 (d, *J*=12.21 Hz, 1 H) 4.52 (d, *J*=9.16 Hz, 1 H) 4.63 (dd, *J*=9.77, 7.32 Hz, 1 H) 5.13 (dd, *J*=10.38, 1.53 Hz, 1 H) 5.33 (dd, *J*=17.09, 1.53 Hz, 1 H) 5.78 (ddd, *J*=17.09, 10.38, 8.85 Hz, 1 H) 5.87 (s, 1 H) 6.71 (br s, 1 H) 6.87 (br s, 1 H) 7.14 (d, *J*=9.16 Hz, 1 H) 7.58 (s, 1 H) 7.72 (dd, *J*=8.85, 2.14 Hz, 1 H) 8.01 (d, *J*=2.14 Hz, 1 H) 8.12 (d, *J*=9.16 Hz, 1 H) 9.54 (s, 1 H); LC-MS, MS *m/z* 754 (M^+ + H).

Compound 32 Isomers:

N-(4,6-dichloro-2-pyridinyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and

N-(4,6-dichloro-2-pyridinyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 32: Preparation of Compounds 32A and 32B



Compounds 32A and 32B

Compounds 32A and 32B were prepared by a similar procedure as that described for the preparation of compound 7, except 2,4,6-trichloropyridine (0.658 g, 3.61 mmol) was used in place of 2-chloropyridine in Step 1, and the reaction scales were different. Also, in Step 3, the product from Step 5, Example 22, was used in place of the product of Step 5, Example 1. Two isomeric compounds were isolated from Step 3: the first isomer to elute from a preparative HPLC column was compound 32A (0.0783 g) isolated as an off-white solid bis-TFA salt, and the second isomer to elute from the preparative HPLC column was compound 32B (0.0207 g) isolated as an off-white solid bis TFA salt. The combined yield for both compounds 32A and 32B was 5.8% over three steps.

Product of Step 1, Example 32: Yellow oil; ^{1}H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.03 (s, 9 H) 1.46 (s, 9 H) 4.10 (d, *J*=8.85 Hz, 1 H) 5.13 (d, *J*=9.16 Hz, 1 H) 6.33 (d, *J*=1.22 Hz, 1 H) 6.60 (d, *J*=1.22 Hz, 1 H); LC-MS, MS *m/z* 334 (M^+ + H).

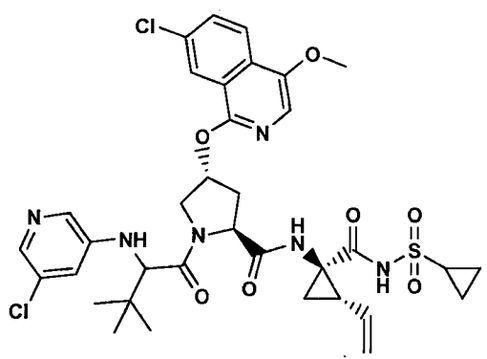
Product of Step 2, Example 32: Sticky brown oil; LC-MS, MS *m/z* 278 (M^+ + H).

Compound 32A: ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.04 - 1.08 (m, 2 H) 1.09 (s, 9 H) 1.21 - 1.29 (m, 2 H) 1.41 (dd, *J*=9.61, 5.34 Hz, 1 H) 1.87 (dd, *J*=8.09, 5.34 Hz, 1 H) 2.19 - 2.31 (m, 2 H) 2.54 (dd, *J*=13.58, 6.87 Hz, 1 H) 2.92 - 2.98 (m, *J*=8.09, 8.09, 4.73, 4.73 Hz, 1 H) 4.00 (s, 3 H) 4.12 (dd, *J*=11.75, 3.81 Hz, 1 H) 4.53 (dd, *J*=10.53, 6.87 Hz, 1 H) 4.68 (d, *J*=11.60 Hz, 1 H) 4.72 (s, 1 H) 5.11 (dd, *J*=10.22, 1.68 Hz, 1 H) 5.28 (dd, *J*=17.24, 1.37 Hz, 1 H) 5.74 (ddd, *J*=17.09, 10.22, 9.00 Hz, 1 H) 5.88 (t, *J*=3.36 Hz, 1 H) 6.26 (d, *J*=1.22 Hz, 1 H) 6.48 (d, *J*=1.22 Hz, 1

H) 7.54 (s, 1 H) 7.64 (dd, *J*=8.85, 2.14 Hz, 1 H) 7.82 (d, *J*=2.14 Hz, 1 H) 8.05 (d, *J*=8.85 Hz, 1 H) 9.14 (s, 1 H); LC-MS, MS *m/z* 795 (M^+ + H).

Compound 32B: ^{1}H NMR (500 MHz, CD_3OD) δ ppm 0.90 (s, 9 H) 0.97 - 1.11 (m, 3 H) 1.26 - 1.37 (m, 2 H) 1.85 (dd, *J*=8.24, 5.19 Hz, 1 H) 2.23 (q, *J*=8.95 Hz, 1 H) 2.35 (ddd, *J*=13.96, 9.84, 4.27 Hz, 1 H) 2.58 (dd, *J*=13.73, 7.32 Hz, 1 H) 2.81 - 2.88 (m, 1 H) 4.01 (s, 3 H) 4.23 (dd, *J*=12.05, 3.51 Hz, 1 H) 4.38 (d, *J*=12.21 Hz, 1 H) 4.56 (dd, *J*=9.92, 7.17 Hz, 1 H) 4.90 (s, 1 H) 5.12 (dd, *J*=10.22, 1.68 Hz, 1 H) 5.31 (dd, *J*=17.24, 1.37 Hz, 1 H) 5.77 (ddd, *J*=17.09, 10.38, 8.85 Hz, 1 H) 5.83 (s, 1 H) 6.56 (d, *J*=1.53 Hz, 1 H) 6.58 (d, *J*=1.53 Hz, 1 H) 7.61 (s, 1 H) 7.71 (dd, *J*=8.85, 2.14 Hz, 1 H) 8.02 (d, *J*=2.14 Hz, 1 H) 8.11 (d, *J*=8.85 Hz, 1 H) 9.35 (s, 1 H); LC-MS, MS *m/z* 795 (M^+ + H).

Example 33: Preparation of Compound 33: N-(5-chloro-3-pyridinyl)-3-methylvalyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide



Compound 33

Compound 33 was prepared by a similar procedure as that described for the preparation of compound 7, except 3,5-dichloropyridine (0.534 g, 3.61 mmol) was used in place of 2-chloropyridine in Step 1, and the reaction scales were different. Also, in Step 3, the product from Step 5, Example 22, was used in place of the product of Step 5, Example 1. Compound 33 (0.187 g, 9.0% yield over 3 steps) was isolated as a beige solid bis TFA salt.

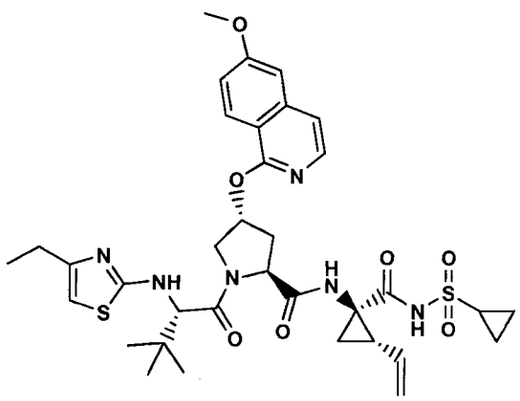
Product of Step 1, Example 33: Yellow oil; ^{1}H NMR (500 MHz, CHLOROFORM-D) δ ppm 1.06 (s, 9 H) 1.44 (s, 9 H) 3.61 (d, *J*=10.07 Hz, 1 H) 4.30

(d, *J*=10.07 Hz, 1 H) 6.91 (t, *J*=2.29 Hz, 1 H) 7.92 (d, *J*=1.83 Hz, 1 H) 7.95 (d, *J*=2.44 Hz, 1 H); LC-MS, MS *m/z* 299 (M^+ + H).

Product of Step 2, Example 33: Sticky brown oil; LC-MS, MS *m/z* 243 (M^+ + H).

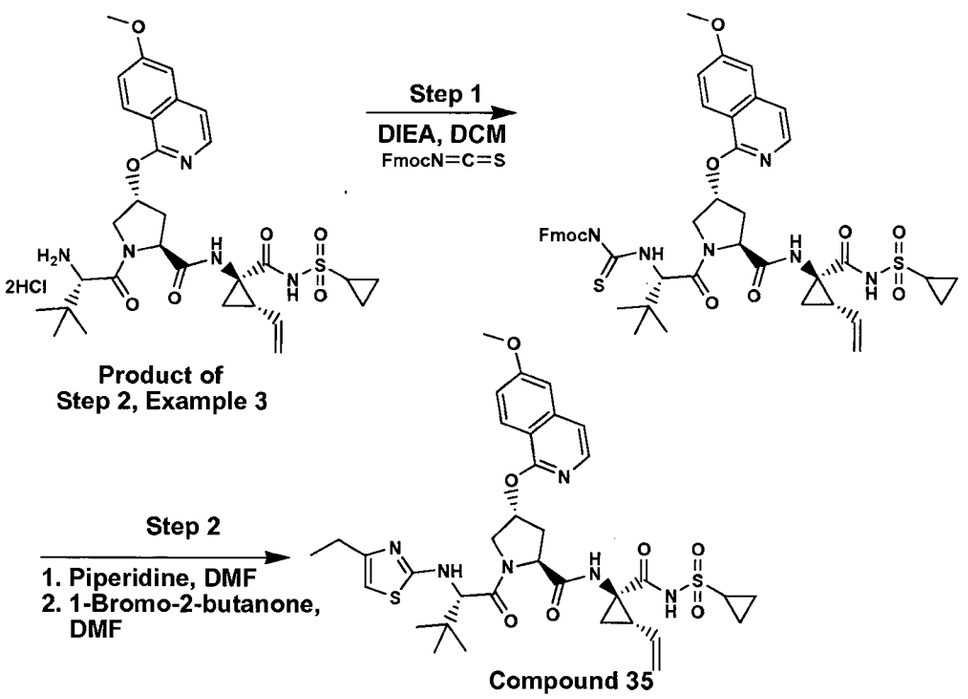
Compound 33: ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.03 - 1.08 (m, 2 H) 1.09 (s, 9 H) 1.22 - 1.27 (m, 2 H) 1.42 (ddd, *J*=9.54, 5.42, 0.92 Hz, 1 H) 1.89 (dd, *J*=8.24, 5.49 Hz, 1 H) 2.19 - 2.29 (m, 2 H) 2.56 (dd, *J*=13.73, 7.02 Hz, 1 H) 2.92 - 2.99 (m, 1 H) 3.96 - 4.05 (m, 4 H) 4.21 (s, 1 H) 4.29 (d, *J*=12.21 Hz, 1 H) 4.60 (dd, *J*=10.22, 7.17 Hz, 1 H) 5.12 (dd, *J*=10.38, 1.53 Hz, 1 H) 5.30 (dd, *J*=17.09, 1.53 Hz, 1 H) 5.74 (ddd, *J*=17.09, 10.38, 8.85 Hz, 1 H) 5.84 (s, 1 H) 7.33 (s, 1 H) 7.54 (s, 1 H) 7.65 (dd, *J*=8.85, 2.14 Hz, 1 H) 7.72 (s, 1 H) 7.81 (d, *J*=1.83 Hz, 1 H) 7.94 (s, 1 H) 8.07 (d, *J*=8.85 Hz, 1 H) 9.20 (s, 1 H); ; LC-MS, MS *m/z* 760 (M^+ + H).

Example 35: Preparation of Compound 35: N-(4-ethyl-1,3-thiazol-2-yl)-3-methyl-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide



Compounds 35

Scheme 1



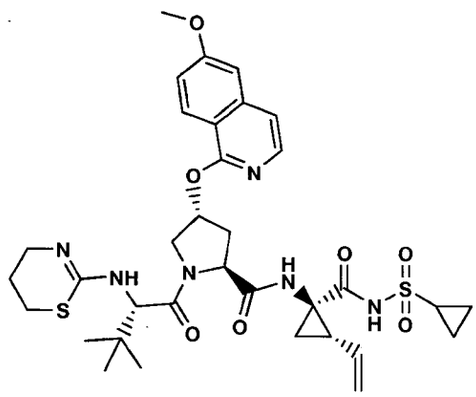
Step 1:

To a solution mixture of product of step 2, Example 3 (1.5g, 2.18 mmol) and DIEA (0.707 g, 5.46 mmol) in DCM (20 mL) was added Fmoc-thioisocyanate (0.799, 2.84 mmol). Reaction mixture was stirred at for 48 h. Reaction was not completed as determined by LC/MS, then was added more Fmoc-thioisocyanate (0.307 g, 1.09 mmol). Reaction mixture was allowed to stir at rt for an additional 24 h. White solid precipitation by-product was removed by vacuum filtration and washed with EtOAc. The liquid filtrate was concentrated, the resulting residue redissolved in EtOAc (100 mL) and washed with 2 x 25 mL H_2O. The aqueous layers were combined and extracted with EtOAc (50 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to a yellow solid. More un-identified by-products were removed by trituration with EtOAc, chilled to 0 °C; solid precipitation was filtered and discared. The liquid filtration was concentrated and residue was purified through a column of SiO_2 which was eluted with 3:1, 1:1 then 1:3 hexanes:EtOAc to give the product of step 1, Example 35 (0.798 g, 41% yield) as a light yellow foarmy solid. LC-MS, MS *m/z* 895 (M^+ + H).

Step 2:

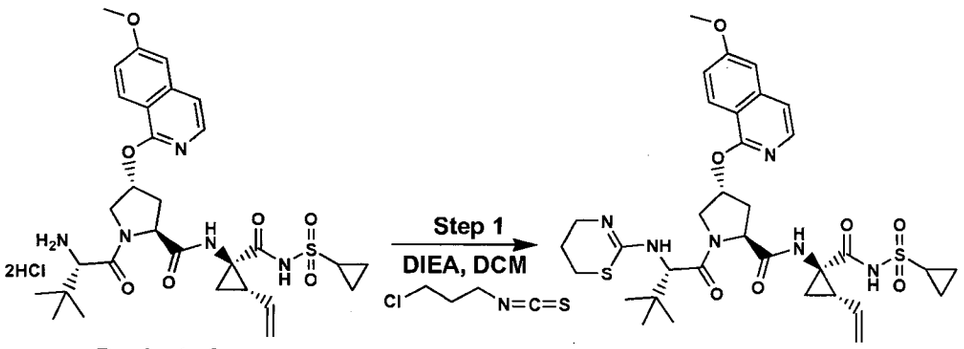
To a yellow solution of the product form step 1, Example 35 (0.489 g, 0.546 mmol) in DMF (4 mL) was added piperidine (1 mL). Reaction was stirred at rt. After 5h solvent was removed under vaccuo and dried to give a solid glassy crude product which was taken up in DMF (5 mL) and treated with 1-bromo-2-butanone (0.275 g, 1.64 mmol). Reaction mixture was stirred at rt overnight. After 14h, solvent was removed under vacuo to give viscous red oil which was redissolved in MeOH and filtered to remove brown gel like substance. The liquid filtrated was concentrated and remaining residue was purified br reversed phase HPLC to give Example 35 (139.7, 35% yield) as a light yellow solid. ^{1}H NMR (500 MHz) δ ppm 0.81 (t, *J*=7.5 Hz, 3 H), 1.06 - 1.12 (m, 3 H), 1.14 (s, 9 H), 1.25 - 1.30 (m, 2 H), 1.46 (dd, *J*=9.6, 5.3 Hz, 1 H), 1.91 (dd, *J*=8.1, 5.3 Hz, 1 H), 1.93 - 1.97 (m, 1 H), 1.99 - 2.07 (m, 1 H), 2.23 - 2.29 (m, 1 H), 2.30 - 2.36 (m, 1 H), 2.59 (dd, *J*=13.4, 6.7 Hz, 1 H), 3.96 (s, 3 H), 4.15 (dd, *J*=11.7, 3.8 Hz, 1 H), 4.46 (s, 1 H), 4.57 (dd, *J*=10.5, 6.9 Hz, 1 H), 4.68 (d, *J*=11.6 Hz, 1 H), 5.15 (d, *J*=10.4 Hz, 1 H), 5.32 (d, *J*=17.1 Hz, 1 H), 5.75 (s, 1 H), 5.76 - 5.82 (m, 1 H), 5.90 (s, 1 H), 7.09 (dd, *J*=8.9, 2.4 Hz, 1 H), 7.23 (d, *J*=2.4 Hz, 1 H), 7.29 (d, *J*=5.8 Hz, 1 H), 7.89 (d, *J*=9.2 Hz, 1 H), 7.93 (d, *J*=6.1 Hz, 1 H). LC-MS, MS *m/z* 725 (M^+ + H).

Example 36: Preparation of Compound 36: N-(5,6-dihydro-4H-1,3-thiazin-2-yl)-3-methyl-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide



Compound 36

Scheme 1



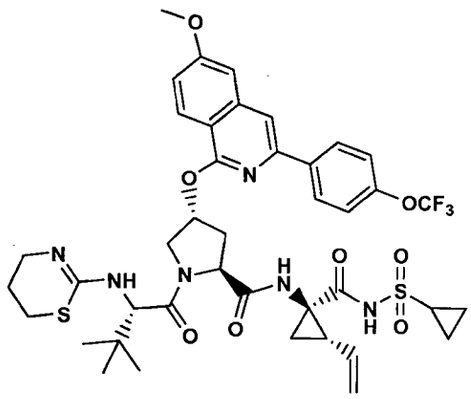
Product of Step 2, Example 3 **Compound 36**

Step 1:

To a solution mixture of the product of step 2, example 3 (0.267 g, 0.389 mmol) and DIEA (0.101 g, 0.778 mmol) in DCM (4 mL) was added 3-chloropropyl isothiocyanate (0.053 g, 0.389 mmol) and heated to 45 °C. After 3 h, solvent was removed and residue was redissolved in hot EtOAc with minimal DCM, Et_2O was added to effect light green precipitation which was obtained by filtration. Product was purified by reversed phase HPLC to give Example 36 (0.166 g, 54%) as light yellow bis-HCl salt solid. ^{1}H NMR (500 MHz, *CD_3OD*) δ ppm 1.12 (s, 9 H), 1.24 - 1.28 (m, 3 H), 1.47 (dd, *J*=9.5, 5.5 Hz, 1 H), 1.94 (dd, *J*=8.2, 5.5 Hz, 1 H), 2.27 - 2.38 (m, 2 H), 2.70 (dd, *J*=13.7, 7.0 Hz, 1 H), 2.94 - 3.01 (m, 1 H), 3.97 (s, 3 H), 4.05 - 4.10 (m, 1 H), 4.12 (q, *J*=7.3 Hz, 1 H), 4.39 (d, *J*=11.9 Hz, 1 H), 4.73 (dd, *J*=10.2, 7.5 Hz, 1 H), 5.17 (dd, *J*=10.4, 1.5 Hz, 1 H), 5.35 (d, *J*=17.1 Hz, 1 H), 5.74 - 5.83 (m, 1 H), 5.91 (s, 1 H), 7.26 (dd, *J*=9.2, 2.4 Hz, 1 H), 7.30 (d, *J*=2.1 Hz, 1 H), 7.35 (d, *J*=6.1 Hz, 1 H), 7.97 (d, *J*=5.8 Hz, 1 H), 8.11 (d, *J*=9.2 Hz, 1 H). LC-MS, MS *m/z* 713 (M^+ + H).

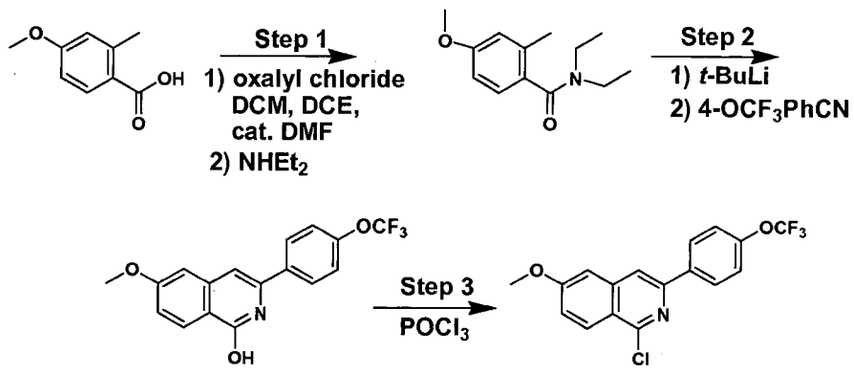
Example 37: Preparation of Compound 37: N-(5,6-dihydro-4H-1,3-thiazin-2-yl)-3-methyl-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-3-(4-(trifluoromethoxy)phenyl)-1-isoquinolinyl)oxy)-L-prolinamide

000156



Compound 37

Scheme 1



Step 1:

A mixture of 4-methoxy-2-methyl-benzoic acid (25.3 g, 152 mmol) in 1:1 DCM:DCE was treated with oxalyl chloride (38.6 g, 304 mmol), followed by addition of DMF (0.111 g, 1.50 mmol). Vigorous gas evolution ensued, and the reaction eventually became clear after 1 h. The volatiles were removed *in vacuo* and the white solid residue was placed under high vacuum for 2 h. The crude material was redissolved in DCM (200 mL) and the mixture was cooled to 0 °C. Diethylamine (22.8 g, 312 mmol) was added dropwise with stirring. The mixture was allowed to warm to rt for 1 h with stirring. The mixture was concentrated *in vacuo* to approximately 1/3 volume, and Et_2O (300 mL) was added and the mixture was chilled. The solid precipitate which had formed was removed by filtration. The filtrate was concentrated to give a viscous brown oil which was redissolved in DCM

(200 mL) and washed with 0.1M HCl (2 x 50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the desired product (33.1 g, 98% yield). LC-MS, MS *m/z* 222 (M^++H).

Step 2:

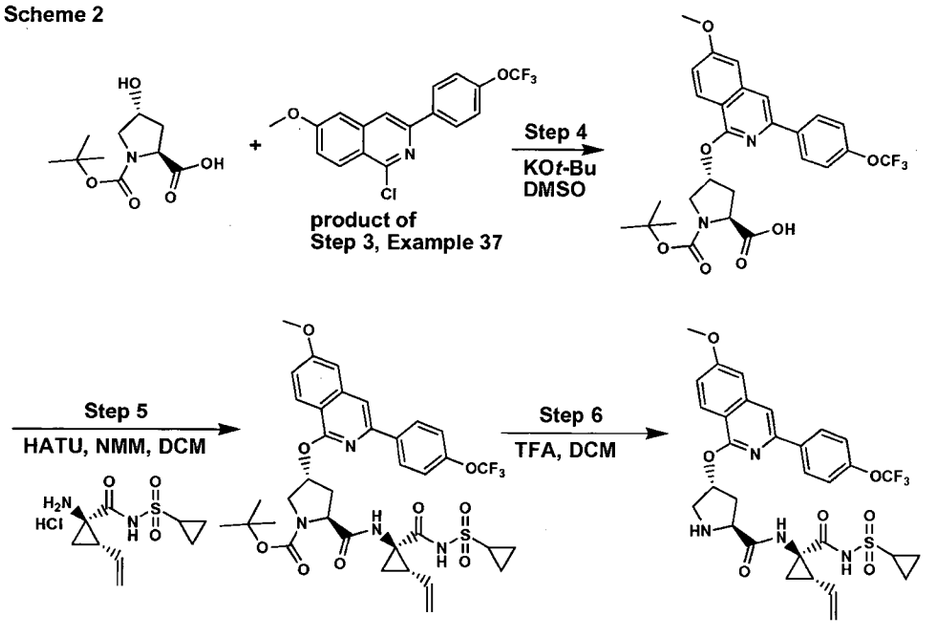
To a stirred solution of N,N-diethyl-4-methoxy-2-methyl-benzamide (10.0 g, 45.2 mmol) in THF (150 mL) at –78 °C under nitrogen atmosphere was added *t*-BuLi (29.2 mL of 1.7M in pentane, 49.7 mmol) dropwise. The resulting red solution was kept at this temperature for additional 10 min before dropwise addition of 4-(trifluoromethoxy)-benzonitrile (9.49 g, 49.7 mmol). The brown solution was stirred at -78 °C for 2 h; tests by LCMS showed incomplete reaction. Thus to the mixture was added an additional amount of 4-(trifluoromethoxy)-benzonitrile (3.38 g, 18.1 mmol) and the resulting mixture was stirred for an additional 1 h. The mixture was then allowed to warm to rt and was quenched by pouring into aqueous 1.0M HCl (50 mL). EtOAc (100 mL) was added and the mixture was shaken and phases were separated. A precipitate occurred within the EtOAc phase which was isolated by filtration and allowed to dry (3.0 g). This 3.0 g of isolated solid was determined to be impure product and was set aside for later purification. The EtOAc filtrate was set aside. The aqueous acid washes were combined and extracted with DCM (3 x 100 mL). The DCM extracts were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. This residue was combined with the original EtOAc filtrate and the combined organics were concentrated to a slurry. A solid was isolated by filtration to give the desired product (8.84 g, 58.0% yield). LC-MS, MS *m/z* 336 (M^++H).

Step 3:

The solid product from Step 2, Example 37 (8.84 g, 26.4 mmol) was dissolved in $POCl_3$ (100 mL) and the mixture was heated to reflux for 3 h. The mixture was concentrated *in vacuo*, and to the resulting residue was added water (100 mL) and EtOAc (100 mL). The rapidly stirred mixture was treated slowly with solid sodium bicarbonate until pH = 7 was reached. The phases were separated, and the aqueous phase was extracted with EtOAc (2 x 40 mL). The organic extracts were combined and washed with saturated aqueous sodium bicarbonate (40 mL) and then

with brine (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product (9.21 g, 98.7% yield) was isolated without chromatography as a slightly yellow viscous oil. ^{1}H NMR (500 MHz, CHLOROFORM-D) δ ppm 3.97 (s, 3 H) 7.11 (d, *J*=2.44 Hz, 1 H) 7.26 (dd, *J*=9.46, 2.44 Hz, 1 H) 7.31 (d, *J*=8.85 Hz, 2 H) 7.84 (s, 1 H) 8.10 (d, *J*=8.85 Hz, 2 H) 8.20 (d, *J*=9.46 Hz, 1 H); LC-MS, MS *m/z* 354 (M^++H).

Scheme 2



Step 4:

To a mechanically stirred solution of Boc-Hyp-OH (6.31 g, 27.3 mmol) in DMSO (100 mL) was added solid potassium *tert*-butoxide (8.05 g, 68.2 mmol). The mixture was stirred for 1.5 h, and the product of Step 3, Example 37 (20.0 g, g, 74.2 mmol) was added in two portions over 15 min. The resulting suspension was stirred for 3 h at rt. The suspension was then diluted with a mixture of pH = 4 buffer (500 mL) and 1.0 M HCl (41 mL) and extracted with EtOAc (3 x 150 mL). The organic extracts were combined and washed with pH = 4 buffer (75 mL) and then with brine (50 mL). The organic was then extracted with a mixture of 1.0M NaOH (30 mL) and water (50 mL) twice, and the combined basic extracts were washed with EtOAc (30 mL). The aqueous basic extracts were treated with 1.0M HCl (approximately 60 mL)

until pH = 4 was achieved, and the desired product was then extracted into EtOAc (3 x 100 mL). The extracts were combined, dried over $MgSO_4$ and filtered. The filtrate was evaporated *in vacuo* to dryness to give a foamy solid. The desired product (13.2 g, 92.7% yield) was isolated after purification by silica gel column chromatography (step gradient DCM, then 40:1 DCM:MeOH, then 10:1 DCM:MeOH) as a glassy solid. LC-MS, MS *m/z* 549 (M^++H).

Step 5:

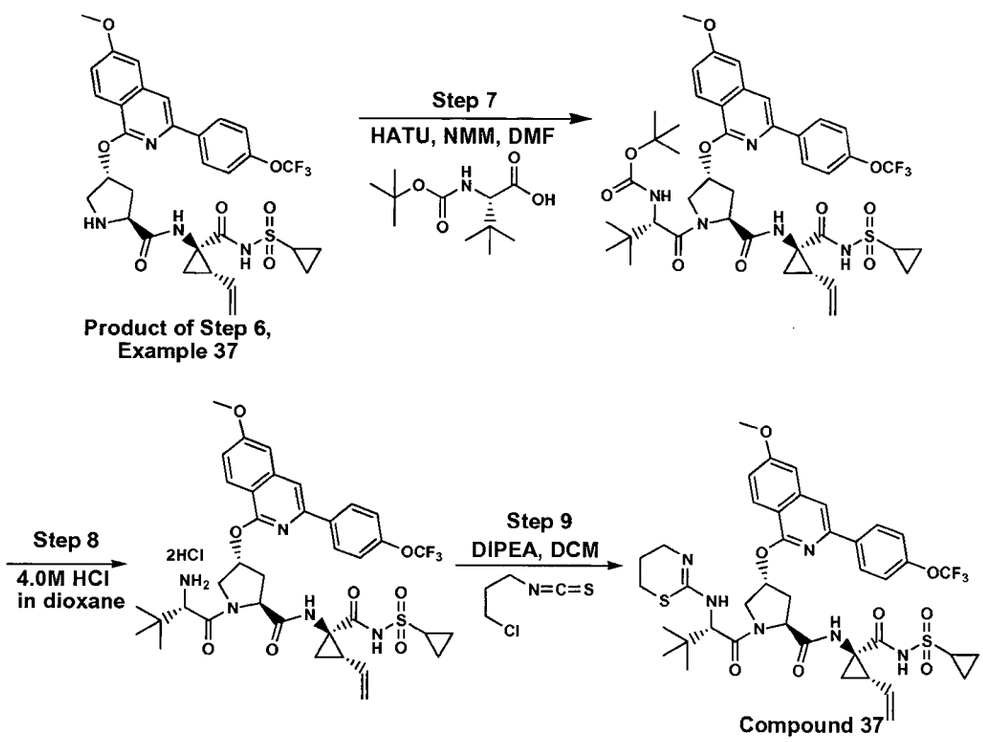
A mixture of the product of Step 4, Example 37 (12.3 g, 22.4 mmol), NMM (6.80 g, 67.3 mmol) and cyclopropanesulfonic acid (1-(*R*)-amino-2-(*S*)-vinyl-cyclopropanecarbonyl)-amide HCl salt (6.28 g, 23.5 mmol) in DCM (250 mL) was treated with HATU (10.23 g, 26.9 mmol), and the resulting solution was stirred at rt overnight. Solvent was removed *in vacuo*, and the residue was taken up in EtOAc (700 mL) and washed with pH = 4 buffer (4 x 200 mL) and with brine (75 mL). The organic was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The product (13.5 g, 79.1% yield) was isolated after purification by silica gel column chromatography (1:1 hexanes:EtOAc) as a white glassy solid. LC-MS, MS *m/z* 761 (M^++H).

Step 6:

To a solution of the product of Step 5, Example 37 (15.0g, 19.6 mmol) in a mixture of DCM (50 mL) and 1,2-DCE (50 mL) was added TFA (100 mL). The mixture was stirred at rt for 1.5 h and was then concentrated *in vacuo*. The residue was determined to be less than 85% pure by LCMS. The crude product (15.1 g) was purified by silica gel column chromatography (step gradient DCM + 0.5% TEA followed by 50 :1 DCM:MeOH + 0.5% TEA followed by 40:1 DCM:MeOH + 0.5% TEA). The pure product fractions were combined to give the desired product (9.13 g, 54% yield) which was determined to have 2.0 equivalents of TEA associated with it. Mixed fractions were combined and concentrated to give 5.27 g of material which was set aside for purification at a later date. ^{1}H NMR (500 MHz, MeOD) δ ppm 0.81 - 0.91 (m, 2 H) 1.02 - 1.13 (m, 2 H) 1.33 (t, *J*=7.32 Hz, 18 H) 1.88 (dd, *J*=7.63, 4.88 Hz, 1 H) 2.11 (dd, 1 H) 2.48 (ddd, *J*=14.19, 9.31, 5.19 Hz, 1 H) 2.77 (dd, *J*=14.34, 7.63 Hz, 1 H) 2.88 (tt, *J*=8.24, 4.88 Hz, 1 H) 3.22 (q, *J*=7.32 Hz, 12 H) 3.66 (d,

J=13.12 Hz, 1 H) 3.79 (dd, *J*=12.97, 4.43 Hz, 1 H) 3.96 (s, 3 H) 4.44 (dd, *J*=9.31, 7.78 Hz, 1 H) 5.03 (dd, *J*=10.38, 1.83 Hz, 1 H) 5.24 (dd, *J*=17.09, 1.83 Hz, 1 H) 5.88 (ddd, *J*=17.17, 10.15, 9.31 Hz, 1 H) 5.99 (t, *J*=4.73 Hz, 1 H) 7.19 (dd, *J*=9.16, 2.44 Hz, 1 H) 7.28 (d, *J*=2.44 Hz, 1 H) 7.38 (d, *J*=8.24 Hz, 2 H) 7.82 (s, 1 H) 8.19 (d, *J*=9.16 Hz, 1 H) 8.22 - 8.27 (m, 2 H); LC-MS, MS *m/z* 661 (M^++H).

Scheme 3



Step 7:

The product of Step 6, Example 37 (6.00 g, 6.95 mmol) was combined with N-Boc-tert-leucine (1.77 g, 7.65 mmol) and HATU (3.17 g, 8.34 mmol) in DCM (75 mL), and the resulting suspension was treated with NMM (1.48 g, 14.6 mmol), and the mixture was stirred at rt for 3 days. The reaction mixture was concentrated *in vacuo* to a residue, redissolved in EtOAc (250 mL) and washed with a 1:1 mixture of pH = 4 buffer and brine (4 x 100 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to a beige foam. Purification by silica gel column chromatography (1:1 hexanes : EtOAc) afforded pure product as an off-white foam (4.62 g, 76.1% yield). LC-MS, MS *m/z* 874 (M^++H).

Step 8:

The product of Step 7, Example 37 (4.61 g, 5.28 mmol) was treated with a mixture of 1,4-dioxane (50 mL) and 4.0M HCl in 1,4-dioxane (50 mL) for 2.5h, resulting in a sticky gel sitting at the bottom of the flask. The mixture was concentrated in vacuo, then the resulting foamy solid was redissolved with DCM (25 mL) and the solution was added dropwise to a rapidly stirred mixture of diethyl ether (100 mL) and 2.0M HCl in ether (100 mL). A white powder precipitated and was isolated by filtration, rinsed with ether and dried under high vacuum. Total recovery was 3.95 g (88.4% yield) of white powder bis HCl salt product. ^{1}H NMR (500 MHz, MeOD) δ ppm 1.09 - 1.15 (m, 2 H) 1.20 (s, 9 H) 1.23 - 1.32 (m, 2 H) 1.46 (dd, *J*=9.46, 5.49 Hz, 1 H) 1.94 (dd, *J*=8.24, 5.49 Hz, 1 H) 2.31 (q, *J*=8.75 Hz, 1 H) 2.42 (ddd, *J*=13.96, 10.15, 4.27 Hz, 1 H) 2.77 (dd, *J*=13.89, 7.17 Hz, 1 H) 2.98 (ddd, *J*=12.67, 8.09, 4.88 Hz, 1 H) 3.99 (s, 3 H) 4.12 (s, 1 H) 4.25 (dd, 1 H) 4.32 (d, 1 H) 4.74 (dd, *J*=10.22, 7.17 Hz, 1 H) 5.17 (dd, *J*=10.68, 1.22 Hz, 1 H) 5.33 (dd, *J*=16.94, 1.07 Hz, 1 H) 5.77 (ddd, *J*=17.17, 10.15, 9.00 Hz, 1 H) 6.15 (s, 1 H) 7.21 (dd, *J*=9.16, 2.44 Hz, 1 H) 7.34 (d, *J*=2.14 Hz, 1 H) 7.40 (d, *J*=8.24 Hz, 2 H) 7.88 (s, 1 H) 8.15 (d, *J*=9.16 Hz, 1 H) 8.29 (d, *J*=8.55 Hz, 2 H) 9.25 (s, 1 H); LC-MS, MS *m/z* 774 (M^++H).

Step 9:

To a mixture of the product of step 8, example 37 (0.271 g, 0.320 mmol) and DIEA (0.083 g, 0.641 mmol) in DCM (5 mL) was added 3-chloropropyl isothiocyanate (0.046 g, 0.336 mmol). The mixture was heated to 45 °C fo 3h then left to stand at rt overnight. The reaction mixture was diluted with DCM (50 mL) and washed with 0.1N HCl (3 mL). The aqueous layer was extracted with DCM (25 mL) and the combined organic layer was washed with 10% aqueous Na_2CO_3 (3 mL), brine, dried over $MgSO_4$ and concentrated to a yellow foam solid. The product was purified by reverse phase preparative HPLC to give Compound 37 as light yellow bis-HCl salt solid. ^{1}H NMR (500 MHz, *MeOD*) δ ppm 1.11 (s, 9 H), 1.15 (d, *J*=1.8 Hz, 1 H), 1.22 - 1.29 (m, 2 H), 1.45 - 1.51 (m, 1 H), 1.78 - 1.87 (m, *J*=8.9 Hz, 1 H), 1.91 - 1.98 (m, 2 H), 2.31 (q, *J*=8.6 Hz, 1 H), 2.37 - 2.45 (m, 1 H), 2.70 - 2.84 (m, 2 H), 2.93 - 3.01 (m, 1 H), 3.98 - 4.02 (m, *J*=1.5 Hz, 3 H), 4.18 (d, *J*=11.3 Hz, 1 H),

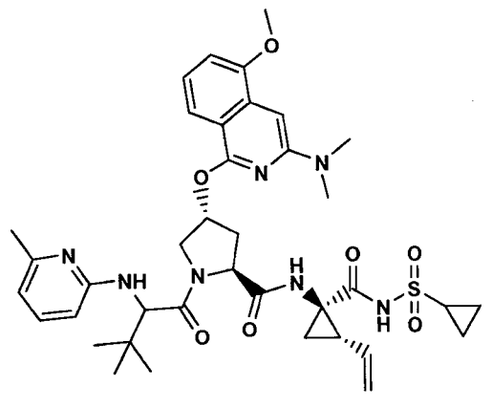
4.28 (s, 1 H), 4.34 - 4.42 (m, 1 H), 4.71 - 4.78 (m, 1 H), 5.17 (d, *J*=10.4 Hz, 1 H), 5.35 (d, *J*=17.1 Hz, 1 H), 5.75 - 5.83 (m, 1 H), 6.15 (s, 1 H), 7.24 (d, *J*=9.2 Hz, 1 H), 7.37 (s, 1 H), 7.42 (d, *J*=7.9 Hz, 1 H), 7.91 (s, 1 H), 8.10 (d, *J*=9.2 Hz, 1 H), 8.31 (dd, *J*=8.9, 1.8 Hz, 2 H); LC-MS, MS *m/z* 873 ($M^+ + H$).

Compound 38 Isomers:

3-methyl-N-(6-methyl-2-pyridinyl)-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((3-(dimethylamino)-5-methoxy-1-isoquinolinyl)oxy)-L-prolinamide and

3-methyl-N-(6-methyl-2-pyridinyl)-D-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((3-(dimethylamino)-5-methoxy-1-isoquinolinyl)oxy)-L-prolinamide

Example 38: Preparation of Compounds 38A and 38B



Compounds 38A and 38B

Compounds 38A and 38B were prepared by a similar procedure as that described for the preparation of compound 17, but with the following exceptions: In Step 1, 3-methoxy-2-methylbenzoic acid was used in place of 4-methoxy-2-methylbenzoic acid. In Step 2, LDA was replaced with KHMDS. And in Step 7, the product of step 1, example 28 was used in place of commercially available 2-(4,6-dimethylpyridin-2-ylamino)-3-methyl butanoic acid. Two isomeric compounds were isolated from Step 7: the first isomer to elute from a preparative HPLC column was compound 38A, and the second isomer to elute from the preparative HPLC column was compound 38B.

Product of Step 1, Example 38: Slightly yellow solid (100% yield). ^{1}H NMR (500 MHz, CHLOROFORM-D) δ ppm 2.42 (s, 3 H) 2.96 (s, 12 H) 3.80 (s, 3 H) 6.81 (d, *J*=7.93 Hz, 1 H) 7.11 (t, *J*=7.93 Hz, 1 H) 7.25 (d, *J*=6.71 Hz, 1 H); LC-MS, MS *m/z* 264 (M^+ + H).

Product of Step 2, Example 38: Yellow solid (89% yield). ^{1}H NMR (500 MHz, CHLOROFORM-D) δ ppm 3.04 (s, 6 H) 3.92 (s, 3 H) 5.89 (s, 1 H) 6.92 (d, *J*=7.63 Hz, 1 H) 7.09 (t, *J*=7.93 Hz, 1 H) 7.82 (d, *J*=7.93 Hz, 1 H) 10.69 (s, 1 H); LC-MS, MS *m/z* 219 (M^+ + H).

Product of Step 3, Example 38: Yellow solid (95% yield). ^{1}H NMR (300 MHz, CHLOROFORM-D) δ ppm 3.12 (s, 6 H) 3.93 (s, 3 H) 6.77 (d, *J*=7.32 Hz, 1 H) 6.83 (s, 1 H) 7.09 (dd, *J*=8.42, 7.68 Hz, 1 H) 7.62 (d, *J*=8.42 Hz, 1 H); LC-MS, MS *m/z* 237 (M^+ + H).

Product of Step 4, Example 38: Yellow solid (92% yield). LC-MS, MS *m/z* 432 (M^+ + H).

Product of Step 5, Example 38: Yellow/green solid (73% yield). LC-MS, MS *m/z* 644 (M^+ + H).

Product of Step 6, Example 38: Yellow solid (95% yield). LC-MS, MS *m/z* 544 (M^+ + H).

Compound 38A (Product of Step 7, Example 38): ^{1}H NMR (500 MHz, *MeOD*) δ ppm 1.07 - 1.14 (m, 2 H), 1.15 (s, 9 H), 1.27 (dd, *J*=4.6, 2.7 Hz, 2 H), 1.43 - 1.49 (m, 1 H), 1.94 (dd, *J*=8.1, 5.3 Hz, 1 H), 2.25 - 2.36 (m, 2 H), 2.41 (s, 3 H), 2.67 (dd, *J*=13.9, 7.5 Hz, 2 H), 2.95 - 3.02 (m, 2 H), 3.16 (s, 6 H), 3.18 - 3.20 (m, 1 H), 3.99 (s, 3 H), 4.10 (dd, *J*=12.1, 3.2 Hz, 1 H), 4.38 (d, *J*=11.9 Hz, 1 H), 4.50 (s, 1 H), 4.69 (dd, *J*=10.1, 7.3 Hz, 1 H), 5.17 (dd, *J*=10.4, 1.5 Hz, 1 H), 5.34 (dd, *J*=17.1, 1.2 Hz, 1 H), 5.73 - 5.82 (m, 1 H), 5.98 (s, 1 H), 6.64 (dd, *J*=9.8, 7.3 Hz, 2 H), 6.90 (d, *J*=6.7 Hz, 1 H), 6.95 (t, *J*=7.9 Hz, 1 H), 7.30 (dd, *J*=9.0, 7.5 Hz, 1 H), 7.33 (d, *J*=7.3 Hz, 1 H); LC-MS, MS *m/z* 748 (M^+ + H).

Compound 38B (Product of Step 7, Example 38): ^{1}H NMR (500 MHz, *MeOD*) δ ppm 0.98 (s, 9 H), 1.05 - 1.10 (m, 2 H), 1.15 (s, 1 H), 1.15 - 1.19 (m, 1 H), 1.23 - 1.28 (m, 1 H), 1.40 (dd, *J*=9.6, 5.0 Hz, 1 H), 1.91 (dd, *J*=8.1, 5.3 Hz, 1 H), 2.31 (q, *J*=8.7 Hz, 1 H), 2.40 - 2.47 (m, 1 H), 2.54 (s, 3 H), 2.68 (dd, *J*=13.9, 7.5 Hz, 2 H), 2.89 - 2.95 (m, 2 H), 3.15 (s, 6 H), 3.18 - 3.20 (m, 1 H), 3.98 (s, 3 H), 4.21 (dd,

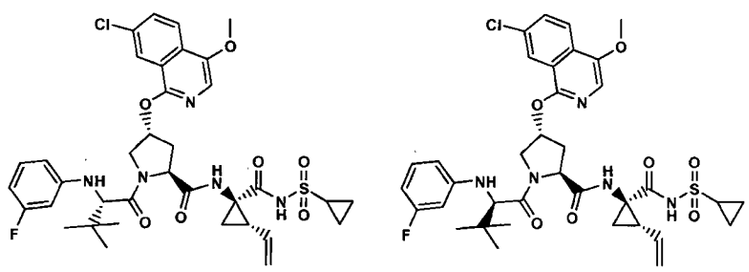
J=12.1, 3.5 Hz, 1 H), 4.44 (d, *J*=12.2 Hz, 1 H), 4.65 (s, 1 H), 4.66 - 4.69 (m, 1 H), 5.16 (dd, *J*=10.4, 1.8 Hz, 1 H), 5.36 (dd, *J*=17.2, 1.4 Hz, 1 H), 5.74 - 5.83 (m, 1 H), 6.02 (s, 1 H), 6.84 (d, *J*=7.3 Hz, 1 H), 6.94 (d, *J*=7.3 Hz, 1 H), 7.04 - 7.09 (m, 2 H), 7.47 (dd, *J*=8.2, 0.9 Hz, 1 H), 7.96 (dd, *J*=9.2, 7.3 Hz, 1 H); LC-MS, MS *m/z* 748 ($M^+ + H$).

Compound 200 Isomers:

N-(3-fluorophenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and

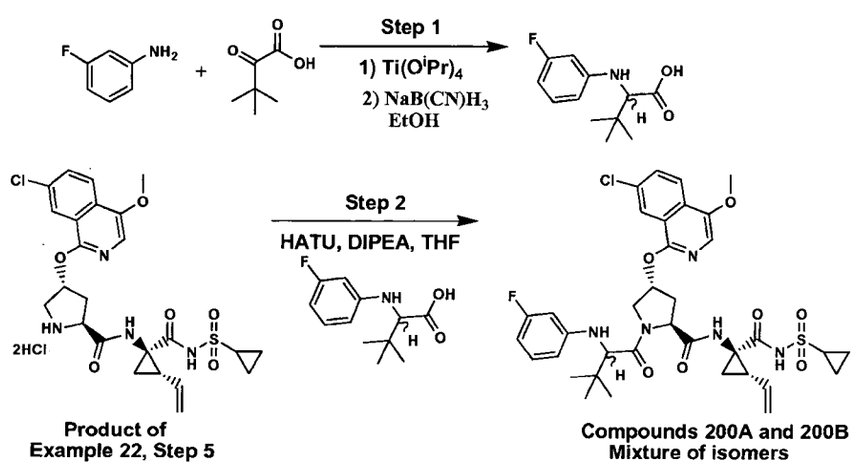
N-(3-fluorophenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 200: Preparation of Compounds 200A and 200B



Compounds 200A and 200B

Scheme 1



Step 1:

To a mixture of 3-fluoroaniline (160 mg, 1.299 mmol) and 3,3-dimethyl-2-oxobutanoic acid (220 mg, 1.690 mmol) in a 100 mL round bottom flask (RBF) at RT was added tetraisopropoxytitanium (2 ml,) via a pipet. The color of the mixture soon changed into a characteristic canary color. The solution was warmed to 75°C for about 15 minutes and the color remained the same. The solution was diluted with absolute ethanol (8 ml) at RT, followed by the addition of 1.5x of sodium cyanotrihydroborate (136 mg, 2.16 mmol), and the remaining half after the bubbling and sizzling was over. The color of the solution became lighter. The solution was mixed with 4 mL of water, forming a suspension. The white PPT was removed by centrifuge, organic residue was extracted into ethyl acetate and the organic phase was dried over Na_2SO_4. Evaporation to dryness under high vacuum (20-40 micronHg) at RT gave a white foam which was used in the next step without further purification. LC-MS, MS *m/z* 226 (M^+ +H).

Step 2:

To the yellow solution of 2-(3-fluorophenylamino)-3,3-dimethylbutanoic acid (0.20 g, 0.888 mmol, from step 1, example 200) and (2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-N-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropyl)pyrrolidine-2-carboxamide (0.10 g, 0.187 mmol, from step 5, example 22) in THF (4 mL) at 0°C was added HATU (0.175 g, 0.46 mmol) followed by diisopropylethyl amine (400 µL, excess). A pale yellow solution was formed after addition of the base. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (25 ml), washed with water (pH~6), and brine. The organic was dried over sodium sulfate, filtered and concentrated, and the residue was purified by reverse phase preparative HPLC to give two separate products with identical MS (*m/z* 226 for $[M+H]^+$) as observed by LCMS. Compound 200A (0.022 g, 16% yield, not optimized) was the first of the two isomers to elute out by reverse phase preparative HPLC. Compound 200B (0.010 g, 7% yield, not optimized) was the second of the two isomers to be eluted by reverse phase preparative HPLC.

Compound 200A: ^1H NMR (400 MHz, CD_3OD) δ ppm 1.12 (s, 9 H), 1.26 - 1.31 (m, 2 H), 1.39 (dd, J=6.71, 4.27 Hz, 2 H), 1.45 (dd, J=9.46, 5.49 Hz, 1 H), 1.90

(dd, J=7.93, 5.49 Hz, 1 H), 2.19 - 2.32 (m, 2 H), 2.55 (dd, J=13.73, 7.02 Hz, 1 H), 2.93 - 3.03 (m, 1 H), 3.69 - 3.78 (m, 1 H), 4.04 (s, 3 H), 4.05 (dd, J=8.85, 3.35 Hz, 1 H), 4.31 (d, J=12.21 Hz, 1 H), 4.55 (dd, J=10.38, 7.02 Hz, 1 H), 5.14 (d, J=10.38 Hz, 1 H), 5.32 (d, J=17.09 Hz, 1 H), 5.71 - 5.83 (m, 2 H), 5.89 - 5.98 (m, 1 H), 6.21 (dd, J=8.09, 1.98 Hz, 1 H), 6.25 - 6.32 (m, 1 H), 6.42 - 6.50 (m, 1 H), 7.57 (s, 1 H), 7.70 (dd, J=8.85, 2.14 Hz, 1 H), 7.83 (d, J=1.83 Hz, 1 H), 8.11 (d, J=8.85 Hz, 1 H), 9.19 (br. s, 1 H); LC-MS, MS *m/z* 743 $[M+H]^+$.

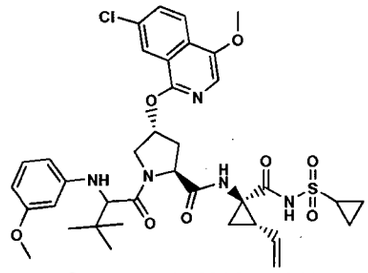
Compound 200B: LC-MS, MS *m/z* 743 $[M+H]^+$.

Compound 201 Isomers:

N-(3-methoxyphenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

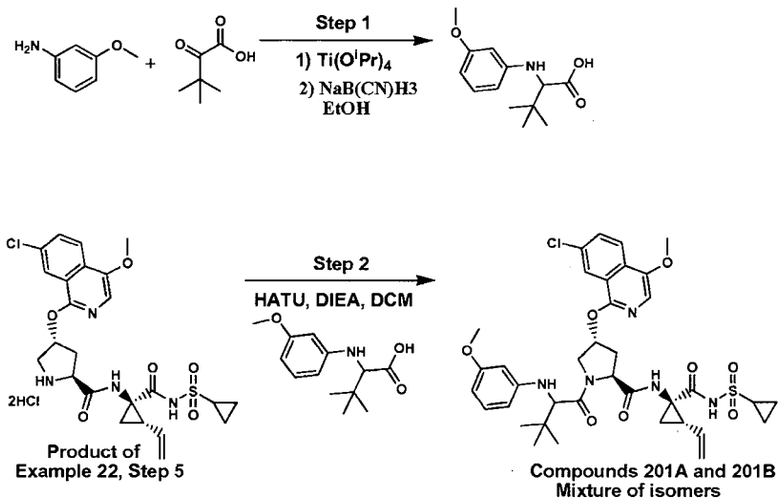
N-(3-methoxyphenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 201: Preparation of Compounds 201A and 201B



Compounds 201A and 201B

Scheme 1



Step 1:

To a mixture of 3-methoxyaniline (160 mg, 1.299 mmol) and 3,3-dimethyl-2-oxobutanoic acid (220 mg, 1.690 mmol) in a 100 mL RBF at RT was added tetraisopropoxytitanium (2 ml,) via a pipet. The color of the mixture soon changed into a characteristic canary color. The solution was warmed to 75°C for about 15 minutes and the color remained the same. The solution was diluted with absolute ethanol (8 ml) at RT, followed by the addition of 1.5x of sodium cyanotrihydroborate (245 mg, 3.90 mmol), and the remaining half after the bubbling and sizzling was over. The color of the solution became lighter. The solution was mixed with 4 mL of water, forming a suspension, the white PPT was removed by centrifuge. The organic was extracted into ethyl acetate, and the organic phase was dried over Na_2SO_4, filtered and evaporated to dryness to give a white foam. This material was carried on to the next step without further purification. LC-MS, MS *m/z* 238 (M^++H).

Step 2:

To the yellow solution of 2-(3-methoxyphenylamino)-3,3-dimethylbutanoic acid (0.045 g, 0.189 mmol, step 1, example 201) and (2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-N-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropyl)pyrrolidine-2-carboxamide (0.101 g, 0.189 mmol, step 5, example 22) in CH_2Cl_2 at 0°C was added HATU (0.144 g, 0.378 mmol) followed by

diisopropylethyl amine (0.061 g, 0.473 mmol). A light yellow solution was formed after addition of the base. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (25 ml) and then washed with water (pH~6) and brine. The organic was dried over sodium sulfate, concentrated, and the residue was purified by reverse phase preparative HPLC to give two separate products with identical MS *m/z* as observed by LCMS. Compound 201A (0.045 g, 32% yield) was the first of the two isomers to elute by reverse phase preparative HPLC. Compound 201B (0.024 g, 16.2% yield) was the second of the two isomers to elute by reverse phase preparative HPLC.

Compound 201A: ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.03 - 1.14 (m, 11 H) 1.21 - 1.32 (m, 2 H) 1.41 (dd, *J*=9.44, 5.41 Hz, 1 H) 1.87 (dd, *J*=8.06, 5.54 Hz, 1 H) 2.16 - 2.26 (m, 2 H) 2.48 (dd, *J*=13.60, 6.80 Hz, 1 H) 2.95 (ddd, *J*=12.78, 8.12, 4.78 Hz, 1 H) 3.95 - 4.07 (m, 5 H) 4.48 (dd, *J*=10.58, 7.05 Hz, 1 H) 5.11 (d, *J*=10.32 Hz, 1 H) 5.29 (d, *J*=17.12 Hz, 1 H) 5.65 - 5.73 (m, 2 H) 5.73 - 5.79 (m, 1 H) 6.15 - 6.21 (m, 1 H) 6.27 (d, *J*=2.01 Hz, 1 H) 6.36 - 6.42 (m, 1 H) 7.50 (s, 1 H) 7.68 (d, *J*=9.06 Hz, 1 H) 7.74 (s, 1 H) 8.08 (d, *J*=8.81 Hz, 1 H); LC-MS, MS *m/z* 753 (M^++H).

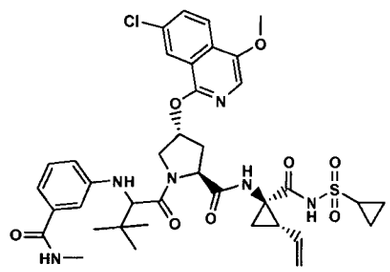
Compound 201B: LC-MS, MS *m/z* 753 (M^++H).

Compound 202 Isomers:

3-methyl-N-(3-(methylcarbamoyl)phenyl)-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and

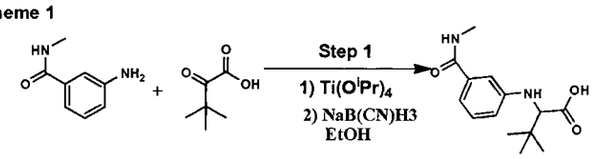
3-methyl-N-(3-(methylcarbamoyl)phenyl)-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

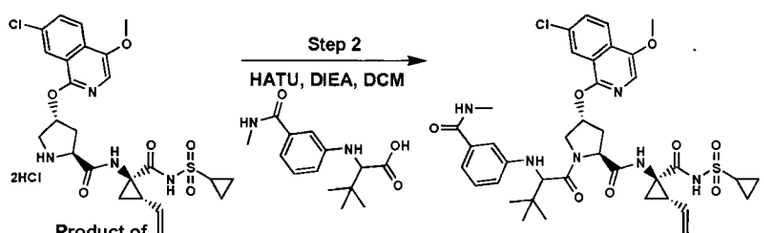
Example 202: Preparation of Compounds 202A and 202B



Compounds 202A and 202B

Scheme 1





Product of Example 22, Step 5

Compounds 202A and 202B Mixture of isomers

Step 1:

To a mixture of 3-amino-N-methylbenzamide (230 mg, 1.532 mmol) and 3,3-dimethyl-2-oxobutanoic acid (199 mg, 1.532 mmol) in a 100 mL RBF at RT was added tetraisopropoxytitanium (2 ml,) via a pipet, The color of the mixture soon changed into a characteristic canary color. The solution was warmed to 75°C for about 15 minutes and the color remained the same. The solution was diluted with absolute ethanol (8 ml) at RT, followed by the addition of 1.5X of sodium cyanotrihydroborate (245 mg, 3.90 mmol), and the remaining half after the bubbling and sizzling was over. The color of the solution became lighter. The solution was mixed with 4 mL of water, forming a suspension, the white PPT was removed by centrifuge, organic was extracted into ethyl acetate, dried over Na_2SO_4. Evaporated into dryness, white foam was obtained and used in the next step without further purification. LC-MS, MS *m/z* 265 (M^++H).

Step 2:

To the yellow solution of (S)-3,3-dimethyl-2-(3-(methylcarbamoyl)phenylamino)butanoic acid (0.050 g, 0.189 mmol, step1, example 202) and (2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-N-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropyl)pyrrolidine-2-carboxamide (0.101 g, 0.189 mmol, step 5, example 22) in CH_2Cl_2 at 0°C was added HATU (0.144 g, 0.378 mmol) followed by diisopropylethyl amine (0.061 g, 0.473 mmol). A light yellow solution was formed after addition of the base. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (25 ml) and was washed with water (pH~6) and brine. The organic was dried over sodium sulfate, then concentrated, and the residue was purified by reverse phase preparative HPLC to give two separate products with identical MS *m/z* as observed by LCMS. Compound 202A (0.061 g, 41% yield) was the first of the two isomers to elute by reverse phase preparative HPLC. Compound 202B (0.015 g, 10.2% yield) was the second of the two isomers to elute by reverse phase preparative HPLC.

Compound 202A: ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.02 - 1.13 (m, 11 H) 1.20 - 1.30 (m, 2 H) 1.42 (dd, *J*=9.44, 5.41 Hz, 1 H) 1.87 (dd, *J*=8.06, 5.54 Hz, 1 H) 2.14 - 2.25 (m, 2 H) 2.47 (dd, *J*=13.72, 6.92 Hz, 1 H) 2.77 (s, 3 H) 2.95 (ddd, *J*=12.65, 7.99, 4.78 Hz, 1 H) 3.94 (dd, *J*=12.21, 3.15 Hz, 1 H) 3.98 (s, 4 H) 4.22 (d, *J*=12.09 Hz, 1 H) 4.51 (dd, *J*=10.32, 7.05 Hz, 1 H) 5.11 (d, *J*=10.32 Hz, 1 H) 5.28 (d, *J*=17.12 Hz, 1 H) 5.69 - 5.79 (m, 2 H) 6.63 - 6.73 (m, 3 H) 7.01 (s, 1 H) 7.48 (s, 1 H) 7.64 (dd, *J*=8.94, 2.14 Hz, 1 H) 7.71 (d, *J*=2.01 Hz, 1 H) 8.05 (d, *J*=8.81 Hz, 1 H); LC-MS, MS *m/z* 781 (M^++H).

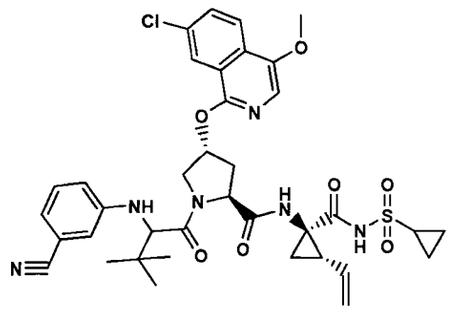
Compound 202B: LC-MS, MS *m/z* 781 (M^++H).

Compound 203 Isomers:

N-(3-cyanophenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and

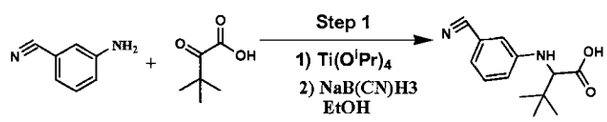
N-(3-cyanophenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

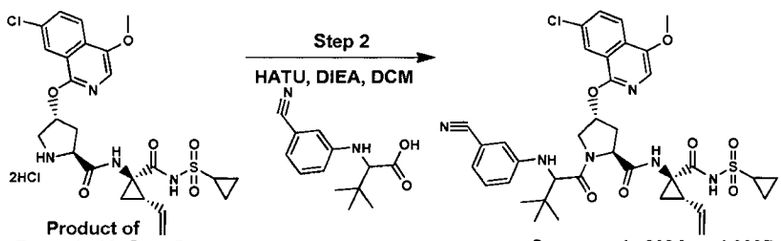
Example 203: Preparation of Compounds 203A and 203B



Compounds 203A and 203B

Scheme 1





Step 1:

To a mixture of 3-aminobenzonitrile (180 mg, 1.524 mmol) and 3,3-dimethyl-2-oxobutanoic acid (198 mg, 1.524 mmol) in a 100 mL RBF at RT was added tetraisopropoxytitanium (2 ml,) via a pipet. The color of the mixture soon changed into a characteristic canary color. The solution was warmed to 75°C for about 15 minutes and the color remained the same. The solution was diluted with absolute ethanol (8 ml) at RT, followed by the addition of 1.5X of sodium cyanotrihydroborate (245 mg, 3.90 mmol), and the remaining half after the bubbling and sizzling was over. The color of the solution became lighter. The solution was mixed with 4 mL of water, forming a suspension, the white PPT was removed by centrifuge, organic was extracted into ethyl acetate, and the organic phase was dried

over Na_2SO_4, filtered, and evaporated into dryness. A yellow oil was obtained and used in the next step without further purification. LC-MS, MS *m/z* 233 (M^++H).

Step 2:

To the yellow solution (S)-2-(3-cyanophenylamino)-3,3-dimethylbutanoic acid (0.044 g, 0.189 mmol, step1, example 203) and (2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-N-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropyl)pyrrolidine-2-carboxamide (0.101 g, 0.189 mmol, step 5, example 22) in CH_2Cl_2 at 0°C was added HATU (0.144 g, 0.378 mmol) followed by diisopropylethyl amine (0.061 g, 0.473 mmol). A light yellow solution was formed after addition of the base. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (25 ml) and then washed with water (pH~6) and brine. The organic was dried over sodium sulfate, filtered, concentrated, and the residue was purified by reverse phase preparative HPLC to give two separate products with identical MS *m/z* as observed by LCMS. Compound 203A (0.025 g, 17.7% yield) was the first of the two isomers to elute by reverse phase preparative HPLC. Compound 203B (0.014 g, 10.0% yield) was the second of the two isomers to elute by reverse phase preparative HPLC.

Compound 203A: ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.07 (s, 11 H) 1.19 - 1.31 (m, 2 H) 1.41 (dd, *J*=9.44, 5.41 Hz, 1 H) 1.87 (dd, *J*=8.06, 5.54 Hz, 1 H) 2.17 - 2.26 (m, 2 H) 2.51 (dd, *J*=13.60, 6.80 Hz, 1 H) 2.88 - 2.98 (m, 1 H) 3.95 - 4.02 (m, 4 H) 4.02 - 4.05 (S, 1 H) 4.21 (d, *J*=12.09 Hz, 1 H) 4.53 (dd, *J*=10.32, 7.05 Hz, 1 H) 5.11 (d, *J*=10.32 Hz, 1 H) 5.28 (d, *J*=17.12 Hz, 1 H) 5.68 - 5.78 (m, 2 H) 6.46 (d, *J*=7.30 Hz, 1 H) 6.57 (t, *J*=7.93 Hz, 1 H) 6.63 - 6.68 (m, 1 H) 6.86 (s, 1 H) 7.50 (s, 1 H) 7.64 (dd, *J*=8.94, 1.38 Hz, 1 H) 7.69 (s, 1 H) 8.05 (d, *J*=8.81 Hz, 1 H); LC-MS, MS *m/z* 749 (M^++H).

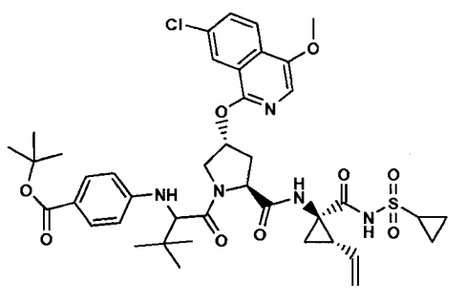
Compound 203B: LC-MS, MS *m/z* 749 (M^++H).

Compound 204 Isomers:

N-(4-(tert-butoxycarbonyl)phenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

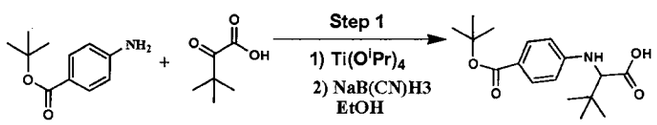
N-(4-(tert-butoxycarbonyl)phenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

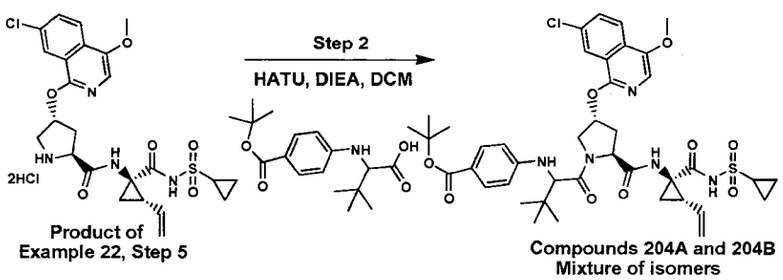
Example 204: Preparation of Compounds 204A and 204B



Compounds 204A and 204B

Scheme 1





Step 1:

To a mixture of tert-butyl 4-aminobenzoate (230 mg, 1.190 mmol) and 3,3-dimethyl-2-oxobutanoic acid (155 mg, 1.190 mmol) in a 100 mL RBF at RT was added tetraisopropoxytitanium (2 ml,) via a pipet. The color of the mixture soon changed into a characteristic canary color. The solution was warmed to 75°C for about 15 minutes and the color remained the same. The solution was diluted with absolute ethanol (8 ml) at RT, followed by the addition of 1.5X of sodium cyanotrihydroborate (245 mg, 3.90 mmol), and the remaining half after the bubbling and sizzling was over. The color of the solution became lighter. The solution was mixed with 4 mL of water, forming a suspension, the white PPT was removed by centrifuge. The organic was extracted into ethyl acetate, and the organic phase was dried over Na_2SO_4, filtered and evaporated to dryness. A yellow oil was obtained and used in the next step without further purification. LC-MS, MS *m/z* 308 (M^++H).

Step 2:

To the yellow solution (S)-2-(4-(tert-butoxycarbonyl)phenylamino)-3,3-dimethylbutanoic acid (0.058 g, 0.189 mmol, step1, example 204) and (2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-N-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropyl)pyrrolidine-2-carboxamide (0.101 g, 0.189 mmol, step 5, example 22) in CH_2Cl_2 at 0°C was added HATU (0.144 g, 0.378 mmol) followed by diisopropylethyl amine (0.061 g, 0.473 mmol). A light yellow solution was formed after addition of the base. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (25 ml), washed with water (pH~6) and brine. The organic was dried over sodium sulfate, concentrated, and the residue was purified by reverse phase preparative HPLC to give two separate products with identical MS *m/z* as observed by LCMS. Compound 204A (0.024 g, 15.4% yield) was the first of the two isomers to elute by reverse phase preparative HPLC. Compound 204B (0.020 g, 12.8% yield) was the second of the two isomers to elute by reverse phase preparative HPLC.

Compound 204A: ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.02 - 1.11 (m, 11 H) 1.19 - 1.30 (m, 2 H) 1.41 (dd, *J*=9.19, 5.41 Hz, 1 H) 1.46 - 1.54 (S, 9 H) 1.86 (dd, *J*=8.06, 5.54 Hz, 1 H) 2.17 - 2.27 (m, 2 H) 2.54 (dd, *J*=13.60, 6.80 Hz, 1 H) 2.95 (ddd, *J*=12.65, 7.99, 4.78 Hz, 1 H) 3.96 - 4.04 (m, 4 H) 4.12 (s, 1 H) 4.37 (d,

J=12.09, 1H) 4.55 (dd, *J*=10.07, 7.30 Hz, 1 H) 5.10 (d, *J*=10.58 Hz, 1 H) 5.28 (d, *J*=17.58 Hz, 1 H) 5.75 (m, 1H) 5.78 (S, 1 H) 6.42 (d, *J*=8.81 Hz, 2 H) 7.28 (d, *J*=8.56 Hz, 2 H) 7.52 (s, 1 H) 7.59 (dd, *J*=8.94, 2.14 Hz, 1 H) 7.75 (d, *J*=1.76 Hz, 1 H) 8.03 (d, *J*=8.81 Hz, 1 H); LC-MS, MS *m/z* 824 (M^++H).

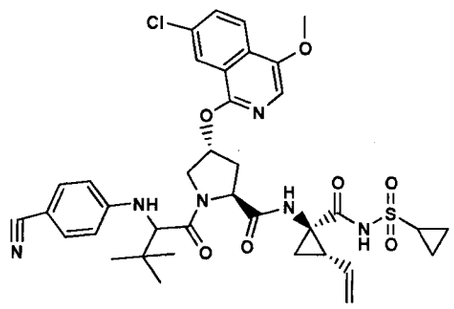
Compound 204B: LC-MS, MS *m/z* 824 (M^++H).

Compound 205 Isomers:

N-(4-cyanophenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and

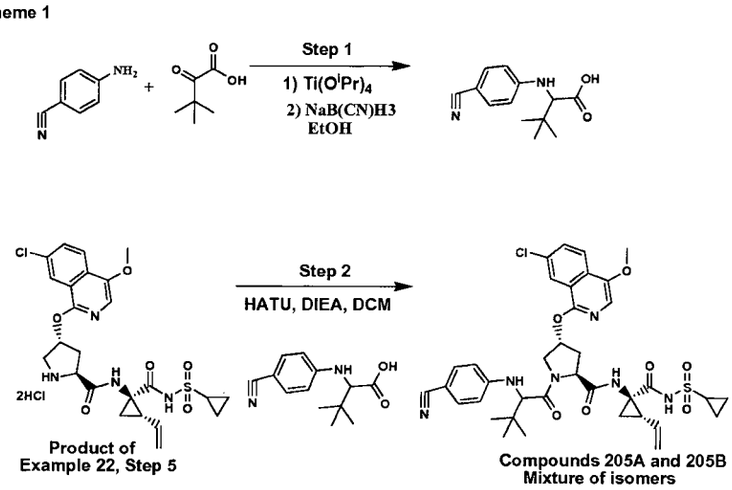
N-(4-cyanophenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 205: Preparation of Compounds 205A and 205B



Compounds 205A and 205B

Scheme 1



Step 1:

To a mixture of 4-aminobenzonitrile (180 mg, 1.524 mmol) and 3,3-dimethyl-2-oxobutanoic acid (198 mg, 1.524 mmol) in a 100 mL RBF at RT was added tetraisopropoxytitanium (2 ml,) via a pipet. The color of the mixture soon changed into a characteristic canary color. The solution was warmed to 75°C for about 15 minutes and the color remained the same. The solution was diluted with absolute ethanol (8 ml) at RT, followed by the addition of 1.5X of sodium cyanotrihydroborate (245 mg, 3.90 mmol), and the remaining half after the bubbling and sizzling was over. The color of the solution became lighter. The solution was mixed with 4 mL of water, forming a suspension, the white PPT was removed by centrifuge. The organic was extracted into ethyl acetate, and the organic phase was dried over Na_2SO_4, filtered, and evaporated into dryness. A yellow oil was obtained and was used in the next step without further purification. LC-MS, MS *m/z* 233 (M^+ +H).

Step 2:

To the yellow solution of 2-(4-cyanophenylamino)-3,3-dimethylbutanoic acid (0.044 g, 0.189 mmol, step1, example 205) and (2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-N-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropyl)pyrrolidine-2-carboxamide (0.101 g, 0.189 mmol, step 5, example 22) in CH_2Cl_2 at 0°C was added HATU (0.144 g, 0.378 mmol) followed by

diisopropylethyl amine (0.061 g, 0.473 mmol). A light yellow solution was formed after addition of the base. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (25 ml), washed with water (pH~6) and brine. The organic was dried over sodium sulfate, filtered, and concentrated, and the residue was purified by reverse phase preparative HPLC to give two separate products with identical MS *m/z* as observed by LCMS. Compound 205A (0.052 g, 37% yield) was the first of the two isomers to elute by reverse phase preparative HPLC. Compound 205B (0.013 g, 9 % yield) was the second of the two isomers to elute by reverse phase preparative HPLC.

Compound 205A: ^{1}H NMR (400 MHz, CD_3OD) δ ppm 0.99 - 1.09 (m, 11 H) 1.17 - 1.26 (m, 2 H) 1.35 - 1.45 (m, 1 H) 1.87 (dd, *J*=8.06, 5.29 Hz, 1 H) 2.17 - 2.28 (m, 2 H) 2.56 (dd, *J*=13.85, 7.05 Hz, 1 H) 2.94 (ddd, *J*=12.84, 8.06, 4.78 Hz, 1 H) 3.95 - 4.04 (m, 4 H) 4.08 (s, 1 H) 4.28 - 4.37 (m, 1 H) 4.56 (dd, *J*=10.32, 7.05 Hz, 1 H) 5.05 - 5.13 (m, 1 H) 5.28 (d, *J*=17.12 Hz, 1 H) 5.66 - 5.75 (m, 1 H) 5.78 (s, 1 H) 6.44 (d, *J*=8.81 Hz, 2 H) 6.80 (d, *J*=8.56 Hz, 2 H) 7.46 - 7.54 (s, 1 H) 7.63 - 7.73 (m, 1 H) 7.74 - 7.81 (s, 1 H) 8.02 - 8.10 (m, 1 H); LC-MS, MS *m/z* 749 (M^++H).

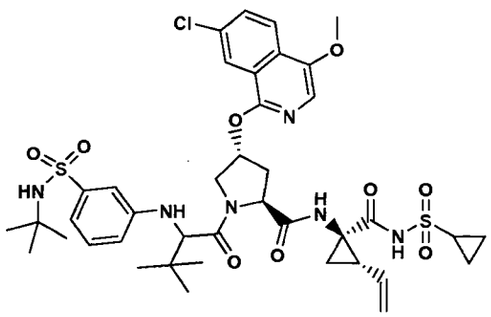
Compound 205B: LC-MS, MS *m/z* 749 (M^++H).

Compound 206 Isomers:

N-(3-(tert-butylsulfamoyl)phenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and

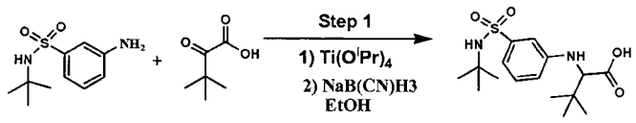
N-(3-(tert-butylsulfamoyl)phenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

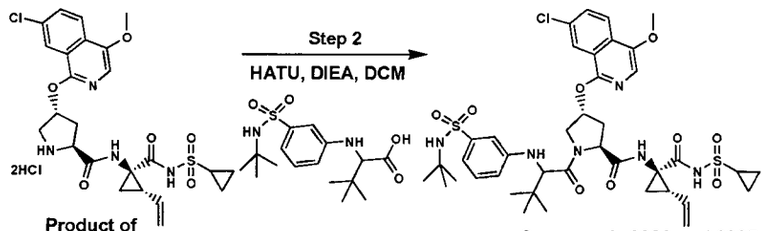
Example 206: Preparation of Compounds 206A and 206B



Compounds 206A and 206B

Scheme 1





Step 1:

To a mixture of 3-amino-N-tert-butylbenzenesulfonamide (180 mg, 0.788 mmol) and 3,3-dimethyl-2-oxobutanoic acid (308 mg, 2.365 mmol) in a 100 mL RBF at RT was added tetraisopropoxytitanium (2 ml,) via a pipet. The color of the mixture soon changed into a characteristic canary color. The solution was warmed to 75°C for about 15 minutes and the color remained the same. The solution was diluted with absolute ethanol (8 ml) at RT, followed by the addition of 1.5X of sodium cyanotrihydroborate (245 mg, 3.90 mmol), and the remaining half after the bubbling and sizzling was over. The color of the solution became lighter. The solution was mixed with 4 mL of water, forming a suspension, the white PPT was removed by centrifuge. The organic was extracted into ethyl acetate, and the organic phase was dried over Na_2SO_4, filtered, and evaporated to dryness. A yellow oil was

obtained and used in the next step without further purification. LC-MS, MS *m/z* 343 (M^++H).

Step 2:

To the yellow solution of 2-(3-(N-tert-butylsulfamoyl)phenylamino)-3,3-dimethylbutanoic acid (0.065 g, 0.189 mmol step1, example 206) and (2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-N-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropyl)pyrrolidine-2-carboxamide (0.101 g, 0.189 mmol, step 5, example 22) in CH_2Cl_2 at 0°C was added HATU (0.144 g, 0.378 mmol) followed by diisopropylethyl amine (0.061 g, 0.473 mmol). A light yellow solution was formed after addition of the base. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (25 ml) and was washed with water (pH~6) and brine. The organic was dried over sodium sulfate, filtered, concentrated, and the residue was purified by reverse phase preparative HPLC to give two separate products with identical MS *m/z* as observed by LCMS. Compound 206A (0.025 g, 15.4% yield) was the first of the two isomers to elute by reverse phase preparative HPLC. Compound 206B (0.013 g, 8 % yield) was the second of the two isomers to elute by reverse phase preparative HPLC.

Compound 206A: ^{1}H NMR (400 MHz, CD_3OD) δ ppm 0.97 - 1.06 (m, 9 H) 1.06 - 1.18 (m, 11 H) 1.18 - 1.29 (m, 2 H) 1.36 - 1.46 (m, 1 H) 1.86 (dd, *J*=8.06, 5.54 Hz, 1 H) 2.18 - 2.29 (m, 2 H) 2.55 (m, 1H) 2.95 (ddd, *J*=12.84, 8.06, 4.78 Hz, 1 H) 3.95 - 4.01 (s, 3 H) 4.02 - 4.12 (m, 2 H) 4.26 (d, *J*=12.09 Hz, 1 H) 4.51 (dd, *J*=10.07, 7.05 Hz, 1 H) 5.10 (dd, *J*=10.32, 1.51 Hz, 1 H) 5.24 - 5.32 (m, 1 H) 5.73 (m, 2 H) 6.52 (m, 1 H) 6.62 (m, 1 H) 6.86 (m, 1 H) 7.15 (d, *J*=2.01 Hz, 1 H) 7.50 - 7.56 (s, 1 H) 7.62 - 7.70 (m, 1 H) 7.83 (s, 1 H) 8.01 - 8.09 (m, 1 H); LC-MS, MS *m/z* 859 (M^+ +H).

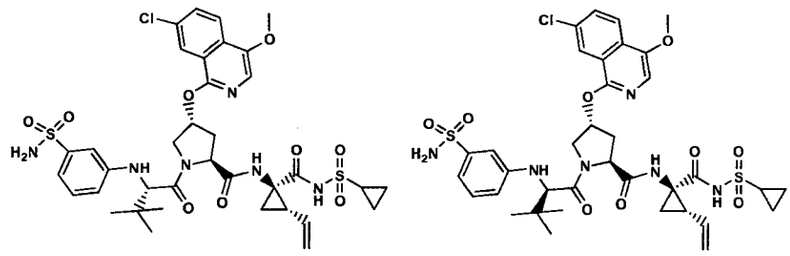
Compound 206B: LC-MS, MS *m/z* 859 (M^++H).

Compound 207 Isomers:

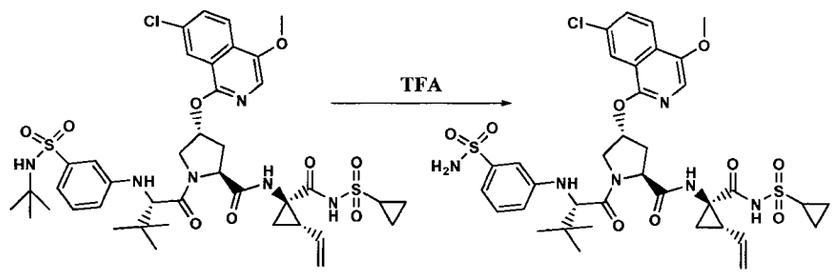
3-methyl-N-(3-sulfamoylphenyl)-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and

3-methyl-N-(3-sulfamoylphenyl)-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 207: Preparation of Compounds 207A and 207B



Compounds 207A and 207B



(2S,4R)-1-((S)-2-(3-(N-tert-butylsulfamoyl)phenylamino)-3,3-dimethylbutanoyl)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-N-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropyl)pyrrolidine-2-carboxamide (compound 206A) was dissolved in 1 ml of 2,2,2-trifluoroacetic acid at 25 °C. The mixture was stirred overnight. The TFA was removed and the residue was purified by preparative HPLC. Compound 207A was thus obtained as a white powder (0.012 g, 64% yield). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.05 - 1.14 (m, 11 H) 1.19 - 1.29 (m, 2 H) 1.41 (dd, *J*=9.44, 5.41 Hz, 1 H) 1.87 (dd, *J*=8.18, 5.41 Hz, 1 H) 2.17 - 2.26 (m, 2 H) 2.52 (dd, *J*=13.85, 7.05 Hz, 1 H) 2.95 (ddd, *J*=12.78, 8.12, 4.78 Hz, 1 H) 3.96 - 4.02 (s, 3 H) 4.02 - 4.10 (m, 2 H) 4.30 (d, *J*=12.09 Hz, 1 H) 4.52 (dd, *J*=10.07,

7.05 Hz, 1 H) 5.11 (dd, *J*=10.32, 1.51 Hz, 1 H) 5.24 - 5.32 (m, 1 H) 5.69 - 5.79 (m, 2 H) 6.49 - 6.55 (m, 1 H) 6.60 (t, *J*=7.81 Hz, 1 H) 6.87 (d, *J*=7.55 Hz, 1 H) 7.16 (s, 1 H) 7.51 - 7.55 (s, 1 H) 7.67 (dd, *J*=8.94, 2.14 Hz, 1 H) 7.85 (d, *J*=2.01 Hz, 1 H) 8.07 (d, *J*=8.81 Hz, 1 H); LC-MS, MS *m/z* 803 (M^++H).

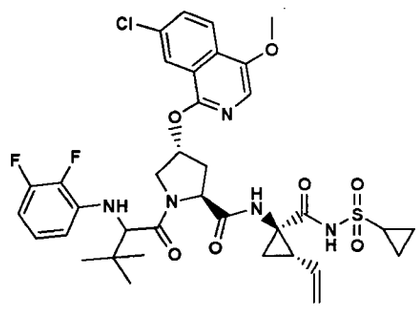
Compound 207B was made from compound 206B by the same procedure as was used for the preparation of compound 207A. LC-MS, MS *m/z* 803 (M^++H).

Compound 208 Isomers:

N-(2,3-difluorophenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and

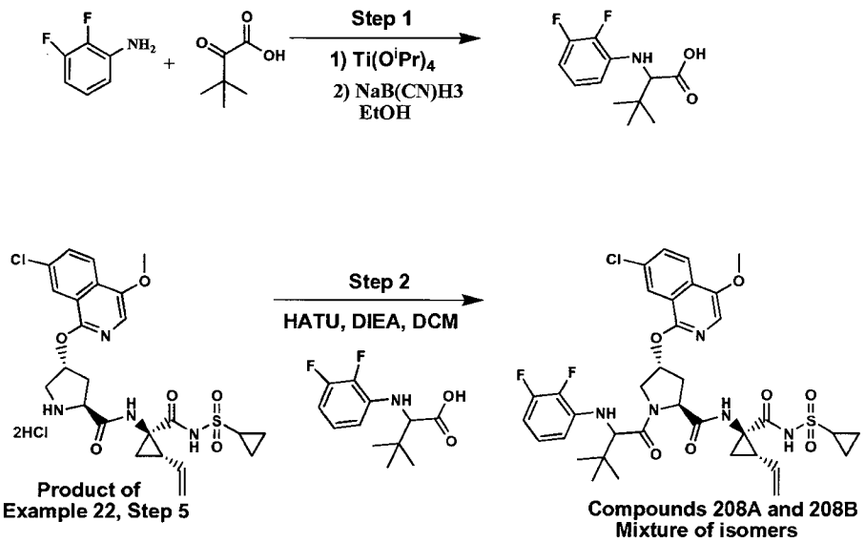
N-(2,3-difluorophenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 208: Preparation of Compounds 208A and 208B



Compounds 208A and 208B

Scheme 1



Step 1:

To a mixture of 2,3-difluoroaniline (180 mg, 1.394 mmol) and 3,3-dimethyl-2-oxobutanoic acid (500 mg, 3.84 mmol) in a 100 ml RBF at RT was added tetraisopropoxytitanium (2 ml,) via a pipet. The color of the mixture soon changed into a characteristic canary color. The solution was warmed to 75°C for about 15 minutes and the color remained the same. The solution was diluted with absolute ethanol (8 ml) at RT, followed by the addition of 1.5X of sodium cyanotrihydroborate (245 mg, 3.90 mmol), and the remaining half after the bubbling and sizzling was over. The color of the solution became lighter. The solution was mixed with 4 mL of water, forming a suspension, the white PPT was removed by centrifuge. The organic was extracted into ethyl acetate, and the organic phase was dried over Na_2SO_4, filtered and evaporated into dryness. A yellow oil was obtained and was used in the next step without further purification. LC-MS, MS *m/z* 244 (M^+ +H).

Step 2:

To the yellow solution of 2-(2,3-difluorophenylamino)-3,3-dimethylbutanoic acid (0.046 g, 0.189 mmol step1, example 208) and (2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-N-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-

vinylcyclopropyl)pyrrolidine-2-carboxamide (0.101 g, 0.189 mmol, step 5, example 22) in CH_2Cl_2 at 0°C was added hatu (0.144 g, 0.378 mmol) followed by diisopropylethyl amine (0.061 g, 0.473 mmol). A light yellow solution was formed after addition of the base. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (25 ml), and the organic was washed with water (pH~6) and brine. The organic was dried over sodium sulfate, filtered, concentrated, and purified by reverse phase preparative HPLC to give two separate products with identical MS *m/z* as observed by LCMS. Compound 208A (0.026 g, 18.4% yield) was the first of the two isomers to elute by reverse phase preparative HPLC. Compound 208B (0.012 g, 9 % yield) was the second of the two isomers to elute by reverse phase preparative HPLC.

Compound 208A: ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.03 - 1.12 (m, 11 H) 1.21 - 1.26 (m, 2 H) 1.41 (dd, *J*=9.44, 5.41 Hz, 1 H) 1.86 (dd, *J*=8.06, 5.54 Hz, 1 H) 2.17 - 2.28 (m, 2 H) 2.53 (dd, *J*=13.60, 7.05 Hz, 1 H) 2.94 (ddd, *J*=12.72, 8.06, 4.66 Hz, 1 H) 3.96 - 4.02 (m, 4 H) 4.02 - 4.07 (s, 1 H) 4.27 (d, *J*=12.09 Hz, 1 H) 4.53 (dd, *J*=10.45, 7.18 Hz, 1 H) 5.10 (d, *J*=10.32 Hz, 1 H) 5.28 (d, *J*=17.12 Hz, 1 H) 5.68 - 5.75 (m, 1 H) 5.77 (s, 1 H) 6.02 - 6.10 (m, 2 H) 6.21 - 6.28 (m, 1 H) 7.55 (s, 1 H) 7.68 (dd, *J*=8.81, 2.01 Hz, 1 H) 7.76 (d, *J*=2.01 Hz, 1 H) 8.09 (d, *J*=8.81 Hz, 1 H); LC-MS, MS *m/z* 760 (M^++H).

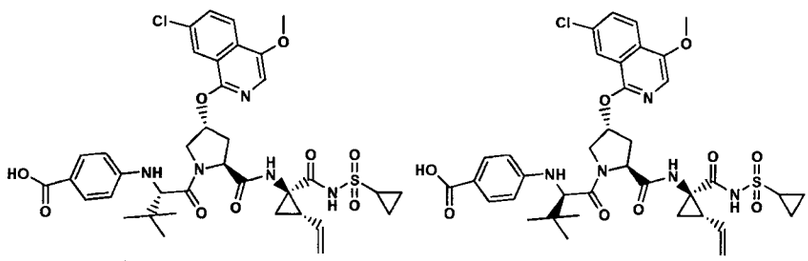
Compound 208B: LC-MS, MS *m/z* 760 (M^++H).

Compound 209 Isomers:

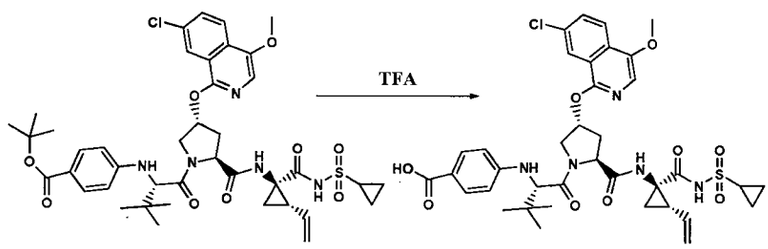
N-(4-carboxyphenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

N-(4-carboxyphenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 209: Preparation of Compounds 209A and 209B



Compounds 209A and 209B



tert-butyl 4-((S)-1-((2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-2-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropylcarbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-ylamino)benzoate (20 mg, 0.024 mmol, compound 204A) was dissolved in CH_2Cl_2 (2 ml) at 25 °C. TFA (0.019 ml, 0.243 mmol) was added dropwise. The mixture was stirred overnight. The TFA was removed and the residue was purified by preparative HPLC. Compound 209A was thus obtained as a white powder (0.018 g, 95% yield). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.05 - 1.14 (m, 11 H) 1.18 - 1.29 (m, 2 H) 1.42 (dd, *J*=9.32, 5.29 Hz, 1 H) 1.87 (dd, *J*=8.06, 5.54 Hz, 1 H) 2.19 - 2.28 (m, 2 H) 2.55 (dd, *J*=13.72, 7.18 Hz, 1 H) 2.95 (ddd, *J*=12.78, 8.12, 4.78 Hz, 1 H) 3.96 - 4.03 (m, 4 H) 4.06 - 4.10 (s, 1 H) 4.36 (d, *J*=12.34 Hz, 1 H) 4.58 (dd, *J*=10.32, 7.05 Hz, 1 H) 5.07 - 5.15 (m, 1 H) 5.29 (d, *J*=17.12 Hz, 1 H) 5.68 - 5.78 (m, 2 H) 6.38 (d, *J*=8.81 Hz, 2 H) 7.22 (d, *J*=8.81 Hz, 2 H) 7.51 (s, 1 H) 7.61 (dd, *J*=8.81, 2.27 Hz, 1 H) 7.79 (d, *J*=2.01 Hz, 1 H) 8.04 (d, *J*=9.06 Hz, 1 H); LC-MS, MS *m/z* 768 (M^++H).

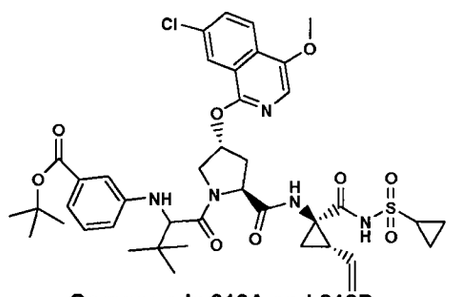
Compound 209B was made from compound 204B by same procedure as was used for the preparation of compound 209A. LC-MS, MS *m/z* 768 (M^++H).

Compound 210 Isomers:

N-(3-(tert-butoxycarbonyl)phenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

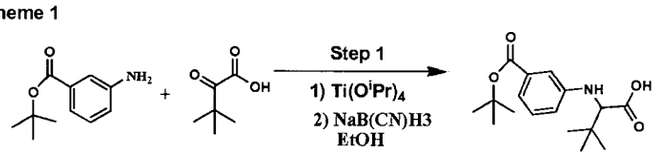
N-(3-(tert-butoxycarbonyl)phenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

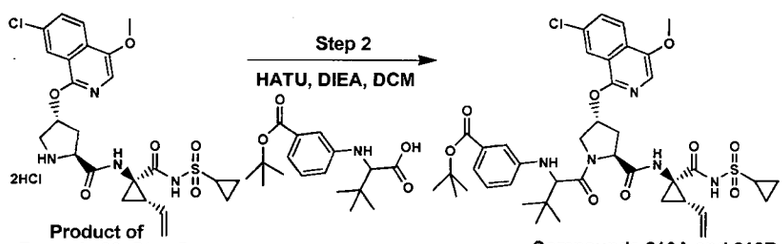
Example 210: Preparation of Compounds 210A and 210B



Compounds 210A and 210B

Scheme 1





Step 1:

To a mixture of 3-amino-N-tert-butylbenzenesulfonamide (180 mg, 0.788 mmol) and 3,3-dimethyl-2-oxobutanoic acid (308 mg, 2.365 mmol) in a 100 mL RBF

at RT was added tetraisopropoxytitanium (2 ml,) via a pipet. The color of the mixture soon changed into a characteristic canary color. The solution was warmed to 75°C for about 15 minutes and the color remained the same. The solution was diluted with absolute ethanol (8 ml) at RT, followed by the addition of 1.5X of sodium cyanotrihydroborate (245 mg, 3.90 mmol), and the remaining half after the bubbling and sizzling was over. The color of the solution became lighter. The solution was mixed with 4 mL of water, forming a suspension, and the white PPT was removed by centrifuge. The organic was extracted into ethyl acetate, and the organic phase was dried over Na_2SO_4, filtered, and evaporated to dryness. A yellow oil was obtained and was used in the next step without further purification. LC-MS, MS *m/z* 308 (M^++H).

Step 2:

To the yellow solution of 2-(3-(N-tert-butylsulfamoyl)phenylamino)-3,3-dimethylbutanoic acid (0.065 g, 0.189 mmol step1, example 210) and (2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-N-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropyl)pyrrolidine-2-carboxamide (0.101 g, 0.189 mmol, step 5, example 22) in CH_2Cl_2 at 0°C was added HATU (0.144 g, 0.378 mmol) followed by diisopropylethyl amine (0.061 g, 0.473 mmol). A light yellow solution was formed after addition of the base. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (25 ml) and was washed with water (pH~6) and brine. The organic was dried over sodium sulfate, filtered, concentrated, and purified by reverse phase preparative HPLC to give two separate products with identical MS *m/z* as observed by LCMS. Compound 210A (0.021 g, 13.5% yield) was the first of the two isomers to elute by reverse phase preparative HPLC. Compound 210B (0.020 g, 13.3 % yield) was the second of the two isomers to elute by reverse phase preparative HPLC.

Compound 210A: ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.04 - 1.14 (m, 11 H) 1.19 - 1.31 (m, 2 H) 1.38 - 1.48 (m, 9 H) 1.50 - 1.60 (m, 1 H)) 1.86 (m, 1 H) 2.15 - 2.24 (m, 2 H) 2.47 (m, 1 H) 2.94 (m, 1 H) 3.92 - 4.04 (m, 4 H) 4.11 (s, 1 H) 4.18 (m, 1 H) 4.46 (m, 1 H) 5.06 - 5.15 (m, 1 H) 5.29 (m, 1 H) 5.67 - 5.77 (m, 2 H) 6.54 (m, 1 H) 6.75 (ddd, *J*=19.83, 7.62, 2.01 Hz, 1 H) 6.89 (m, 1 H) 7.31 (s, 1 H) 7.49 (s, 1 H) 7.59 - 7.68 (m, 2 H) 8.04 (t, *J*=8.44 Hz, 1 H); LC-MS, MS *m/z* 824 (M^++H).

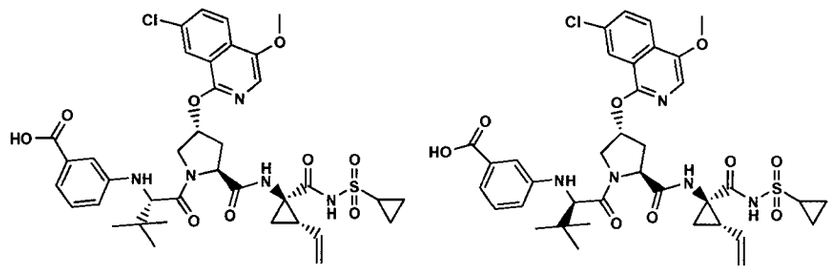
Compound 210B: LC-MS, MS *m/z* 824 (M^++H).

Compound 211 Isomers:

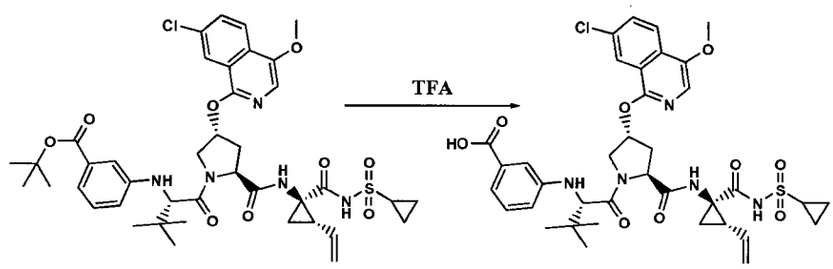
N-(3-carboxyphenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and

N-(3-carboxyphenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 211: Preparation of Compounds 211A and 211B



Compounds 211A and 211B



tert-butyl 3-((S)-1-((2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-2-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropylcarbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-ylamino)benzoate (20 mg, 0.024 mmol, compound 210A) was dissolved in CH2Cl2 (2 ml) at 25 °C. TFA (0.019 ml, 0.243 mmol) was added dropwise. The mixture was stirred overnight. The TFA was removed and the residue was purified by preparative HPLC. Compound 211A was obtained as a white powder (0.005g, 26.8% yield). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.04 - 1.14 (m,

11 H) 1.19 - 1.30 (m, 2 H) 1.38 - 1.46 (m, 1 H) 1.86 (dd, *J*=8.18, 5.41 Hz, 1 H) 2.21 (ddd, *J*=13.91, 9.76, 3.78 Hz, 2 H) 2.48 (dd, *J*=13.72, 6.92 Hz, 1 H) 2.95 (ddd, *J*=12.84, 8.06, 4.78 Hz, 1 H) 3.94 - 4.02 (m, 5 H) 4.15 (d, *J*=12.09 Hz, 1 H) 4.46 - 4.56 (m, 1 H) 5.10 (dd, *J*=10.32, 1.51 Hz, 1 H) 5.28 (dd, *J*=17.25, 1.39 Hz, 1 H) 5.68 - 5.78 (m, 2 H) 6.48 - 6.56 (m, 1 H) 6.63 (dd, *J*=7.81, 2.01 Hz, 1 H) 6.84 (d, *J*=7.81 Hz, 1 H) 7.17 - 7.28 (m, 1 H) 7.42 - 7.49 (m, 1 H) 7.62 (td, *J*=8.56, 2.01 Hz, 2 H) 7.97 - 8.05 (m, 1 H); LC-MS, MS *m/z* 768 (M^++H).

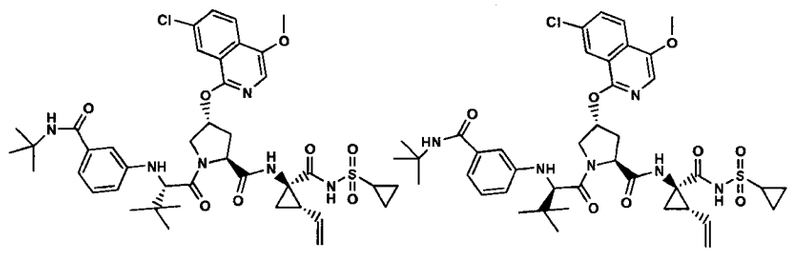
Compound 211B was made from compound 210B by the same procedure as was used for the preparation of compound 211A. LC-MS, MS *m/z* 768 (M^++H).

Compound 212 Isomers:

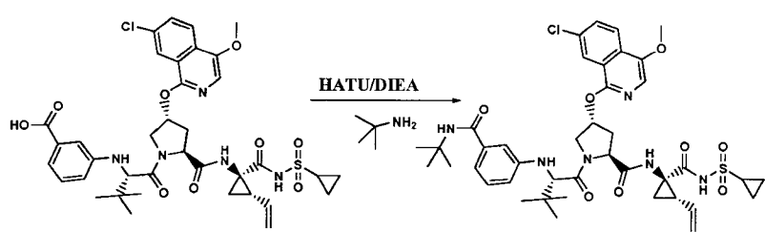
N-(3-(tert-butylcarbamoyl)phenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and

N-(3-(tert-butylcarbamoyl)phenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 212: Preparation of Compounds 212A and 212B



Compounds 212A and 212B



To the solution of 3-((S)-1-((2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-2-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-

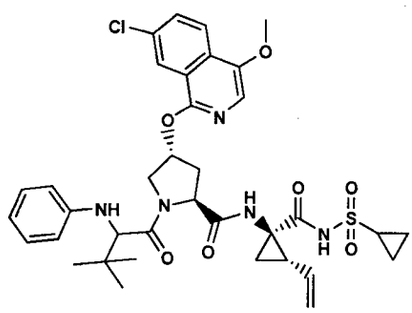
vinylcyclopropylcarbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-ylamino)benzoic acid (60 mg, 0.078 mmol, compound 211A) and 2-methylpropan-2-amine (11.42 mg, 0.156 mmol) in methylene chloride at 0°C was added HATU (59.4 mg, 0.156 mmol) followed by diisopropylethyl amine (25.2 mg, 0.195 mmol). A light yellow solution was formed after addition of the base. The mixture was stirred at room temperature for two hours. The reaction mixture was diluted with ethyl acetate (25 ml), washed with water (pH~6) and brine. The organic was dried over sodium sulfate, filtered, and concentrated. A yellow oil was obtained. Purification by preparative HPLC gave Compound 212A as a white powder (0.036g, 56% yield). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.04 - 1.14 (m, 11 H) 1.23 - 1.34 (m, 11 H) 1.41 (ddd, *J*=14.73, 5.29, 5.16 Hz, 1 H) 1.86 (dd, *J*=8.18, 5.41 Hz, 1 H) 2.16 - 2.25 (m, 2 H) 2.48 (dd, *J*=13.72, 6.92 Hz, 1 H) 2.95 (ddd, *J*=12.84, 8.06, 4.78 Hz, 1 H) 3.97 - 4.00 (m, 3 H) 4.02 - 4.11 (m, 2 H) 4.26 (d, *J*=12.34 Hz, 1 H) 4.46 (dd, *J*=10.20, 6.92 Hz, 1 H) 5.10 (dd, *J*=10.20, 1.64 Hz, 1 H) 5.23 - 5.31 (m, 1 H) 5.68 - 5.78 (m, 2 H) 6.51 - 6.60 (m, 2 H) 6.69 - 6.78 (m, 1 H) 7.09 (d, *J*=2.01 Hz, 1 H) 7.50 - 7.55 (m, 1 H) 7.63 - 7.73 (m, 2 H) 8.07 (d, *J*=9.06 Hz, 1 H); LC-MS, MS *m/z* 823 (M^++H).

Compound 212B was made from compound 211B by the same procedure used for preparation of compound 212A. LC-MS, MS *m/z* 768 (M^++H).

Compound 213 Isomers:

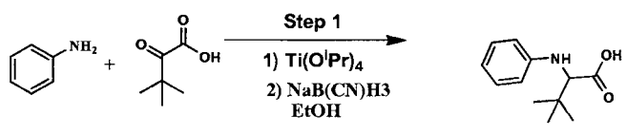
3-methyl-N-phenyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and 3-methyl-N-phenyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

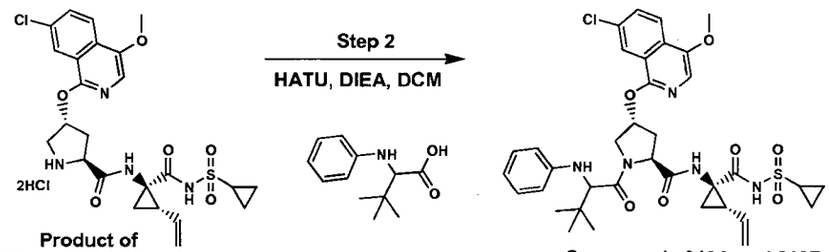
Example 213: Preparation of Compounds 213A and 213B



Compounds 213A and 213B

Scheme 1





Step 1:

To a mixture of aniline (180 mg, 1.94 mmol) and 3,3-dimethyl-2-oxobutanoic acid (500 mg, 3.84 mmol) in a 100 ml RBF at RT was added tetraisopropoxytitanium (2 ml,) via a pipet. The color of the mixture soon changed into a characteristic canary color. The solution was warmed to 75°C for about 15 minutes and the color remained the same. The solution was diluted with absolute ethanol (8 ml) at RT, followed by the addition of 1.5X of sodium cyanotrihydroborate (245 mg, 3.90 mmol), and the remaining half after the bubbling and sizzling was over. The color of the solution became lighter. The solution was mixed with 4 mL of water, forming a suspension, and the white PPT was removed by centrifuge. The organic was extracted into ethyl acetate, and the organic phase was dried over Na_2SO_4, filtered, and evaporated to dryness. A yellow oil was obtained

and was used in the next step without further purification. LC-MS, MS *m/z* 208 (M^+ +H).

Step 2:

To the yellow solution of 2-phenylamino-3,3-dimethylbutanoic acid (0.039 g, 0.189 mmol step1, example 213) and (2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-N-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropyl)pyrrolidine-2-carboxamide (0.101 g, 0.189 mmol, step 5, example 22) in CH_2Cl_2 at 0°C was added HATU (0.144 g, 0.378 mmol) followed by diisopropylethyl amine (0.061 g, 0.473 mmol). A light yellow solution was formed after addition of the base. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (25 ml), washed with water (pH~6) and brine. The organic was dried over sodium sulfate, filtered, concentrated, and the residue was purified by reverse phase preparative HPLC to give two separate products with identical MS *m/z* as observed by LCMS. Compound 213A (0.0032 g, 2.3% yield) was the first of the two isomers to elute by reverse phase preparative HPLC. Compound 213B (0.0035 g, 2.3% yield) was the second of the two isomers to elute by reverse phase preparative HPLC.

Compound 213A: ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.01 - 1.10 (m, 2 H) 1.11 - 1.21 (m, 9 H) 1.21 - 1.32 (m, 2 H) 1.35 - 1.46 (m, 1 H) 1.87 (dd, *J*=8.18, 5.41 Hz, 1 H) 2.16 - 2.26 (m, 2 H) 2.49 (dd, *J*=13.85, 6.80 Hz, 1 H) 2.95 (ddd, *J*=12.84, 8.06, 4.78 Hz, 1 H) 3.94 - 4.02 (m, 4 H) 4.04 - 4.10 (m, 2 H) 4.46 (dd, *J*=10.70, 6.92 Hz, 1 H) 5.11 (dd, *J*=10.32, 1.51 Hz, 1 H) 5.29 (dd, *J*=17.12, 1.26 Hz, 1 H) 5.67 - 5.78 (m, 2 H) 6.23 (t, *J*=7.30 Hz, 1 H) 6.58 - 6.63 (m, 2 H) 6.65 - 6.70 (m, 1 H) 7.49 - 7.56 (m, 1 H) 7.67 - 7.76 (m, 2 H) 8.11 (d, *J*=8.81 Hz, 1 H); LC-MS, MS *m/z* 724 (M^+ +H).

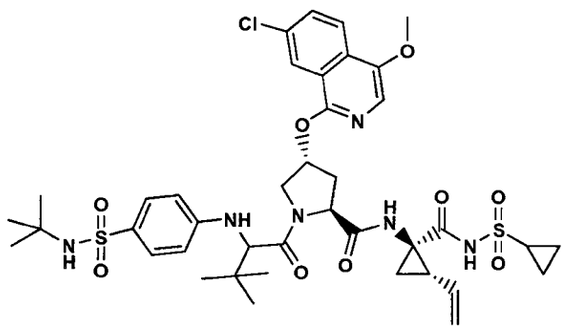
Compound 213B: LC-MS, MS *m/z* 724 (M^+ +H).

Compound 214 Isomers:

N-(4-(tert-butylsulfamoyl)phenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and

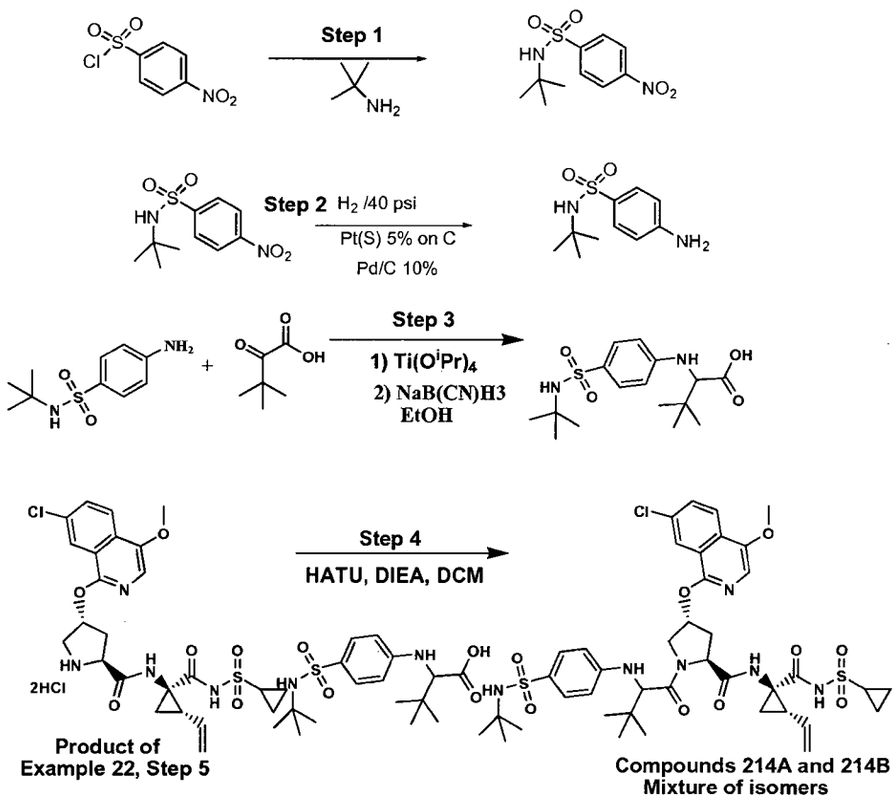
N-(4-(tert-butylsulfamoyl)phenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 214: Preparation of Compounds 214A and 214B



Compounds 214A and 214B

Scheme 1



Step 1:

To 4-nitrobenzene-1-sulfonyl chloride (500 mg, 2.256 mmol) in CH_2Cl_2 (20 ml) at 0-25°C was added 2-methylpropan-2-amine (825 mg, 11.28 mmol). The mixture was stirred over the weekend. A light brown suspension formed. LC-MS, MS *m/z* 208 (M^++H). showed the reaction was complete. Diluted the reaction mixture with ethyl acetate (20 ml), washed with water, brine. The organic layer was dried and concentrated to dryness. The residue was used in the next step without further purification.

Step 2:

N-tert-butyl-4-nitrobenzenesulfonamide (500 mg, 1.936 mmol) from step 1 was dissolved in methanol (30 ml). Pd-C was added under nitrogen. The flask was pressurized with hydrogen gas to 40 PSI and shaken on a Parr apparatus overnight. Pd-C was filtered away, evaporated solvent to dryness. The residue was used directly in the next step without further purification. LC-MS, MS *m/z* 229 (M^++H).

Step 3

To a mixture of 4-amino-N-tert-butylbenzenesulfonamide (180 mg, 0.788 mmol, from step 2) and 3,3-dimethyl-2-oxobutanoic acid (308 mg, 2.4 mmol) in a 100 ml RBF at RT was added tetraisopropoxytitanium (2 ml,) via a pipet. The color of the mixture soon changed into a characteristic canary color. The solution was warmed to 75°C for about 15 minutes and the color remained the same. The solution was diluted with absolute ethanol (8 ml) at RT, followed by the addition of 1.5X of sodium cyanotrihydroborate (245 mg, 3.90 mmol), and the remaining half after the bubbling and sizzling was over. The color of the solution became lighter. The solution was mixed with 4 mL of water, forming a suspension, and the white PPT was removed by centrifuge. The organic was extracted into ethyl acetate, and the organic phase was dried over Na_2SO_4, filtered, and evaporated to dryness. A yellow oil was obtained and was used directly in the next step without further purification. LC-MS, MS *m/z* 343 (M^++H).

Step 4:

To the yellow solution of 2-(4-(N-tert-butylsulfamoyl)phenylamino)-3,3-dimethylbutanoic acid (0.066 g, 0.189 mmol step1, example 214) and (2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-N-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropyl)pyrrolidine-2-carboxamide (0.101 g, 0.189 mmol, step 5, example 22) in CH_2Cl_2 at 0°C was added HATU (0.144 g, 0.378 mmol) followed by diisopropylethyl amine (0.061 g, 0.473 mmol). A light yellow solution was formed after addition of the base. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (25 ml) and was washed with water (pH~6) and brine. The organic was dried over sodium sulfate, filtered, concentrated, and the residue was purified by reverse phase preparative HPLC to give two separate products with identical MS *m/z* as observed by LCMS. Compound 214A (0.021 g, 13.0% yield) was the first of the two isomers to elute by reverse phase preparative HPLC. Compound 214B (0.0022 g, 13.5.0% yield) was the second of the two isomers to elute by reverse phase preparative HPLC.

Compound 214A: ^{1}H NMR (500 MHz, CD_3OD) δ ppm 0.98 - 1.06 (m, 9 H) 1.08 - 1.16 (m, 12 H) 1.27 - 1.36 (m, 2 H) 1.46 (dd, *J*=9.46, 5.49 Hz, 1 H) 1.91 (dd, *J*=7.93, 5.49 Hz, 1 H) 2.24 - 2.33 (m, 2 H) 2.60 (d, *J*=6.10 Hz, 1 H) 2.96 - 3.01 (m, 1

H) 4.03 (s, 3 H) 4.09 - 4.13 (m, 2 H) 4.47 (d, *J*=11.90 Hz, 1 H) 4.63 (dd, *J*=10.22, 7.17 Hz, 1 H) 5.15 (d, *J*=10.38 Hz, 1 H) 5.30 - 5.35 (m, 1 H) 5.74 - 5.80 (m, 2 H) 6.52 (d, *J*=8.85 Hz, 2 H) 7.16 (d, *J*=8.85 Hz, 2 H) 7.60 (s, 1 H) 7.71 (dd, *J*=8.85, 2.14 Hz, 1 H) 7.98 (d, *J*=1.83 Hz, 1 H) 8.14 (d, *J*=8.85 Hz, 1 H); LC-MS, MS *m/z* 859 (M^++H).

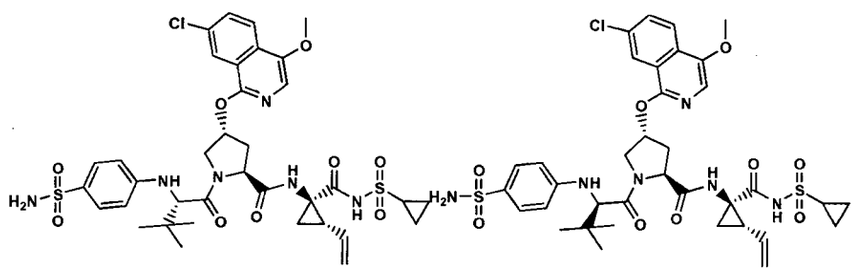
Compound 214B: LC-MS, MS *m/z* 859 (M^++H).

Compound 215 Isomers:

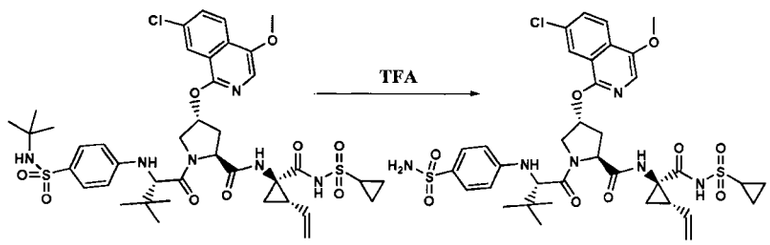
3-methyl-N-(4-sulfamoylphenyl)-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and

3-methyl-N-(4-sulfamoylphenyl)-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 215: Preparation of Compounds 215A and 215B



Compounds 215A and 215B



(2S,4R)-1-((S)-2-(3-(N-tert-butylsulfamoyl)phenylamino)-3,3-dimethylbutanoyl)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-N-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropyl)pyrrolidine-2-carboxamide (20

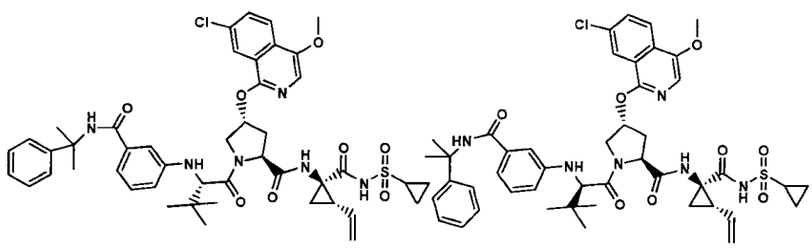
mg, 0.024 mmol, compound 214A) was dissolved in TFA (2 ml) at 25 °C. the mixture was stirred overnight. The TFA was removed and the residue was purified by preparative HPLC. Compound 215A was thus obtained as a white powder (0.013g, 69.5% yield). ^{1}H NMR (400 MHz, CD_3OD) δ) 1.01 - 1.13 (m, 11 H) 1.27 - 1.37 (m, 2 H) 1.40 - 1.44 (m, 1 H) 1.87 (dd, *J*=8.18, 5.41 Hz, 1 H) 2.20 - 2.28 (m, 2 H) 2.57 (dd, *J*=13.72, 7.18 Hz, 1H) 2.92 - 2.98 (m, 1 H) 3.98 - 4.06 (m, 4 H) 4.09 (s, 1 H) 4.37 (d, *J*=12.09 Hz, 1 H) 4.58 (dd, *J*=10.07, 7.05 Hz, 1 H) 5.11 (dd, *J*=10.32, 1.51 Hz, 1 H) 5.32 (m, 1 H) 5.69 - 5.78 (m, 2 H) 6.48 - 6.53 (m, 2 H) 7.19 - 7.26 (m, 2 H) 7.53 - 7.56 (s, 41H) 7.65 (dd, *J*=8.94, 2.14 Hz, 1 H) 7.90 (d, *J*=2.01 Hz, 1 H) 8.07 (d, *J*=8.81 Hz, 1 H); LC-MS, MS *m/z* 803 (M^++H).

Compound 215B was made from compound 214B by the same procedure as was used for the preparation of compound 215A. LC-MS, MS *m/z* 803 (M^++H).

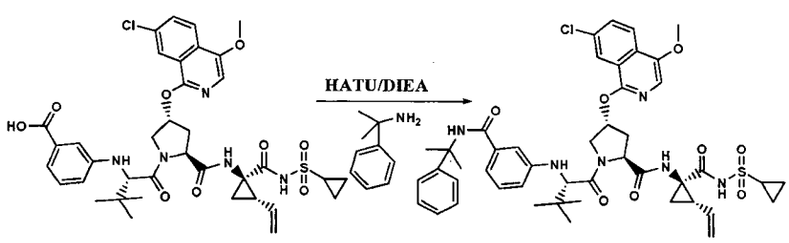
Compound 216 Isomers:

3-methyl-N-(3-((1-methyl-1-phenylethyl)carbamoyl)phenyl)-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and 3-methyl-N-(3-((1-methyl-1-phenylethyl)carbamoyl)phenyl)-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 216: Preparation of Compounds 216A and 216B



Compounds 216A and 216B



To the solution of 3-((S)-1-((2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-2-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropylcarbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-ylamino)benzoic acid (60 mg, 0.078 mmol, compound 211A) and 2-phenylpropan-2-amine (21.12 mg, 0.156 mmol) in methylenechloride at 0°C was added HATU (59.4 mg, 0.156 mmol) followed by diisopropylethyl amine (25.2 mg, 0.195 mmol). A light yellow solution was formed after addition of the base. The mixture was stirred at room temperature for two hours. The reaction mixture was diluted with ethyl acetate (25 ml) and was washed with water (pH~6) and brine. The organic was dried over sodium sulfate, filtered, and concentrated to a yellow oil. Purification by preparative gave Compound 216A as a white powder (0.056g, 81% yield). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.03 - 1.13 (m, 11 H) 1.19 - 1.30 (m, 2 H) 1.41 (dd, *J*=9.44, 5.41 Hz, 1 H) 1.63 (d, *J*=5.79 Hz, 6 H) 1.85 (dd, *J*=8.06, 5.54 Hz, 1 H) 2.16 - 2.25 (m, 2 H) 2.49 (dd, *J*=13.72, 6.92 Hz, 1 H) 2.91 - 2.98 (m, 1 H) 3.99 (s, 3 H) 4.06 (dd, *J*=12.09, 3.53 Hz, 1 H) 4.10 (s, 1 H) 4.30 (d, *J*=12.09 Hz, 1 H) 4.46 (dd, *J*=10.07, 7.05 Hz, 1 H) 5.10 (dd, *J*=10.45, 1.64 Hz, 1 H) 5.25-5.29 (dd, J=17.12, *J*=1.51 Hz, 1H) 5.68 - 5.79 (m, 2 H) 6.52 - 6.59 (m, 2H) 6.82 (dd, *J*=6.42, 1.89 Hz, 1 H) 7.10 - 7.13 (m, 2 H) 7.17 - 7.23 (m, 2 H) 7.29 - 7.34 (m, 2 H) 7.54 (s, 1 H) 7.67 (dd, *J*=8.94, 2.14 Hz, 1 H) 7.74 (d, *J*=2.01 Hz, 1 H) 8.09 (d, *J*=8.81 Hz, 1 H); LC-MS, MS *m/z* 886 (M^++H).

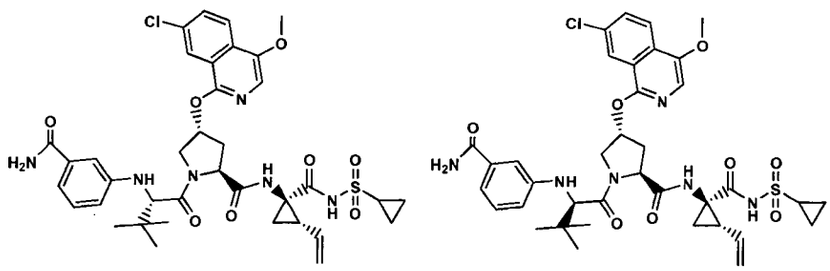
Compound 216B was made from compound 211B by the same procedure as was used for the preparation of compound 216A. LC-MS, MS *m/z* 886 (M^++H).

Compound 217 Isomers:

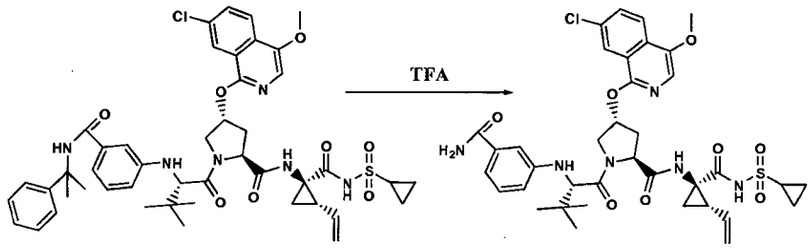
N-(3-carbamoylphenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and

N-(3-carbamoylphenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 217: Preparation of Compounds 217A and 217B



Compounds 217A and 217B



(2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-N-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropyl)-1-((S)-3,3-dimethyl-2-(3-(2-phenylpropan-2-ylcarbamoyl)phenylamino)butanoyl)pyrrolidine-2-carboxamide (50 mg, 0.056 mmol compound 216A) was dissolved in 1 ml of 2,2,2-trifluoroacetic acid at 25 °C. The resulting solution was stirred overnight. The TFA was removed and the residue was purified by preparative HPLC to give Compound 217A as a white powder (0.023g, 46% yield). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.03 - 1.12 (m, 11 H) 1.19 - 1.30 (m, 2 H) 1.42 (dd, *J*=9.44, 5.41 Hz, 1 H) 1.87 (dd, *J*=8.06, 5.54 Hz, 1 H) 2.16 - 2.26 (m, 2 H) 2.49 (dd, *J*=13.72, 6.92 Hz, 1 H) 2.92 - 2.99 (m, 1 H) 3.96 - 4.05 (m, 5 H) 4.20 (t, *J*=11.83 Hz, 1 H) 4.51 (dd, *J*=10.58, 7.05 Hz, 1 H) 5.11 (dd, *J*=10.32, 1.76 Hz, 1 H) 5.29 (dd, *J*=17.25, 1.39 Hz, 1 H) 5.69 - 5.79 (m, 2 H) 6.56 - 6.66 (m, 2 H) 6.76 (d, *J*=7.55 Hz, 1 H) 7.11 (d, *J*=1.76 Hz, 1 H) 7.47 - 7.52 (s, 1 H) 7.66 (dd, *J*=8.81, 2.27 Hz, 1 H) 7.74 (d, *J*=1.76 Hz, 1 H) 8.07 (d, *J*=8.81 Hz, 1 H); LC-MS, MS *m/z* 767 (M^++H).

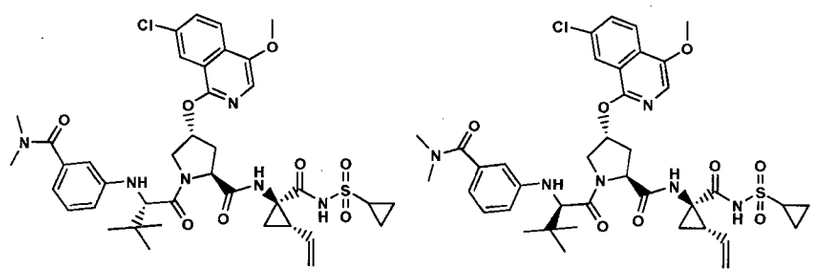
Compound 217B was made from compound 216B by the same procedure as was used for the preparation of compound 217A. LC-MS, MS *m/z* 767(M^++H).

Compound 218 Isomers:

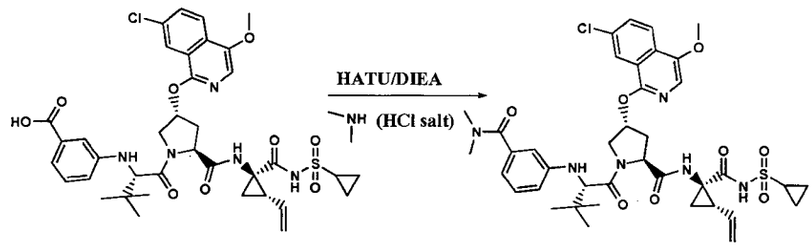
N-(3-(dimethylcarbamoyl)phenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and

N-(3-(dimethylcarbamoyl)phenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 218: Preparation of Compounds 218A and 218B



Compounds 218A and 218B



To the solution of 3-((S)-1-((2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-2-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropylcarbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-ylamino)benzoic acid (60 mg, 0.078 mmol, compound 211A) and dimethylaminehydrochloride (12.6 mg, 0.156 mmol) in methylenechloride at 0°C was added HATU (59.4 mg, 0.156 mmol) followed by diisopropylethyl amine (25.2 mg, 0.195 mmol). A light yellow solution was formed after addition of the base. The mixture was stirred at room temperature for two hours. The reaction mixture was diluted with ethyl acetate (25 ml) and was washed with water (pH~6) and brine. The organic was dried over sodium sulfate, filtered, and concentrated to a yellow oil. Purification by preparative HPLC afforded Compound 218A as a white powder

(0.035g, 58% yield). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.03 - 1.13 (m, 11 H) 1.16 - 1.28 (m, 2 H) 1.38 - 1.45 (m, 1 H) 1.86 (dd, *J*=8.18, 5.41 Hz, 1 H) 2.18 - 2.27 (m, 2 H) 2.51 (dd, *J*=13.72, 6.92 Hz, 1 H) 2.77 - 2.87 (m, 3 H) 2.91 - 3.00 (m, 4 H) 3.96 - 4.07 (m, 5 H) 4.23 (d, *J*=12.34 Hz, 1 H) 4.48 (dd, *J*=10.32, 7.05 Hz, 1 H) 5.11 (dd, *J*=10.32, 1.51 Hz, 1 H) 5.28 (dd, *J*=17.12, 1.51 Hz, 1 H) 5.69 - 5.79 (m, 2 H) 6.30 - 6.36 (m, 1 H) 6.47 - 6.54 (m, 2 H) 6.76 (d, *J*=1.26 Hz, 1 H) 7.52 - 7.56 (m, 1 H) 7.68 (dd, *J*=8.94, 2.14 Hz, 1 H) 7.81 (d, *J*=2.01 Hz, 1 H) 8.04 - 8.11 (m, 1 H); LC-MS, MS *m/z* 795 (M^++H).

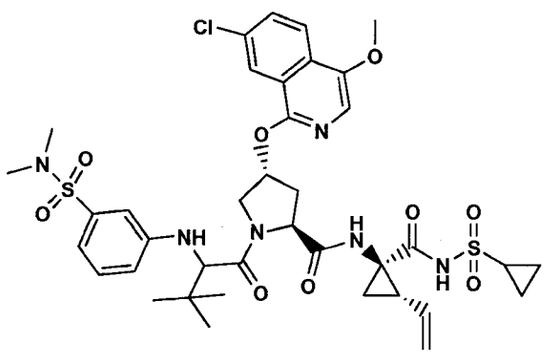
Compound 218B was made from compound 211B by the same procedure as was used for the preparation of compound 218A. LC-MS, MS *m/z* 795 (M^++H).

Compound 219 Isomers:

N-(3-(dimethylsulfamoyl)phenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and

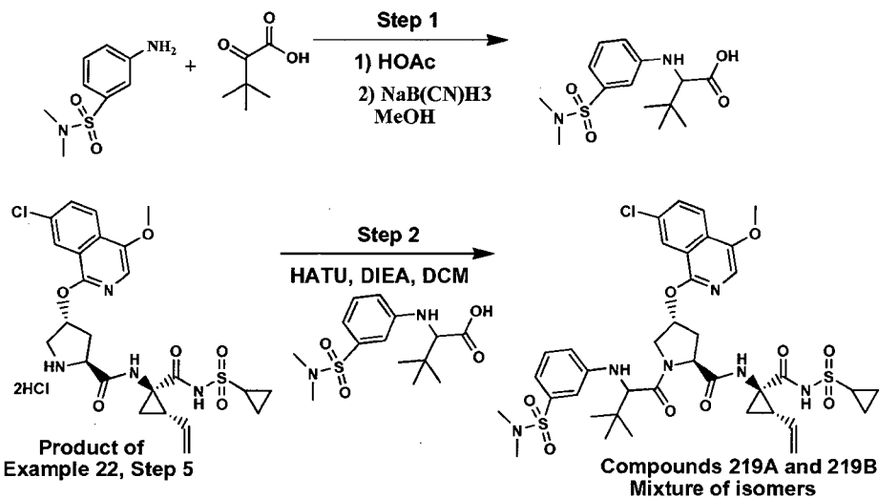
N-(3-(dimethylsulfamoyl)phenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 219: Preparation of Compounds 219A and 219B



Compounds 219A and 219B

Scheme 1



Step 1:

To a mixture of 3-amino-N,N-dimethylbenzenesulfonamide (203 mg, 1.014 mmol) and 3,3-dimethyl-2-oxobutanoic acid (264 mg, 2.027 mmol)) in a 100 ml RBF at RT was added acetic acid (2 ml,) via a pipet. The color of the mixture soon changed into a characteristic canary color. The solution was warmed to 75°C for about 120 minutes and the color remained the same. The solution was diluted with methanol (2 ml) at RT, followed by the addition of 1.5X of sodium cyanotrihydroborate (245 mg, 3.90 mmol), and the remaining half after the bubbling and sizzling was over. The color of the solution became lighter. Added 30 ml of water to the mixture, then extracted it with 10 ml of ethyl acetate (adjust pH to 4). Then the organic was washed by sodium bicarbonate at pH=8. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The oily residue was dried under high vacuum. A yellow oil was obtained and was used directly in the next step without further purification. LC-MS, MS *m/z* 315 (M^++H).

Step 2:

To the yellow solution of 2-(3-(N,N-dimethylsulfamoyl)phenylamino)-3,3-dimethylbutanoic acid (59.4 mg, 0.189 mmol, step1, example 219) and (2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-N-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropyl)pyrrolidine-2-carboxamide

(0.150 g, 0.28 mmol, step 5, example 22) in CH_2Cl_2 at 0°C was added HATU (0.144 g, 0.378 mmol) followed by diisopropylethyl amine (0.061 g, 0.473 mmol). A light yellow solution was formed after addition of the base. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (25 ml) and was washed with water (pH~6) and brine. The organic was dried over sodium sulfate, filtered, concentrated, and the residue was purified by reverse phase preparative HPLC to give two separate products with identical MS *m/z* as observed by LCMS. Compound 219A (0.062 g, 39.5% yield) was the first of the two isomers to elute by reverse phase preparative HPLC. Compound 219B (0.038 g, 24.2% yield) was the second of the two isomers to elute by reverse phase preparative HPLC.

Compound 219A: ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.02 - 1.12 (m, 9 H) 1.17 - 1.20 (m, 2 H) 1.22 - 1.29 (m, 2 H) 1.32 - 1.44 (m, 1 H) 1.87 (dt, *J*=8.25, 5.57 Hz, 1 H) 2.16 - 2.28 (m, 2 H) 2.46 - 2.57 (m, 7 H) 2.90 - 2.98 (m, 1 H) 3.96 - 4.00 (s, 3 H) 4.03 - 4.10 (m, 2 H) 4.30 (t, *J*=11.96 Hz, 1 H) 4.47 - 4.58 (m, 1 H) 5.10 (dd, *J*=10.32, 1.76 Hz, 1 H) 5.29 (ddd, *J*=17.12, 7.93, 1.39 Hz, 1 H) 5.68 - 5.79 (m, 2 H) 6.55 - 6.67 (m, 3 H) 7.02 (s, 1 H) 7.50 - 7.55 (m, 1 H) 7.63 - 7.69 (m, 1 H) 7.81 (d, *J*=2.01 Hz, 1 H) 8.02 - 8.09 (m, 1 H); LC-MS, MS *m/z* 831 (M^++H).

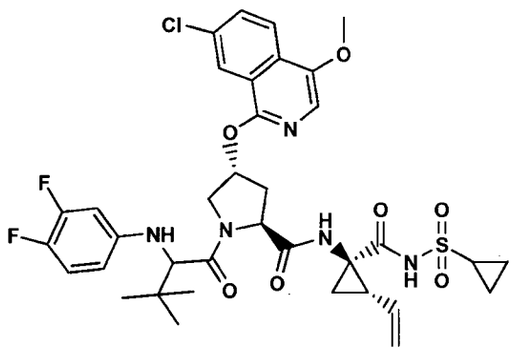
Compound 219B: LC-MS, MS *m/z* 831 (M^++H).

Compound 220 Isomers:

N-(3,4-difluorophenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and

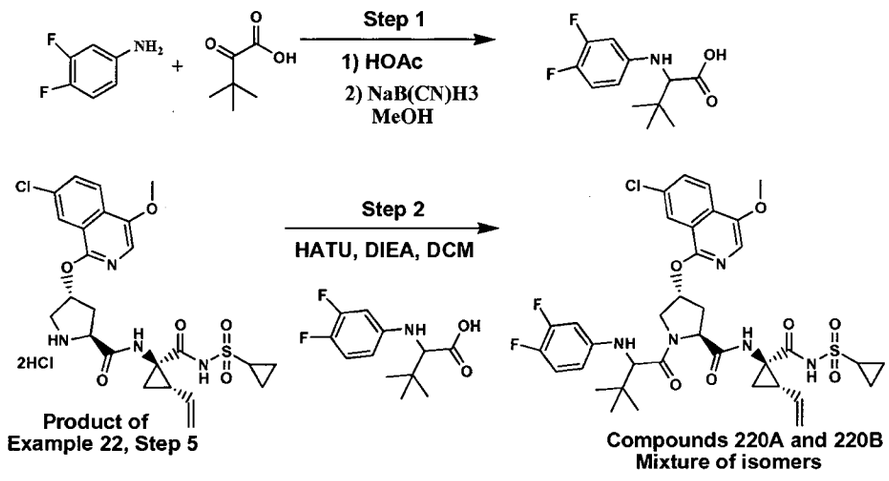
N-(3,4-difluorophenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 220: Preparation of Compounds 220A and 220B



Compounds 220A and 220B

Scheme 1



Step 1:

To a mixture of 3,4-difluoroaniline (180 mg, 1.394 mmol) and 3,3-dimethyl-2-oxobutanoic acid (500 mg, 3.84 mmol) in a 25 ml RBF at RT was added 2 ml of acetic acid. The solution was warmed to 75°C for about 120 minutes. The solution was diluted with methanol (2 ml) at RT, followed by the addition of 1.5X of sodium cyanotrihydroborate (245 mg, 3.90 mmol), and the remaining half after the bubbling and sizzling was over. The color of the solution became lighter. Added 30 ml of water to the mixture, then extracted it with 10 ml of ethyl acetate (adjust pH to 4). The organic was washed with sodium bicarbonate at PH=8. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The resulting oily residue was dried

under high vacuum. A yellow oil was thus obtained and was used directly in the next step without further purification. LC-MS, MS *m/z* 244 (M^++H).

Step 2:

To the yellow solution of 2-(3, 4-difluorophenylamino)-3,3-dimethylbutanoic acid (0.046 g, 0.189 mmol, step1, example 208) and (2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-N-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropyl)pyrrolidine-2-carboxamide (0.101 g, 0.189 mmol, step 5, example 22) in CH_2Cl_2 at 0°C was added HATU (0.144 g, 0.378 mmol) followed by diisopropylethyl amine (0.061 g, 0.473 mmol). A light yellow solution was formed after addition of the base. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (25 ml) and was washed with water (pH~6) and brine. The organic was dried over sodium sulfate, filtered, concentrated, and the residue was purified by reverse phase preparative HPLC to give two separate products with identical MS *m/z* as observed by LCMS. Compound 220A (0.033 g, 23.0% yield) was the first of the two isomers to elute by reverse phase preparative HPLC. Compound 220B (0.026 g, 19 % yield) was the second of the two isomers to elute by reverse phase preparative HPLC.

Compound 220A: ^{1}H NMR (500 MHz, CD_3OD) δ ppm 1.07 - 1.16 (m, 11 H) 1.23 - 1.31 (m, 2 H) 1.41 - 1.49 (m, 1 H) 1.90 (dd, *J*=8.24, 5.49 Hz, 1 H) 2.21 - 2.29 (m, 2 H) 2.55 (dd, *J*=13.58, 6.56 Hz, 2 H) 2.92 - 3.00 (m, 1 H) 3.88 - 3.95 (s, 1 H) 3.97 - 4.04 (m, 4 H) 4.27 (d, *J*=12.21 Hz, 1 H) 4.57 (dd, *J*=10.53, 7.17 Hz, 1 H) 5.14 (d, *J*=10.38 Hz, 1 H) 5.32 (d, *J*=17.40 Hz, 1 H) 5.73 - 5.81 (m, 2 H) 6.15 (d, *J*=8.85 Hz, 1 H) 6.26 - 6.34 (m, 1 H) 6.44 (ddd, *J*=13.12, 6.71, 2.75 Hz, 1 H) 7.55 (s, 1 H) 7.66 - 7.73 (m, 1 H) 7.80 (d, *J*=2.14 Hz, 1 H) 8.07 - 8.14 (m, 1 H); LC-MS, MS *m/z* 760 (M^++H).

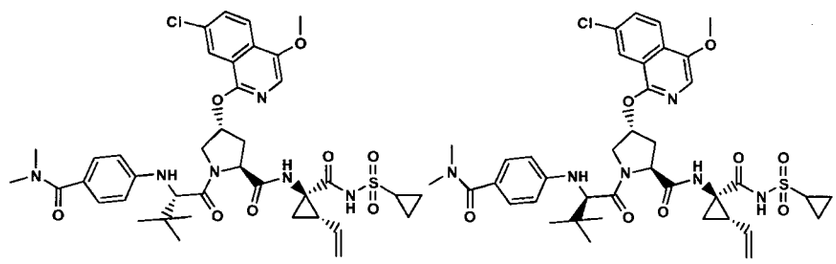
Compound 220B: LC-MS, MS *m/z* 760 (M^++H).

Compound 221 Isomers:

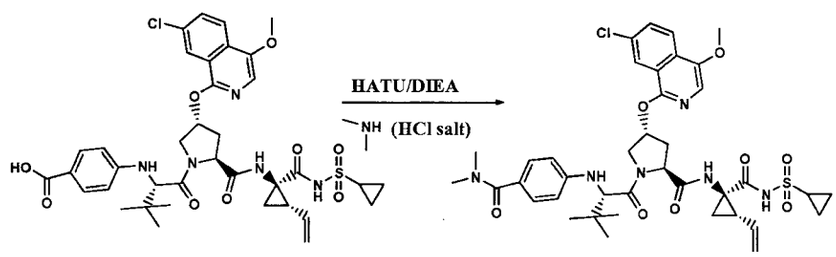
N-(4-(dimethylcarbamoyl)phenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and

N-(4-(dimethylcarbamoyl)phenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 221: Preparation of Compounds 221A and 221B



Compounds 221A and 221B



To the solution of 4-((S)-1-((2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-2-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropylcarbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-ylamino)benzoic acid (20 mg, 0.026 mmol, compound 209A) and dimethylaminehydrochloride (4.2mg, 0.052 mmol) in methylene chloride at 0°C was added HATU (20 mg, 0.052 mmol) followed by diisopropylethyl amine (8.4 mg, 0.065 mmol). A light yellow solution was formed after addition of the base. The mixture was stirred at room temperature for two hours. The reaction mixture was diluted with ethyl acetate (25 ml) and was washed with water (pH~6) and brine. The organic was dried over sodium sulfate, filtered, and concentrated to a yellow oil.

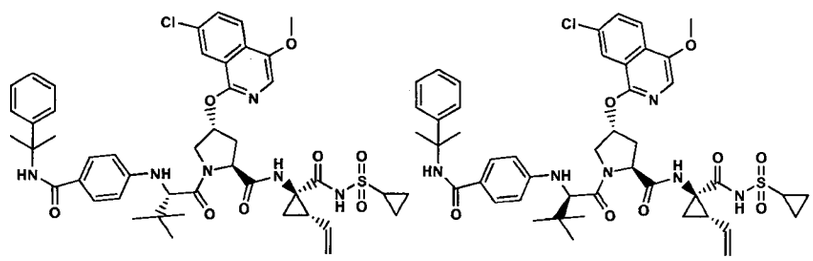
Purification by preparative HPLC afforded Compound 221A as a white powder (0.04g, 19% yield). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.02 - 1.13 (m, 11 H) 1.20 - 1.33 (m, 2 H) 1.41 (dd, *J*=9.44, 5.41 Hz, 1 H) 1.86 (dd, *J*=8.06, 5.54 Hz, 1 H) 2.18 - 2.30 (m, 2 H) 2.57 (dd, *J*=13.72, 7.18 Hz, 1H) 2.77 - 2.89 (s, 3 H) 2.89 - 3.00 (m, 4H) 3.99 - 4.09 (m, 5 H) 4.48 (d, *J*=12.84 Hz, 1 H) 4.55 (dd, *J*=10.58, 7.05 Hz, 1 H) 5.11 (dd, *J*=10.32, 1.51 Hz, 1 H) 5.28 (dd, *J*=17.12, 1.26 Hz, 1 H) 5.68 - 5.80 (m, 2 H) 6.41 (d, *J*=8.81 Hz, 2 H) 6.66 (d, *J*=8.81 Hz, 2 H) 7.61 (s, 1 H) 7.69 (dd, *J*=8.94, 2.14 Hz, 1 H) 7.92 (d, *J*=2.01 Hz, 1 H) 8.12 (d, *J*=9.07 Hz, 1 H); LC-MS, MS *m/z* 795 (M^++H).

Compound 221B was made from compound 209B by the same procedure as was used for the preparation of compound 221A. LC-MS, MS *m/z* 795 (M^++H).

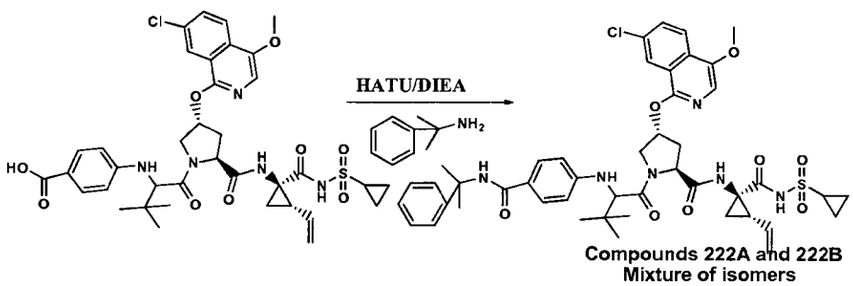
Compound 222 Isomers:

3-methyl-N-(4-((1-methyl-1-phenylethyl)carbamoyl)phenyl)-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and 3-methyl-N-(4-((1-methyl-1-phenylethyl)carbamoyl)phenyl)-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 222: Preparation of Compounds 222A and 222B



Compounds 222A and 222B



To the solution of 4-((S)-1-((2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-2-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropylcarbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-ylamino)benzoic acid (60 mg, 0.078 mmol, compound 209A) and 2-phenylpropane-2-amine (10.56mg, 0.078 mmol) in methylene chloride at 0°C was added HATU (60 mg, 0.156 mmol) followed by diisopropylethyl amine (25 mg, 0.21 mmol). A light yellow solution was formed after addition of the base. The mixture was stirred at room temperature for two hours. The reaction mixture was diluted with ethyl acetate (25 ml). and was washed with water (pH~6) and brine. The organic was dried over sodium sulfate, filtered, and concentrated to a yellow oil. Purification by preparative HPLC gave two separate products with identical MS *m/z* as observed by LCMS.

Compound 222A: White powder (0.01g, 14.6% yield). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.03 - 1.12 (m, 11 H) 1.20 - 1.26 (m, 2 H) 1.41 (dd, *J*=9.44, 5.41 Hz, 1 H) 1.70 (d, *J*=3.02 Hz, 6 H) 1.87 (dd, *J*=8.18, 5.41 Hz, 1 H) 2.18 - 2.27 (m, 2 H) 2.54 (dd, *J*=13.72, 6.92 Hz, 1 H) 2.92 - 2.98 (m, 1 H) 3.95 - 4.06 (m, 4 H) 4.11 (s, 1 H) 4.38 (d, *J*=12.09 Hz, 1 H) 4.55 (dd, *J*=10.07, 7.05 Hz, 1 H) 5.11 (dd, *J*=10.45, 1.64 Hz, 1 H) 5.26 -5.30 (dd, *J*=17.12 , *J*=1.26 Hz, 1 H)) 5.69 - 5.80 (m, 2 H) 6.49 (d, *J*=8.81 Hz, 2 H) 7.12 - 7.17 (m, 1 H) 7.22 - 7.28 (m, 3 H) 7.33 - 7.40 (m, 2 H) 7.54 (s, 1 H) 7.60 (dd, *J*=8.94, 2.14 Hz, 1 H) 7.83 (d, *J*=2.27 Hz, 1 H) 8.04 (d, *J*=9.06 Hz, 1 H); LC-MS, MS *m/z* 886 (M^++H).

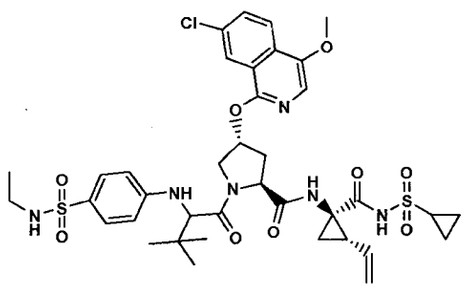
Compound 222B: LC-MS, MS *m/z* 886 (M^++H).

Compound 223 Isomers:

N-(4-(ethylsulfamoyl)phenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and

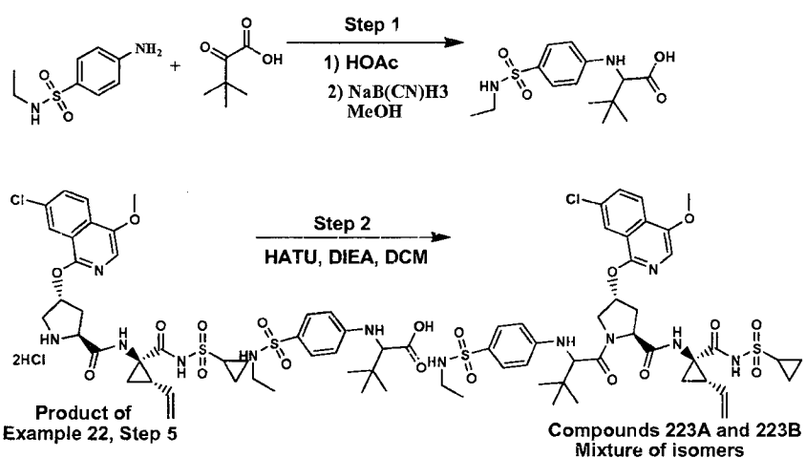
N-(4-(ethylsulfamoyl)phenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 223: Preparation of Compounds 223A and 223B



Compounds 223A and 223B

Scheme 1



Step 1

To a mixture of 4-amino-N-ethylbenzenesulfonamide (203 mg, 1.014 mmol) and 3,3-dimethyl-2-oxobutanoic acid (264 mg, 2.027 mmol) in a 25 ml RBF at RT was added acetic acid (2 ml,) via a pipet. The color of the mixture soon changed into a characteristic canary color. The solution was warmed to 75°C for about 120

minutes and the color remained the same. The solution was diluted with methanol (2 ml) at RT, followed by the addition of 1.5X of sodium cyanotrihydroborate (245 mg, 3.90 mmol), and the remaining half after the bubbling and sizzling was over. The color of the solution became lighter. Added 30 ml of water to the mixture, then extracted it with 10 ml of ethyl acetate (adjust pH to 4). The organic was washed with sodium bicarbonate at pH=8. The organic layer dried over Na_2SO_4, filtered, and concentrated to an oily residue which was dried under high vacuum. The yellow oil thus obtained was used directly in the next step without further purification. LC-MS, MS *m/z* 315 (M^++H).

Step 2:

To the yellow solution of 2-(4-(N-ethylsulfamoyl)phenylamino)-3,3-dimethylbutanoic acid (0.059 g, 0.189 mmol step1, example 223) and (2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-N-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropyl)pyrrolidine-2-carboxamide (0.101 g, 0.189 mmol, step 5, example 22) in CH_2Cl_2 at 0°C was added HATU (0.144 g, 0.378 mmol) followed by diisopropylethyl amine (0.061 g, 0.473 mmol). A light yellow solution was formed after addition of the base. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (25 ml) and was washed with water (pH~6) and brine. The organic was dried over sodium sulfate, filtered, concentrated, and the residue was purified by reverse phase preparative HPLC to give two separate products with identical MS *m/z* as observed by LCMS. Compound 223A (0.033 g, 21.0% yield) was the first of the two isomers to elute by reverse phase preparative HPLC. Compound 223B (0.024 g, 15.3.0% yield) was the second of the two isomers to elute by reverse phase preparative HPLC.

Compound 223A: ^{1}H NMR (400 MHz, CD_3OD) δ ppm 0.92 (t, *J*=7.30 Hz, 3 H) 1.02 - 1.11 (m, 11 H) 1.19 - 1.29 (m, 2 H) 1.42 (dd, *J*=9.44, 5.41 Hz, 1 H) 1.87 (dd, *J*=8.18, 5.41 Hz, 1 H) 2.20 - 2.29 (m, 2 H) 2.54 - 2.64 (m, 3 H) 2.95 (ddd, *J*=12.84, 8.06, 4.78 Hz, 1 H) 3.96 - 4.01 (s, 3 H) 4.01 - 4.09 (m, 2 H) 4.45 (d, *J*=12.09 Hz, 1 H) 4.59 (dd, *J*=10.07, 7.05 Hz, 1 H) 5.11 (dd, *J*=10.32, 1.76 Hz, 1 H) 5.29 (dd, *J*=17.25, 1.39 Hz, 1 H) 5.68 - 5.78 (m, 2 H) 6.45 - 6.50 (m, 2 H) 7.04 - 7.09 (m, 2 H) 7.55 (s, 1 H) 7.65 (dd, *J*=8.81, 2.27 Hz, 1 H) 7.90 (d, *J*=1.76 Hz, 1 H) 8.08 (d, *J*=9.06 Hz, 1 H); LC-MS, MS *m/z* 831 (M^++H).

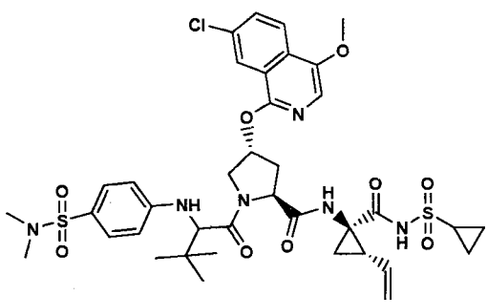
Compound 223B: LC-MS, MS *m/z* 831 (M^++H).

Compound 224 Isomers:

N-(4-(dimethylsulfamoyl)phenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and

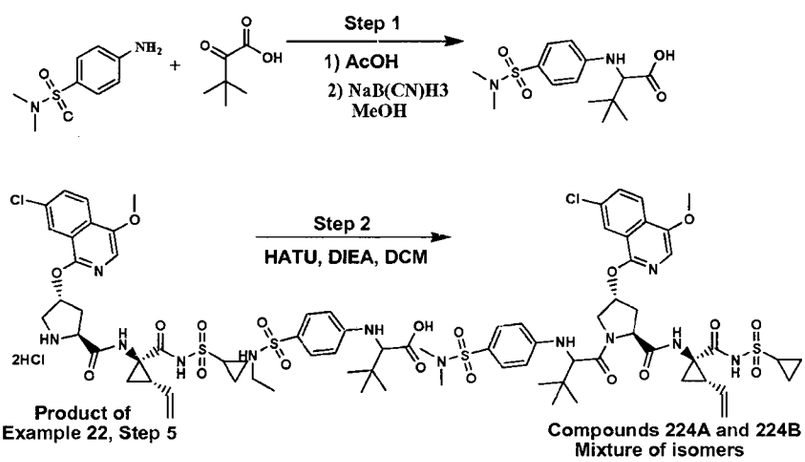
N-(4-(dimethylsulfamoyl)phenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 224: Preparation of Compounds 224A and 224B



Compounds 224A and 224B

Scheme 1



Step 1

To a mixture of 4-amino-N-ethylbenzenesulfonamide (203 mg, 1.014 mmol) and 3,3-dimethyl-2-oxobutanoic acid (264 mg, 2.027 mmol) in a 100 ml RBF at RT

was added 2 ml of acetic acid. The solution was warmed to 75°C for about 120 minutes. The solution was diluted with methanol (2 ml) at RT, followed by the addition of 1.5X of sodium cyanotrihydroborate (245 mg, 3.90 mmol), and the remaining half after the bubbling and sizzling was over. The color of the solution became lighter. Added 30 ml of water to the mixture, then extracted it with 10 ml of ethyl acetate (adjust pH to 4) . The organic was washed with sodium bicarbonate at pH=8. The organic layer was dried over Na_2SO_4, filtered, and concentrated to a yellow oil which was dried under high vacuum. This material was used directly in the next step without further purification. LC-MS, MS *m/z* 315 (M^++H).

Step 2:

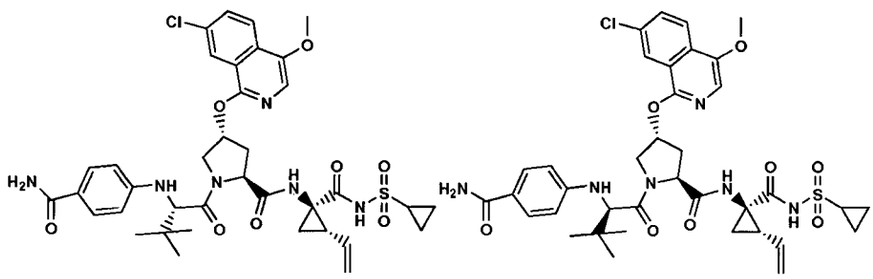
To the yellow solution of 2-(4-(N, N-dimethylsulfamoyl)phenylamino)-3,3-dimethylbutanoic acid (0.059 g, 0.189 mmol step1, example 224) and (2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-N-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropyl)pyrrolidine-2-carboxamide (0.101 g, 0.189 mmol, step 5, example 22) in CH_2Cl_2 at 0°C was added HATU (0.144 g, 0.378 mmol) followed by diisopropylethyl amine (0.061 g, 0.473 mmol). A light yellow solution was formed after addition of the base. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (25 ml) and was washed with water (pH~6) and brine. The organic was dried over sodium sulfate, filtered, concentrated, and the residue was purified by reverse phase preparative HPLC to give two separate products with identical MS *m/z* as observed by LCMS. Compound 224A (0.020 g, 13.0% yield) was the first of the two isomers to elute by reverse phase preparative HPLC. Compound 224B (0.014 g, 9.0% yield) was the second of the two isomers to elute by reverse phase preparative HPLC.

Compound 224A: ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.03 - 1.12 (m, 11 H) 1.22 - 1.26 (m, 2 H) 1.42 (dd, *J*=9.32, 5.54 Hz, 1 H) 1.88 (dd, *J*=8.18, 5.41 Hz, 1 H) 2.20 - 2.31 (m, 2 H) 2.35 - 2.40 (m, 6 H) 2.53 - 2.64 (m, 1 H) 2.91 - 3.00 (m, 1 H) 3.95 - 4.00 (s, 3 H) 4.03 - 4.09 (m, 2 H) 4.51 (d, *J*=12.09 Hz, 1 H) 4.57 - 4.67 (m, 1 H) 5.11 (dd, *J*=10.32, 1.51 Hz, 1 H) 5.29 (dd, *J*=17.12, 1.26 Hz, 1 H) 5.68 - 5.79 (m, 2 H) 6.47 (d, *J*=9.06 Hz, 2 H) 6.93 (d, *J*=8.81 Hz, 2 H) 7.53 - 7.57 (s, 1 H) 7.63 - 7.69 (m, 1 H) 7.91 (d, *J*=2.01 Hz, 1 H) 8.03 - 8.12 (m, 1 H); LC-MS, MS *m/z* 831 (M^+ +H).

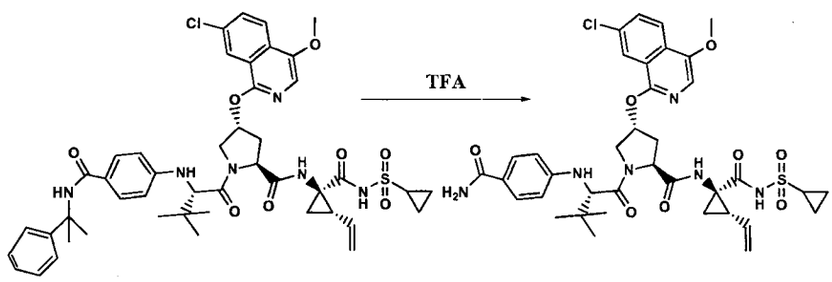
Compound 224B: LC-MS, MS *m/z* 831 (M^++H).

Compound 226 Isomers:
N-(4-carbamoylphenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and
N-(4-carbamoylphenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 226: Preparation of Compounds 226A and 226B



Compounds 226A and 226B



(2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-N-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropyl)-1-((S)-3,3-dimethyl-2-(4-(2-phenylpropan-2-ylcarbamoyl)phenylamino)butanoyl)pyrrolidine-2-carboxamide (8 mg, 0.009 mmol, compound 222A) was dissolved in 1 ml of 2,2,2-trifluoroacetic acid at 25 °C. The resulting mixture was stirred overnight. The TFA was removed and the residue was purified by preparative HPLC to afford Compound 226A as a white powder (0.005g, 81% yield). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.04 - 1.12 (m, 11

H) 1.23 - 1.33 (m, 2H) 1.42 (dd, *J*=9.57, 5.29 Hz, 1 H) 1.87 (dd, *J*=8.18, 5.41 Hz, 1 H) 2.19 - 2.27 (m, 2 H) 2.54 (dd, *J*=13.72, 7.43 Hz, 1 H) 2.92 - 2.98 (m, 1 H) 3.98 - 4.05 (m, 4 H) 4.12 (s, 1 H) 4.33 (d, *J*=12.59 Hz, 1 H) 4.55 (dd, *J*=10.32, 7.05 Hz, 1 H) 5.11 (dd, *J*=10.32, 1.76 Hz, 1 H) 5.27 (m, 2 H) 5.72 - 5.79 (m, 2 H) 6.45 - 6.49 (m, 2 H) 7.22 - 7.25 (2, 4 H) 7.52 (s, 1 H) 7.62 (dd, *J*=8.94, 2.14 Hz, 1 H) 7.79 (d, *J*=2.01 Hz, 1 H) 8.05 (d, *J*=8.81 Hz, 1 H); LC-MS, MS *m/z* 767 (M^++H).

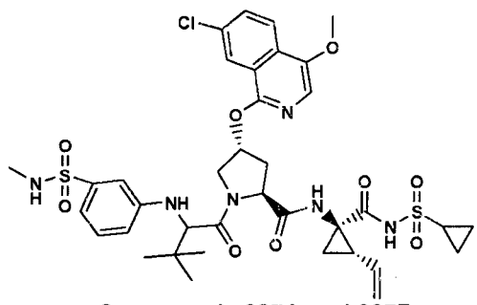
Compound 226B was made from compound 222B by the same procedure as was used for the preparation of compound 226A. LC-MS, MS *m/z* 767(M^++H).

Compound 227 Isomers:

3-methyl-N-(3-(methylsulfamoyl)phenyl)-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and

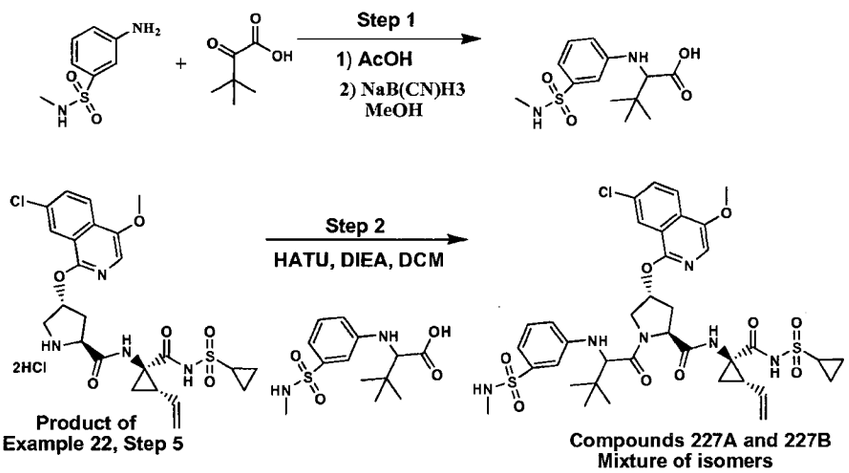
3-methyl-N-(3-(methylsulfamoyl)phenyl)-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 227: Preparation of Compounds 227A and 227B



Compounds 227A and 227B

Scheme 1



Step 1

To a mixture of 3-amino-N-methylbenzenesulfonamide (203 mg, 1.09 mmol) and 3,3-dimethyl-2-oxobutanoic acid (264 mg, 2.027 mmol) in a 25 ml RBF at RT was added 2 ml of acetic acid. The solution was warmed to 75°C for about 120 minutes. The solution was diluted with methanol (2 ml) at RT, followed by the addition of 1.5X of sodium cyanotrihydroborate (245 mg, 3.90 mmol), and the remaining half after the bubbling and sizzling was over. The color of the solution became lighter. Added 30 ml of water to the mixture, then extracted it with 10 ml of ethyl acetate (adjust pH to 4). The organic was washed with sodium bicarbonate at pH=8. The organic layer was dried over Na_2SO_4, filtered, and concentrated to a yellow oil which was dried under high vacuum. This material was used directly in the next step without further purification. LC-MS, MS *m/z* 301 (M^++H).

Step 2:

To the yellow solution of 2-(3-(N,-methylsulfamoyl)phenylamino)-3,3-dimethylbutanoic acid (0.034 g, 0.114 mmol step1, example 227) and (2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-N-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropyl)pyrrolidine-2-carboxamide (0.101 g, 0.189 mmol, step 5, example 22) in CH_2Cl_2 at 0°C was added HATU (0.087 g, 0.228 mmol) followed by diisopropylethyl amine (0.061 g, 0.473 mmol). A light

yellow solution was formed after addition of the base. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (25 ml) and was washed with water (pH~6) and brine. The organic was dried over sodium sulfate, filtered, concentrated, and the residue was purified by reverse phase preparative HPLC to give two separate products with identical MS *m/z* as observed by LCMS. Compound 227A (0.013 g, 14.0% yield) was the first of the two isomers to elute by reverse phase preparative HPLC. Compound 227B (0.009 g, 9.0% yield) was the second of the two isomers to elute by reverse phase preparative HPLC.

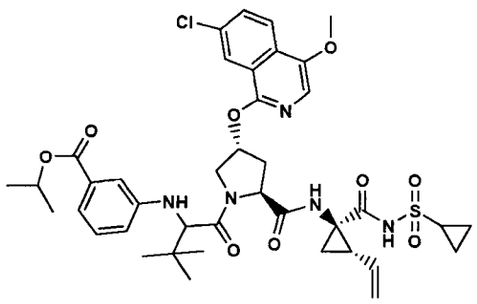
Compound 227A: ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.04 - 1.12 (m, 11 H) 1.17 - 1.27 (m, 2 H) 1.42 (dd, *J*=9.44, 5.41 Hz, 1 H) 1.87 (dd, *J*=8.18, 5.41 Hz, 1 H) 2.18 - 2.27 (m, 2 H) 2.38 (s, 3 H) 2.52 (dd, *J*=13.47, 6.92 Hz, 1 H) 2.95 (ddd, *J*=12.78, 8.12, 4.78 Hz, 1 H) 3.97 - 4.01 (s, 3 H) 4.03 - 4.11 (m, 2 H) 4.30 (d, *J*=12.09 Hz, 1 H) 4.52 (dd, *J*=10.07, 7.05 Hz, 1 H) 5.11 (dd, *J*=10.32, 1.51 Hz, 1 H) 5.28 (dd, *J*=17.25, 1.38 Hz, 1 H) 5.69 - 5.79 (m, 2 H) 6.53 - 6.63 (m, 2 H) 6.77 (d, *J*=7.55 Hz, 1 H) 7.08 (t, *J*=1.89 Hz, 1 H) 7.53 - 7.57 (m, 1 H) 7.65 - 7.69 (m, 1 H) 7.84 (d, *J*=1.76 Hz, 1 H) 8.08 (d, *J*=8.81 Hz, 1 H); LC-MS, MS *m/z* 817 (M^++H).

Compound 227B: LC-MS, MS *m/z* 817 (M^++H).

Compound 231 Isomers:

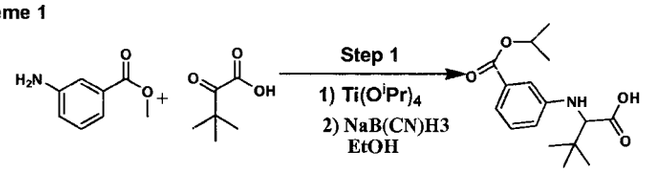
N-(3-(isopropoxycarbonyl)phenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and N-(3-(isopropoxycarbonyl)phenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

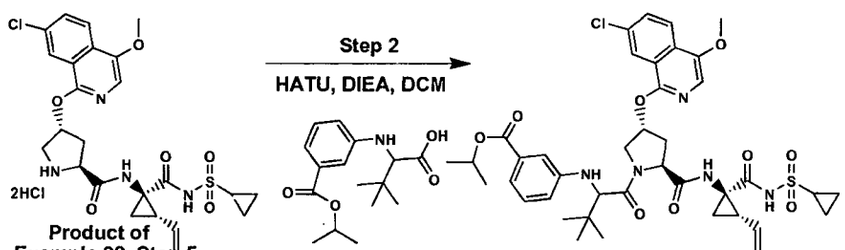
Example 231: Preparation of Compounds 231A and 231B



Compounds 231A and 231B

Scheme 1





Step 1:

To a mixture of methyl 3-benzoate (230 mg, 1.52 mmol) and 3,3-dimethyl-2-oxobutanoic acid (198 mg, 1.52 mmol) in a 100 mL RBF at RT was added tetraisopropoxytitanium (2 ml,) via a pipet. The color of the mixture soon changed into a characteristic canary color. The solution was warmed to 75°C for about 15 minutes and the color remained the same. The solution was diluted with absolute ethanol (8 ml) at RT, followed by the addition of 1.5X of sodium cyanotrihydroborate (245 mg, 3.90 mmol), and the remaining half after the bubbling and sizzling was over. The color of the solution became lighter. The solution was mixed with 4 mL of water, forming a suspension, the white PPT was removed by centrifuge. The organic was extracted into ethyl acetate, and the organic phase was

dried over Na_2SO_4, filtered, and evaporated to a white foam. This material was used directly in the next step without further purification. LC-MS, MS *m/z* 294 (M^++H)

Step 2:

To the yellow solution of 2-(3-(isopropoxycarbonyl)phenylamino)-3,3-dimethylbutanoic acid (0.055 g, 0.189 mmol, step 1, example 231) and (2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-N-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropyl)pyrrolidine-2-carboxamide (0.101 g, 0.189 mmol, step 5, example 22) in CH_2Cl_2 at 0°C was added HATU (0.144 g, 0.378 mmol) followed by diisopropylethyl amine (0.061 g, 0.473 mmol). A light yellow solution was formed after addition of base. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (25 ml) and was washed with water (pH~6) and brine. The organic was dried over sodium sulfate, filtered, concentrated, and the residue was purified by reverse phase preparative HPLC to give two separate products with identical MS *m/z* as observed by LCMS. Compound 231A (0.0235 g, 15.3.0% yield) was the first of the two isomers to elute by reverse phase preparative HPLC. Compound 231B (0.0175 g, 11.6% yield) was the second of the two isomers to elute by reverse phase preparative HPLC.

Compound 231A: ^{1}H NMR (400 MHz, CD_3OD) δ ppm 1.04 - 1.14 (m, 11 H) 1.19 - 1.29 (m, 6 H) 1.29 - 1.38 (m, 2 H) 1.38 - 1.43 (m, 1 H) 1.81 - 1.89 (m, 1 H) 2.16 - 2.25 (m, 2 H) 2.47 (dd, *J*=13.60, 7.05 Hz, 1 H) 2.95 (ddd, *J*=12.78, 8.12, 4.78 Hz, 1 H) 3.96 - 4.02 (m, 4 H) 4.02 - 4.08 (m, 1 H) 4.14 - 4.24 (m, 1 H) 4.42 - 4.53 (m, 1 H) 4.93 - 5.03 (m, *J*=6.24, 6.24, 6.24, 6.24, 6.24 Hz, 1 H) 5.06 - 5.16 (m, 1 H) 5.20 - 5.32 (m, 1 H) 5.68 - 5.78 (m, 2 H) 6.54 (t, *J*=7.81 Hz, 1 H) 6.60 - 6.69 (m, 1 H) 6.87 (d, *J*=7.55 Hz, 1 H) 7.20 - 7.26 (m, 1 H) 7.45 - 7.52 (m, 1 H) 7.58 - 7.68 (m, 2 H) 7.97 - 8.06 (m, 1 H); LC-MS, MS *m/z* 810 (M^++H).

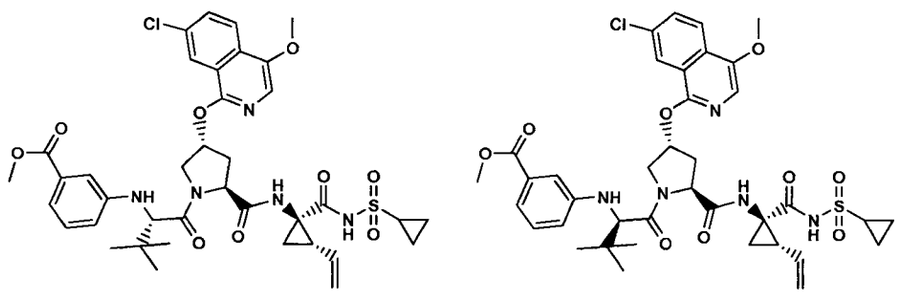
Compound 231B: LC-MS, MS *m/z* 810 (M^++H).

Compound 232 Isomers:

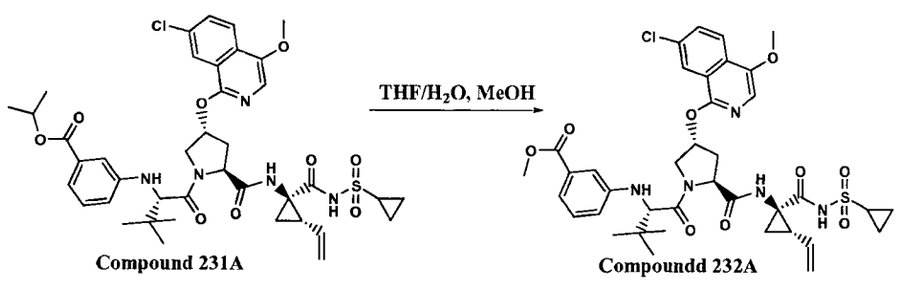
N-(3-(methoxycarbonyl)phenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide and

N-(3-(methoxycarbonyl)phenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide

Example 232: Preparation of Compounds 232A and 232B



Compounds 232A and 232B



Compound 231A **Compoundd 232A**

isopropyl 3-((S)-1-((2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-2-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropylcarbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-ylamino)benzoate (20 mg, 0.025 mmol, compound 231A) was dissolved in THF (0.200 ml) and MeOH (.2 ml) at 25 °C. 1.0M aqueous lithium hydroxide (0.049 ml, 0.049 mmol) was added dropwise, and the mixture was stirred for 4 hours. The reaction mixture was diluted with ethyl acetate (25 ml) and was washed with water (pH~4) and brine. The organic was dried over sodium sulfate, filtered, concentrated, and the residue was purified by reverse phase preparative HPLC to give Compound 232A (0.005 g, 25.6%). ^{1}H NMR (400 MHz, CD_3OD) δ

ppm 0.89 - 1.02 (m, 2 H) 1.04 - 1.12 (m, 11 H) 1.29 - 1.36 (m, 2 H) 1.42 (dd, *J*=9.44, 5.41 Hz, 1 H) 1.87 (dd, *J*=8.06, 5.54 Hz, 1 H) 2.16 - 2.25 (m, 2 H) 2.46 (d, *J*=6.55 Hz, 1 H) 2.91 - 2.99 (m, 1 H) 3.63 - 3.71 (m, 3 H) 3.93 - 4.03 (m, 4 H) 4.08 (m, 1 H) 4.21 (s, 1 H) 4.51 (dd, *J*=10.32, 7.05 Hz, 1 H) 5.06 - 5.16 (m, 1 H) 5.28 (d, *J*=17.37 Hz, 1H) 5.70 - 5.79 (m, 2 H) 6.58 (t, *J*=7.81 Hz, 1 H) 6.69 (dd, *J*=8.06, 1.51 Hz, 1 H) 6.80 (d, *J*=7.55 Hz, 1 H) 7.18 (s, 1 H) 7.50 (s, 1 H) 7.61 - 7.69 (m, 2 H) 8.04 - 8.11 (m, 1 H); LC-MS, MS *m/z* 782 (M^++H).

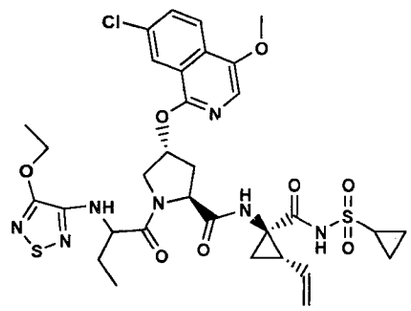
Compound 232B was made from compound 231B by same method as described for the preparation of compound 232A. LC-MS, MS *m/z* 782 (M^++H).

Compound 233 Isomers:

(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-1-((2S)-2-((4-ethoxy-1,2,5-thiadiazol-3-yl)amino)butanoyl)-L-prolinamide and

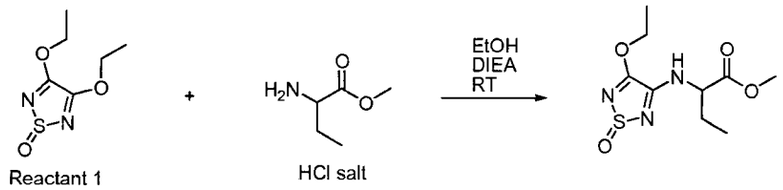
(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-1-((2R)-2-((4-ethoxy-1,2,5-thiadiazol-3-yl)amino)butanoyl)-L-prolinamide

Example 233: Preparation of Compounds 233A and 233B



Compounds 233A and 233B

Step 1

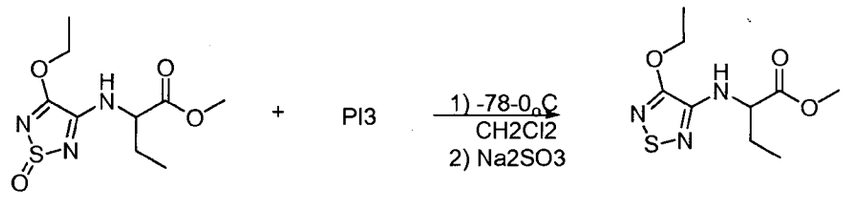


Reactant 1 HCl salt

Step 1:

To a solution of Reactant 1 (0.114 g, 0.6 mmol) in EtOH (5 ml) at 25°C was added methyl 2-aminobutanoate (0.070 g, 0.600 mmol) followed by DIEA (0.210 ml, 1.200 mmol). The mixture was stirred overnight at room temperature. Solvent was removed, and the material was dried under high vacuum. This material was used directly in the next step without further purification.

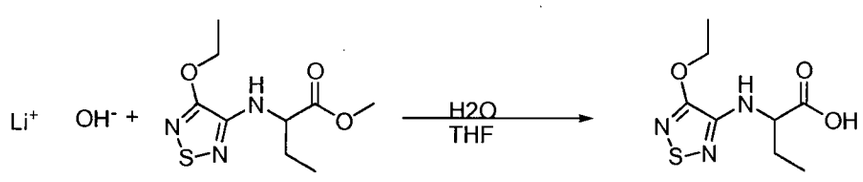
step 2



Step 2:

To a yellow solution of the product of example 233, step 1 (0.157 g, .6 mmol) in CH_2Cl_2 (8 ml) at -78°C was added triiodophosphine (0.247 g, 0.600 mmol). An orange suspension was obtained. The mixture was allowed to warm up to 0°C over 2 h. A dark brown solution formed. The reaction mixture was diluted with ethyl acetate (15ml) and washed with sodium bisulfite (2 g in 10 ml of water), H_2O, and sat NaCl. The organic was dried over Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel column (elution with 5-15 % ethyl acetate in hexanes). A colorless oil was thus obtained.

step 3

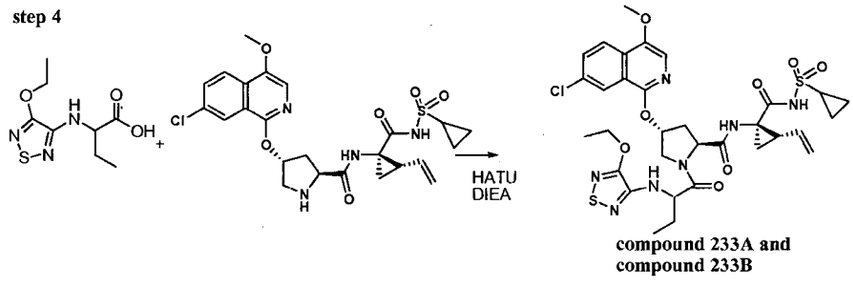


Step 3:

To the solution of methyl 2-(4-ethoxy-1,2,5-thiadiazol-3-ylamino)butanoate (57 mg, 0.232 mmol) in 4 ml of THF at rt was added lithium hydroxide (6.68 mg,

0.279 mmol) and water (0.6 ml). The mixture was stirred for 2 h. The mixture was adjusted to pH4 and was extracted with ethyl acetate (10 ml x 2). The organic layers were combined and washed with water (1 x 10 mL). The organic was dried over Na_2SO_4, filtered and concentrated to afford a white solid.

step 4



compound 233A and compound 233B

Step 4:

To the yellow solution of 2-(4-ethoxy-1,2,5-thiadiazol-3-ylamino)butanoic acid (23.34 mg, 0.101 mmol) and (2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-N-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropyl)pyrrolidine-2-carboxamide (54 mg, 0.101 mmol) at 0°C was added HATU (77 mg, 0.202 mmol) followed by diisopropylethyl amine (32.6 mg, 0.252 mmol). A yellow solution was formed. The mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate (15 ml) and was washed with H_2O (pH=6) and brine. The organic was dried over Na_2SO_4, filtered and concentrated. The crude material was purified by preparative HPLC to give two separate products with identical MS *m/z* as observed by LCMS. Compound 233A (0.046 g, 5.3% yield) was the first of the two isomers to elute by reverse phase preparative HPLC. Compound 233B (0.085 g, 10% yield was the second of the two isomers to elute by reverse phase preparative HPLC.

Compound 233A: LC-MS, MS *m/z* 748 (M^++H).

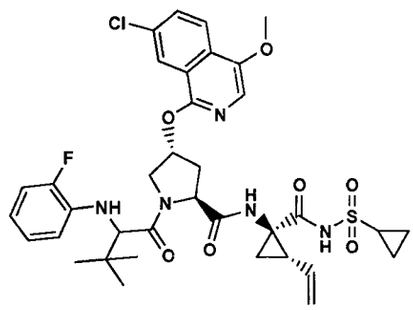
Compound 233B: LC-MS, MS *m/z* 748 (M^++H).

Compound 234 Isomers:

N-(2-fluorophenyl)-3-methyl-D-valyl-(4R)-4-[(7-chloro-4-methoxy-1-isoquinolinyl)oxy]-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-L-prolinamide and

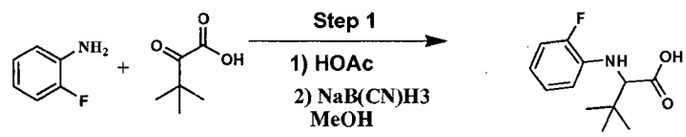
N-(2-fluorophenyl)-3-methyl-L-valyl-(4R)-4-[(7-chloro-4-methoxy-1-isoquinolinyl)oxy]-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-L-prolinamide

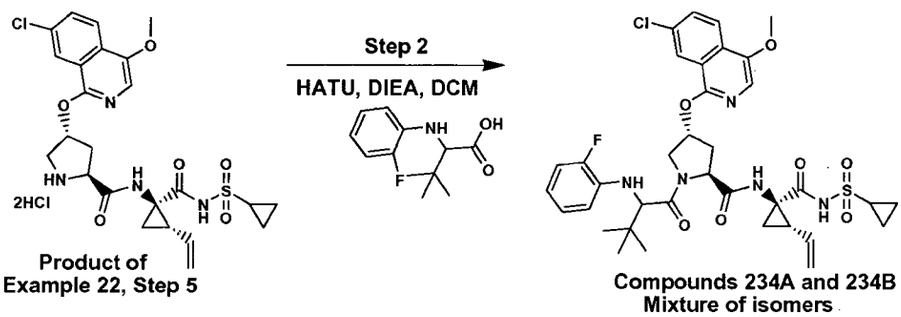
Example 234: Preparation of Compounds 234A and 234B



Compounds 234A and 234B

Scheme 1





Product of Example 22, Step 5

Compounds 234A and 234B Mixture of isomers

Step 1:

To a mixture of 2-fluoroaniline (203 mg, 1.827 mmol) and 3,3-dimethyl-2-oxobutanoic acid (476 mg, 3.65 mmol) in a 100 ml RBF at RT was added acetic acid (2 ml) via a pipet. The color of the mixture soon changed into a characteristic canary

color. The solution was warmed to 75°C for about 120 minutes and the color remained the same. The solution was diluted with methanol (2 ml) at RT, followed by the addition of 0.5X of sodium cyanotrihydroborate (230 mg, 3.65 mmol)), and the remaining half after the bubbling and sizzling was over. The color of the solution became lighter. Added 30 ml of water to the mixture, then extracted it with 10 ml of ethyl acetate (adjust pH to 4). Then the organic was washed with sodium bicarbonate at pH=8. The organic layer dried over Na_2SO_4, filtered, and concentrated to a yellow oil. The material was purified by preparative HPLC and carried into the next step. LC-MS, MS *m/z* 226 (M^+ +H).

Step 2:

To the yellow solution of 2-(2-fluorophenylamino)-3,3-dimethylbutanoic acid (63.2 mg, 0.280 mmol, step 1, example 234) and (2S,4R)-4-(7-chloro-4-methoxyisoquinolin-1-yloxy)-N-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropyl)pyrrolidine-2-carboxamide (0.150 g, 0.28 mmol, step 5, example 22) in CH_2Cl_2 at 0°C was added HATU (0.213 g, 0.561 mmol) followed by diisopropylethyl amine (0.091 g, 0.701 mmol). A light yellow solution was formed after addition of the base. The mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (25 ml) and was washed with water (pH~6) and brine. The organic was dried over sodium sulfate, filtered, concentrated, and the residue was purified by reverse phase preparative HPLC to give two separate products with identical MS *m/z* as observed by LCMS. Compound 234A (0.050 g, 24% yield) was the first of the two isomers to elute by reverse phase preparative HPLC. Compound 234B (0.038 g, 18.2% yield) was the second of the two isomers to elute by reverse phase preparative HPLC.

Compound 234A: ^{1}H NMR (400 MHz, CD_3OD) δ ppm 0.99 - 1.08 (m, 2 H) 1.09 - 1.17 (m, 9 H) 1.20 - 1.29 (m, 2 H) 1.40 (dd, *J*=9.44, 5.41 Hz, 1 H) 1.86 (dd, *J*=8.06, 5.54 Hz, 1 H) 2.17 - 2.27 (m, 2 H) 2.52 (dd, *J*=13.72, 6.92 Hz, 1 H) 2.94 (ddd, *J*=12.78, 8.12, 4.78 Hz, 1 H) 3.97 - 4.04 (m, 5 H) 4.27 (d, *J*=12.09 Hz, 1 H) 4.50 (dd, *J*=10.45, 6.92 Hz, 1 H) 5.11 (dd, *J*=10.32, 1.51 Hz, 1 H) 5.28 (dd, *J*=17.12, 1.51 Hz, 1 H) 5.67 - 5.77 (m, 2 H) 6.08 - 6.14 (m, 1 H) 6.14 - 6.20 (m, 1 H) 6.40 - 6.47 (m, 1 H) 6.58 (ddd, *J*=11.96, 8.06, 1.39 Hz, 1 H) 7.56 (s, 1 H) 7.69 (dd, *J*=8.81,

2.01 Hz, 1 H) 7.77 (d, *J*=2.01 Hz, 1 H) 8.10 (d, *J*=8.81 Hz, 1 H); LC-MS, MS *m/z* 742 (M^++H).

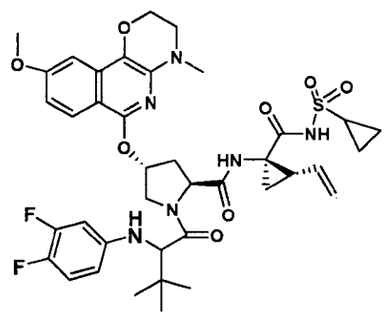
Compound 234B: LC-MS, MS *m/z* 742 (M^++H).

Compound 235 Isomers:

N-(3,4-difluorophenyl)-3-methyl-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((9-methoxy-4-methyl-3,4-dihydro-2H-[1,4]oxazino[3,2-c]isoquinolin-6-yl)oxy)-L-prolinamide and

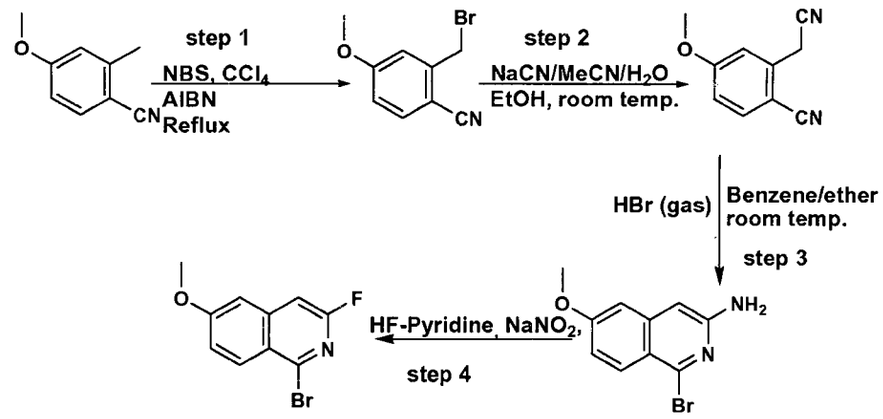
N-(3,4-difluorophenyl)-3-methyl-D-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((9-methoxy-4-methyl-3,4-dihydro-2H-[1,4]oxazino[3,2-c]isoquinolin-6-yl)oxy)-L-prolinamide

Example 235: Preparation of Compounds 235A and 235B



Compounds 235A and 235B
Mixture of isomers

scheme 1



Step1

4-methoxy-2-methylbenzonitrile (50 g, 340 mmole) and NBS (62g, 350 mmole) were suspended in CCl_4 (500 ml) and AIBN (5g, 10% wt) was added. The mixture was heated at flux overnight. Filtered off precipitate and removed the solvent. The brown oil was purified by flash column (2-5% acetone:hexanes). White crystal (36 g) were obtained.

Step 2

2-(Bromomethyl)-4-methoxybenzonitrile (36 g, example 235, step 1) was suspended in 200 ml of ethanol, 200 ml of acetonitrile was added followed by KCN (8.3 g) and 150 ml of water. Mixture was stirred and the colorless solution turned to yellow. The reaction was complete after 4 hours of stirring. The volatiles were removed under vacuum, and the residual solid was redissolved in ethyl acetate (200 ml) and washed with water (100 ml) and brine (100ml). The organics were then dried over sodium sulfate. Ethyl acetate was removed and the residue was recrystalized from ethyl acetate and dichloride methane to provide 17g of 2-(cyanomethyl)-4-methoxybenzonitrile.

Step 3

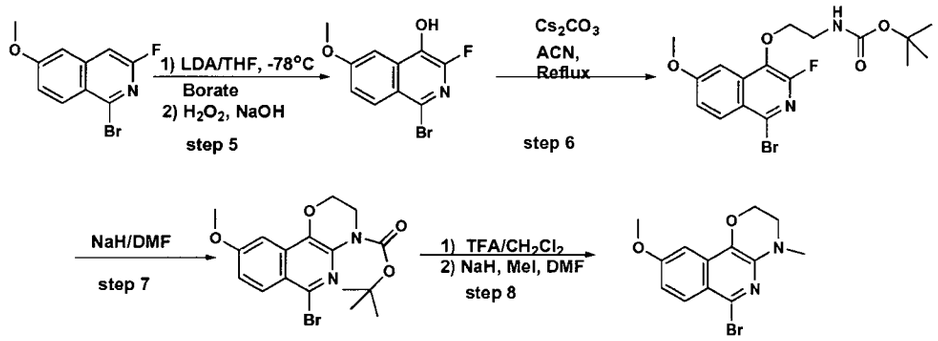
See J. Med. Chem., 1970, Vol. 13, No. 4, pp 613 for preparation of 1-bromo-6-methoxyisoquinolin-3-amine.

Step 4

1-bromo-6-methoxyisoquinolin-3-amine (1.5 g, example 235, step 3) was dissolved in HF-Py (12.5 ml) at -10°C, and $NaNO_2$ (600 mg) was added. A yellow solid was

observed to form. The reaction mixture was suspended in large amount of water, adjusted PH to 5, extracted with ethyl acetate (3X30 ml), washed with water and brine, then dried over sodium sulfate. Light yellow solid (1.2 g) was obtained after flash column purification.

scheme 2



Step 5

1-bromo-3-fluoro-6-methoxyisoquinoline (322 mg, 1.26 mmol, example 235, step 4) was dissolved in THF (7 ml) at -78°C, LDA (1.5 M, 2.52 ml) was added dropwise, stirred for 30 min, then isopropyl borate (477 mg, 585 *u*l) was added. 30 minutes later, the reaction was quenched by sat. NH_4Cl and 1 N HCl, extracted with ethyl acetate (3X30 ml). Removed solvent to dryness. The residue was dissolved in CH_2Cl_2 (8 ml), NaOH (1 N, 4 ml) was added followed by H_2O_2 (1.2 ml, 50 %). Gas evolution was observed. Stirred for 30 min. Yellow paste formed. The mixture was taken up in 50 ml of ethyl acetate, the organic layer was washed with sodium bisulfite solution, and brine, then dried over sodium sulfate. Purified by silica gel (eluted with 5-10% ethyl acetate: hexane). 200 mg of yellow solid obtained.

Step 6

1-bromo-3-fluoro-6-methoxyisoquinolin-4-ol (160 mg, example 235, step 5) was dissolved in acetonitrile (10 ml) at rt, Cs_2CO_3 (215 mg) and tert-butyl 2-bromoethylcarbamate (60 ul) were added. The resulted mixture was brought to reflux for 2 hours. The solvent was removed and the residue was taken up in 30 ml of ethyl acetate, washed with water and brine, dried over sodium sulfate. The residue was

purified by flash column with 5% acetone:hexanes. White solid (169 mg) was obtained.

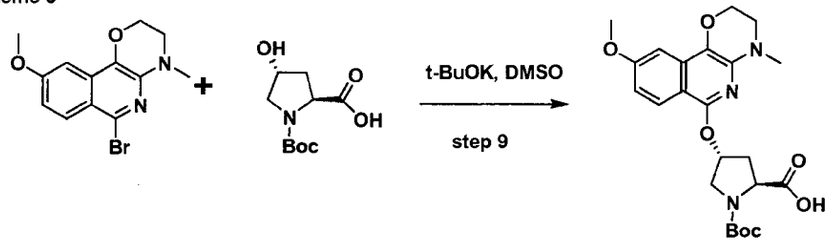
Step 7

Tert-butyl 2-(1-bromo-3-fluoro-6-methoxyisoquinolin-4-yloxy)ethylcarbamate (169 mg, example 235, step 6) was dissolved in 10 ml of DMF at 0°C, 24 mg of sodium hydride (95%) was added, stirred overnight. The reaction mixture was diluted with 50 ml of water, extracted with ethyl acetate (3X20 ml). The organic was combined and washed with water (2X10 ml), brine (20 ml), dried over sodium sulfate. The solvent was removed and the residue was purified by flash column with 2.5-10% acetone:hexanes. White solid (100 mg) was obtained.

Step 8

Tert-butyl 6-bromo-9-methoxy-2H-[1,4]oxazino[3,2-c]isoquinoline-4(3H)-carboxylate (20 mg, example 235, step 7) was dissolved in 5 ml of CH2Cl2 at 0°C, 2 ml of TFA added, stirred for 2 hours. The reaction mixture was dried under vacuum, the residue was redissolved in ethyl acetate and washed with water (PH~5), brine, dried over sodium sulfate. Solvent was removed to dryness and the solid obtained was dissolved in DMF (5 ml) at room temperature, treated with NaH (10 mg), followed by MeI (10 ul). Stirred for 60 min. The reaction mixture was diluted with 50 ml of water, extracted with ethyl acetate (3X20 ml). The organic was combined and washed with water (2X10 ml), brine (20 ml), dried over sodium sulfate. The solvent was removed and the residue was purified by flash column with 5-15% acetone:hexanes. White solid (10 mg) was obtained. NMR 1H NMR (400 MHz, CHLOROFORM-D) δ ppm 2.89 (s, 3 H) 3.16 - 3.21 (m, 2 H) 4.40 - 4.44 (m, 2 H) 7.05 (dd, *J*=9.32, 2.52 Hz, 1 H) 7.20 (d, *J*=2.52 Hz, 1 H) 8.04 (d, *J*=9.32 Hz, 1 H)

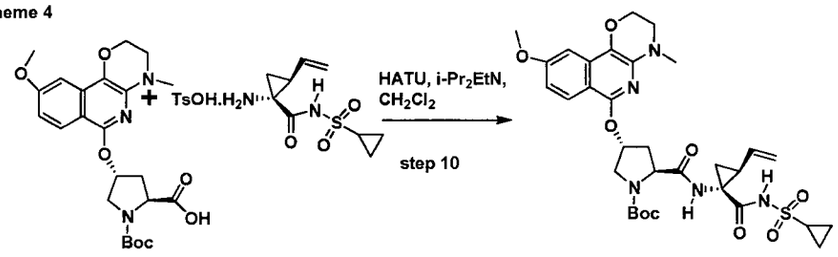
scheme 3



Step 9

A solution of 6-bromo-9-methoxy-4-methyl-3, 4-dihydro-2H-[1,4]oxazino[3,2-c]isoquinoline (62 mg, 0.2 mmol, example 235, step 8), Boc-L-Hyp-OH (50.8 mg, 0.22 mmol), t-BuOK (82 m g, 0.60 mmol) in DMSO (2 mL) was stirred for 3 h. The reaction was quenched with water (5 mL) at 0 ^{0}C and neutralized with 1 N HCl to pH 5, extracted with EtOAc (40 mL), washed with brine (10 mL) and water (15 mLx2), dried over $MgSO_4$, concentrated to give a crude product (90 mg) as a solid, which was used in the next step without further purification.

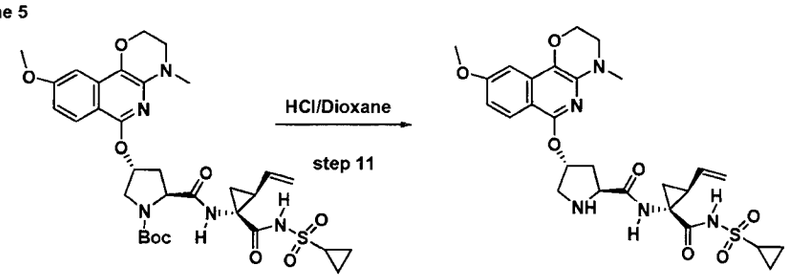
scheme 4



Step 10

To a solution of (2S,4R)-1-(tert-butoxycarbonyl)-4-(9-methoxy-4-methyl-3,4-dihydro-2H-[1,4]oxazino[3,2-c]isoquinolin-6-yloxy)pyrrolidine-2-carboxylic acid (90 mg, example 235, step 9), (1R,2S)-1-amino-N-(cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide · TsOH salt (90 mg), i-Pr_2EtN (0.5 mL) in CH_2Cl_2 (5 mL) was added HATU (112 mg). The resulting mixture was stirred for 16 h. After concentration, the residue was extracted with EtOAc (30 mL), washed with 1 N HCl (10mL x 3), water (10 mL x 2), and brine (10 ml x 2), dried over $MgSO_4$, concentrated, purified by prep HPLC. 113 mg solid obtained

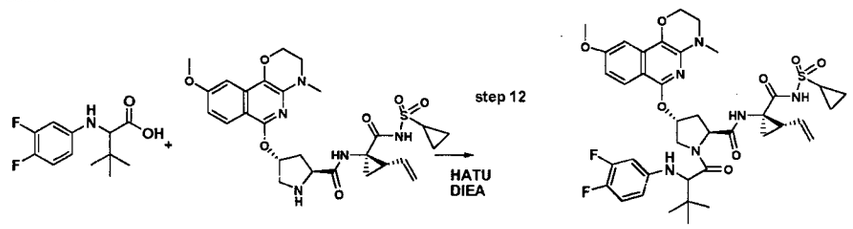
scheme 5



Step 11

(2S,4R)-tert-butyl 2-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropylcarbamoyl)-4-(9-methoxy-4-methyl-3,4-dihydro-2H-[1,4]oxazino[3,2-c]isoquinolin-6-yloxy)pyrrolidine-1-carboxylate (50 mg, example 235, step 10) was dissolved in 2 ml of 4N HCl in dioxane, stirred for 2 hours. The solvent was removed to dryness, the resulted brown solid was used as is.

scheme 6



Step 12

To the yellow solution of 2-(3,4-difluorophenylamino)-3,3-dimethylbutanoic acid (0.043 g, 0.175 mmol, from example 220 , step 1) and (2S,4R)-N-((1R,2S)-1-(cyclopropylsulfonylcarbamoyl)-2-vinylcyclopropyl)-4-(9-methoxy-4-methyl-3,4-dihydro-2H-[1,4]oxazino[3,2-c]isoquinolin-6-yloxy)pyrrolidine-2-carboxamide (20 mg, example 235, step 11) at 0°C was added HATU (0.133 g, 0.350 mmol) followed by diisopropylethyl amine (0.057 g, 0.437 mmol). brown solution was formed after addition of base. The mixture was stirred at room temperature.

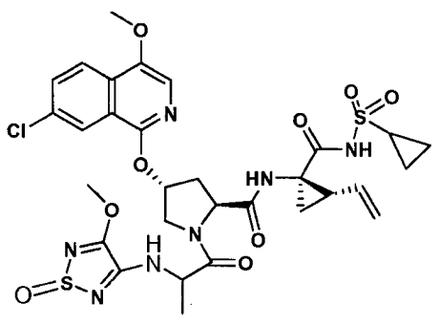
The reaction mixture was diluted with ethyl acetate. Washed with water and brine. Dried over sodium sulfate. Purified by prep HPLC to give two separate products with identical MS *m/z* as observed by LCMS. Compound 235A (0.0008 g, 3.0% yield) was the first of the two isomers to elute by reverse phase preparative HPLC. Compound 235B (0.003 g, 11.0% yield) was the second of the two isomers to elute

by reverse phase preparative HPLC. Compound 235A: LC-MS, MS *m/z* 798 (M^+ +H)

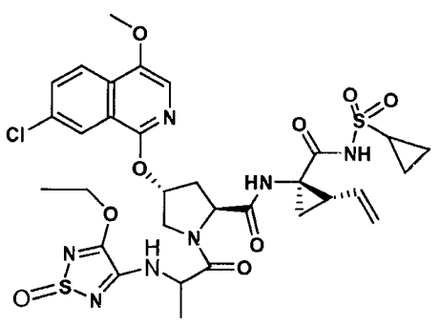
1H NMR (400 MHz, MeOD) δ ppm 1.01 - 1.10 (m, 11 H) 1.41 (m, 2 H) 1.86 (dd, *J*=8.18, 5.41 Hz, 1 H) 2.13 - 2.24 (m, 2 H) 2.50 (d, *J*=6.80 Hz, 1 H) 2.90 - 3.01 (m, 1 H) 3.02 - 3.09 (m, 3 H) 3.42 (d, *J*=2.52 Hz, 2 H) 3.91 - 4.01 (m, 5 H) 4.22 - 4.32 (m, 1 H) 4.42 - 4.48 (m, 1 H) 4.50 - 4.59 (m, 2 H) 5.11 (dd, *J*=10.32, 1.76 Hz, 1 H) 5.28 (dd, *J*=17.25, 1.39 Hz, 1 H) 5.67 - 5.78 (m, 2 H) 6.19 - 6.24 (m, 1 H) 6.35 - 6.40 (m, 1 H) 6.49 - 6.56 (m, 1 H) 6.87 (dd, *J*=9.07, 2.27 Hz, 1 H) 7.13 - 7.17 (m, 1 H) 7.60 (d, *J*=2.27 Hz, 1 H) Compound 235: LC-MS, MS *m/z* 798 (M^+ +H)

Compounds 236, 237, 238, 239, 240, 241, 242, 243 were prepared using the methods described herein.

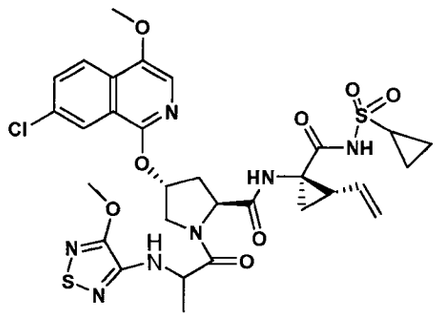
Example 236: Compound 236.



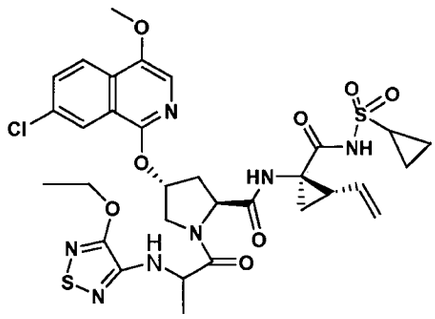
Example 237: Compound 237.



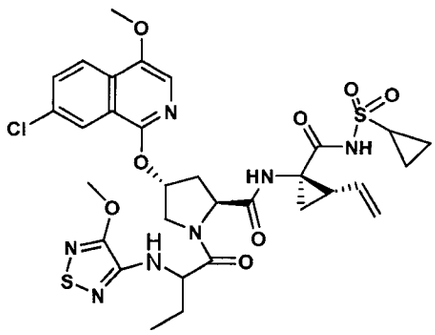
Example 238: Compound 238.



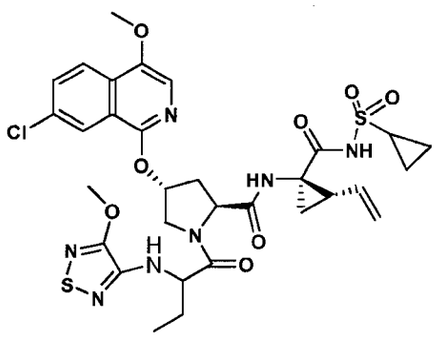
Example 239: Compound 239.



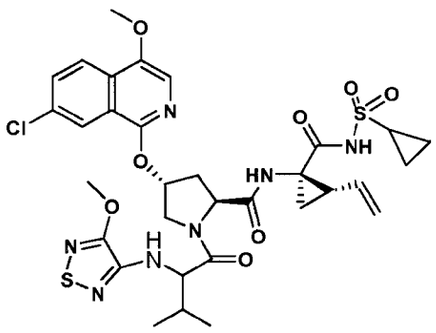
Example 240: Compound 240.



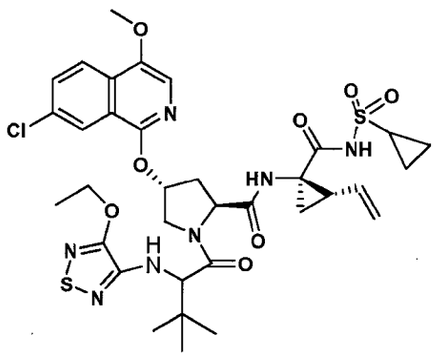
Example 241: Compound 241.



Example 242: Compound 242.

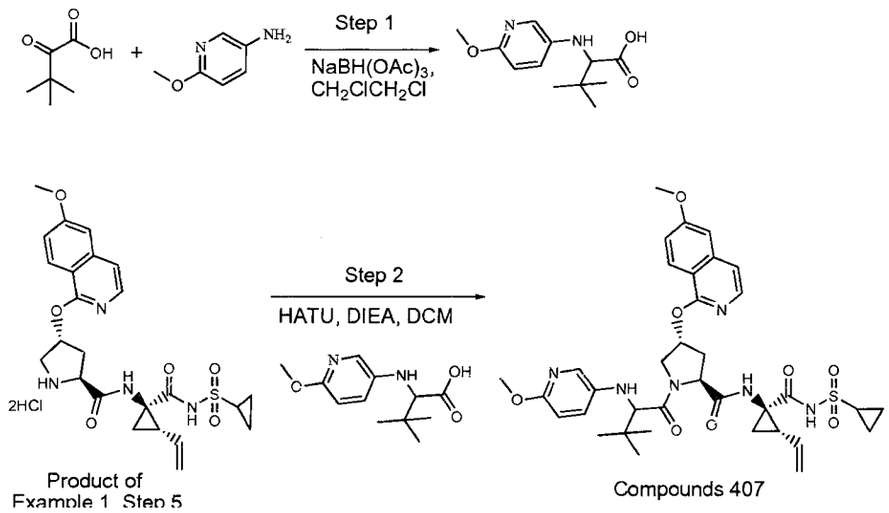


Example 243: Compound 243.



Example 407: Preparation of Compounds 407

Scheme 1



Step 1:

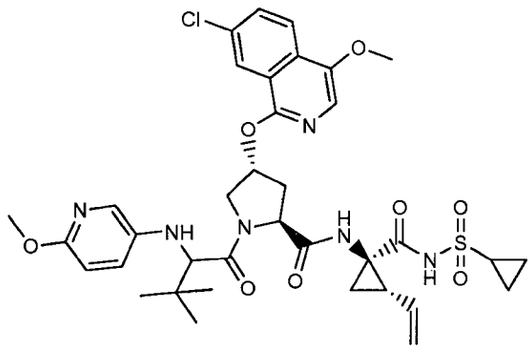
A mixture of 6-methoxypyridin-3-amine (372 mg, 3 mmol), 3,3-dimethyl-2-oxobutanoic acid (781 mg, 6.00 mmol), and sodium triacetoxyhydroborate (1907 mg, 9.00 mmol) in CH_2ClCH_2Cl (5 ml) was stirred for 24 h. The reaction was quenched with saturated NH_4Cl (20 mL), diluted with EtOAc (50 mL), washed with brine (20 ml), dried over $MgSO_4$, filtrated, concentrated. Concentration gave 0.71 g (99%) of a crude desired product which was used in the next step without further purification. purification. ^1H NMR (400 MHz, CCl_3D) δ ppm 1.09 (s, 9H), 3.63 (s, 1H), 3.85 (s, 3 H), 6.63 (d, J=8.81 Hz, 1 H), 7.07 (dd, J=8.81, 3.02 Hz, 1 H), 7.63 (d, J=3.02 Hz, 1 H); LC-MS, MS *m/z* 239 (M^++H).

Step 2:

To a mixture of the product of Step 5, Example 1 (150 mg, 0.3 mmol), was added the product of Step 1, Example 407 (71 mg, 0.3 mmol), and Hunig'sBase (0.524 ml, 3 mmol) in CH_2Cl_2 (5 ml) was added HATU (171 mg, 0.45 mmol). After stirring for 16 h and concentration, purification of the residue by reverse phase preparative HPLC gave two products with identical *m/z* by LCMS. Compound 407A was the first of the two isomers to elute by reverse phase preparative HPLC and was obtained as a solid (37 mg, 18% yield). Compound 407B was the second of the two isomers to elute by reverse phase preparative HPLC and was obtained as a solid (31 mg, 14% yield). Compound 407: LC-MS, MS *m/z* 721 (M^++H). Compound 407B:

LC-MS, MS *m/z* 721 (M^++H).

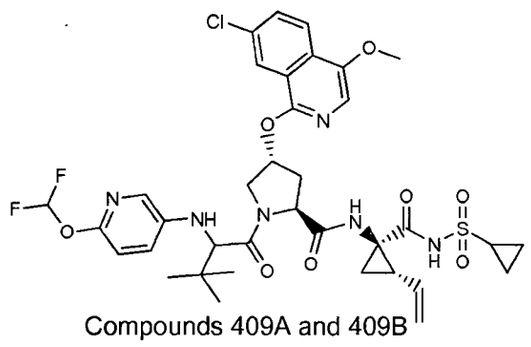
Example 408: Preparation of Compounds 408A and 408B



Compounds 408A and 408B

Compounds 408 were prepared by the same procedure as that described for the preparation of Compound 407, except that the product of Step 5 of Scheme 2 in Example 22 (182 mg, 0.299 mmol) was used in the synthesis of Compound 408. Compound 408A was the first of the two isomers to elute by reverse phase preparative HPLC and was obtained as a solid (66 mg, 29% yield). Compound 408B was the second of the two isomers to elute by reverse phase preparative HPLC and was obtained as a solid (46 mg, 20% yield). Compound 408A: LC-MS, MS *m/z* 755 (M^++H). Compound 408B: LC-MS, MS *m/z* 755 (M^++H).

Example 409: Preparation of Compounds 409A and 409B



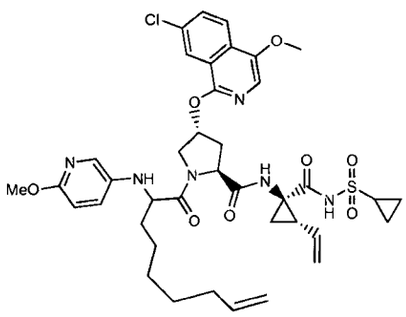
Compounds 409A and 409B

Compounds 409 were prepared by the same procedure as that described for the preparation of Compound 407, except 6-(difluoromethoxy)pyridin-3-amine was used in Step 1 and the product of Step 5 of Scheme 2 in Example 22 (182 mg, 0.299 mmol) was used in Step 2. Compound 409A was the first of the two isomers to elute

by reverse phase preparative HPLC and was obtained as a solid (45 mg, 33% yield). Compound 409B was the second of the two isomers to elute by reverse phase preparative HPLC and was obtained as a solid (50 mg, 37% yield). Compound 409A: LC-MS, MS *m/z* 791 (M^++H). Compound 409B: LC-MS, MS *m/z* 791 (M^++H).

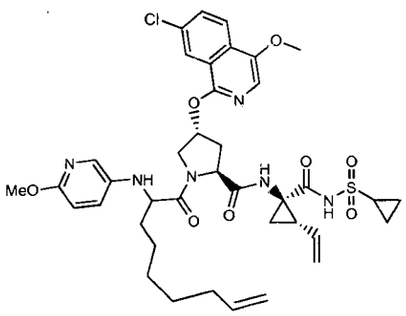
Compounds 410 and 411 were prepared according to the methods described herein.

Example 410: Preparation of Compounds 410



Compound 410

Example 411: Preparation of Compounds 411

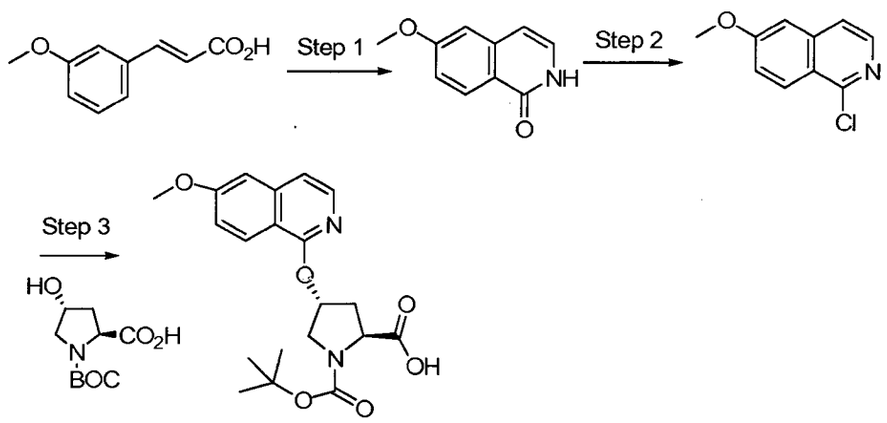


Compound 411

Example 412 Preparation of Intermediates

Example of preparations of P2 isoquinoline intermediates for incorporation into compounds of Formula 1

Method A



Step 1:

To a solution of 3-methoxy cinnamic acid (11.04 g, 62 mmol) and triethylamine (12.52 g, 124 mmol) in acetone (80 mL) was added ethyl chloroformate (approximately 1.5 equivalents) dropwise at 0^0C. After stirring at this temperature for 1 h, aqueous NaN_3 (6.40 g, 100 mmol in 35 mL H_2O; appropriate precautions must be taken when using sodium azide) was added dropwise and the reaction mixture was stirred for 16 h at the ambient temperature. Water (100 mL) was added to the mixture and the volatile was removed in vacuo. The resulting slurry was extracted with toluene (3X50 mL) and the combined organic layers were dried over $MgSO_4$. This dried solution was added dropwise to a heated solution of diphenylmethane (50 mL) and tributylamine (30 mL) at 190^0C. The toluene was distilled off as added. After complete addition, the reaction temperature was raised to 210^0C for 2 h. After cooling, the precipitated product was collected by filtration, washed with hexane (2X50 mL), and dried to yield the desired product as a white solid (5.53 g, 51%) (Nicolas Briet *at el*, Tetrahedron, 2002, 5761-5766). MS *m/z* 176 (M^++H).

An altenative procedure to the above employs diphenylphosphoryl azide for the conversion of the carboxylic acid to the corresponding acylazide. In a one pot procedure then the acid is converted to the corresponding quinolone. The process is described below for the prepapration of 4-methyl-*2H*-isoquinolin-1-one from 3-phenyl-but-2-enoic acid:

A solution of 3-phenyl-but-2-enoic acid (16.2 g), diphenylphosphoryl azide (27.5 g), and triethylamine (10.1 g) in benzene (100 mL) was stirred for 1 h. After filtration

through a silica gel plug washing with benzene and concentration, the residue was dissolved in diphenylmethane (80 mL) and refluxed for 3 h. After cooling to rt, solids were collected through a plug washing with benzene and dried to give 10 g (63%) of the desired 4-methyl-*2H*-isoquinolin-1-one as a solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 2.30 (s, 3 H), 7.00 (s, 1 H), 7.54 (m, 1 H), 7.77 (m, 2 H), 8.33 (d, *J*=7.34 Hz, 1 H).

Step 2:

6-Methoxy-*2H*-isoquinolin-1-one (5.0 g, 28.4 mmol) in $POCl_3$ (10 mL) was heated to gentle reflux for 3 h the evaporated *in vacuo* (Nicolas Briet *at el*, **Tetrahedron**, 2002, 5761-5766). The residue was poured into iced water (20 mL) and neutralized to pH 10 with 10 M NaOH. Extracted with $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$, filtered, evaporated. The residue was purified by flash chromatography (1:1 hexane-EtOAc) to afford 4.41 g (80%) of the desired product as a white solid.

^{1}H NMR (CD_3OD) δ 3.98 (s, 3H), 7.34-7.38 (m, 2 H), 7.69 (d, *J*=5.5 Hz, 1H), 8.10 (d, *J*=6.0 Hz, 1H), 8.23 (d, *J*=9.5 Hz, 1H). MS *m/z* 194 (M^++H).

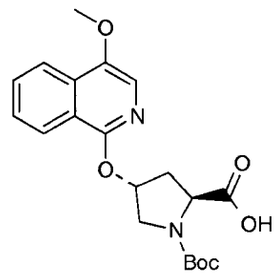
Step 3:

To a solution of N-BOC-3-(*R*)-hydroxy-L-proline (892 mg, 3.89 mmol) in DMSO (40 mL) at the ambient temperature was added potassium tert-butoxide (1.34 g, 12.0 mmol) in one portion. The formed suspension was stirred at this temperature for 30 min before being cooled to 10^0C. 1-chloro-6-methoxy-isoquinoline (example 11, Step 2) (785 mg, 4.05 mmol) was added as solid in one portion and the final mixture was stirred at the ambient temperature for 12 h. Quenched with iced 5% citric acid (aq), extracted with EtOAC (100 mL). The aqueous phase was extracted with EtOAC again. The combined organic layers were washed with 5% citric acid (aq) and brine respectively, dried over $MgSO_4$, filtered. The filtrate was evaporated in vacuo to dryness to yield 1.49 g (99%) of the desired product as an off-white foam. This material was used in the next step reaction as crude without further purification.

^{1}H NMR (CD_3OD) δ 1.42, 1.44 (rotamers, 9H), 2.38-2.43 (m, 1H), 2.66-2.72 (m, 1H), 3.80-3.87 (m, 2H), 3.92 (s, 3H), 4.44-4.52 (m, 1H), 5.73 (b, 1H), 7.16-7.18 (m,

2H), 7.24-7.25 (m, 1H), 7.87-7.88 (m, 1H), 8.07 (d, *J*=8.5 Hz, 1H). MS *m/z* 389 (M^++H).

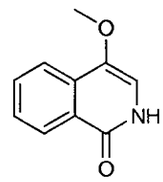
The following intermediates were prepared as described herein and can be incorporated into compounds of Formula 1



Step 1:

Modifications: 15 g 3-methoxy-3-phenyl-acrylic acid used, 250 mg product obtained (2% yield).

Product:

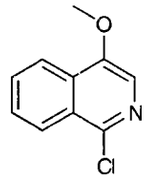


^{1}H NMR (400 MHz, CD_3COCD_3) δ ppm 3.85 (s, 3 H), 6.96 (s, 1 H), 7.54 (m, 1 H), 7.71 (m, 1 H), 7.86 (d, *J*=8.07 Hz, 1 H), 8.31 (d, *J*=8.07 Hz, 1 H).

Step 2:

Modifications: 200 mg 4-methoxy-2*H*-isoquinolin-1-one used, 150 mg product obtained (68% yield).

Product:

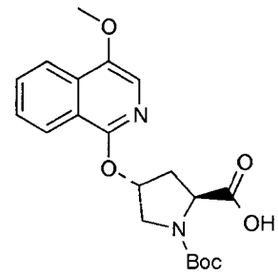


^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.05 (s, 2 H), 7.71 (m, 1 H), 7.72 (m, 2 H), 7.80 (s, 1 H), 8.23 (dd, *J*=18.71, 7.70 Hz, 2 H).

Step 3:

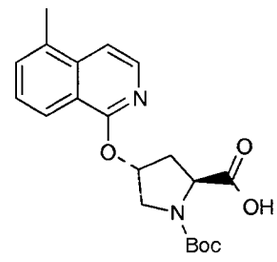
Modifications: 122 mg 1-chloro-4-methoxy-isoquinoline used, 218 mg product obtained (89% yield).

Product:



MS: $(M+Na)^+$ 411.

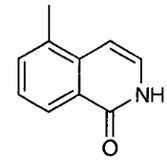
The following intermediates were prepared as described herein and can be incorporated into compounds of Formula I



Step 1:

Modifications: 20 g 2-methylcinnamic acid used, 14.3 g product obtained (72% yield)

Product:

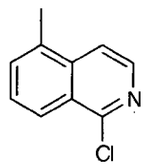


Data: ^{1}H NMR (400 MHz, CD_3OD) δ ppm 2.54 (s, 1 H), 6.69 (d, *J*=7.3 Hz, 1 H), 7.23 (d, *J*=7.3 Hz, 1 H), 7.39 (t, *J*=7.8 Hz, 1 H), 7.50 (d, *J*=7.1 Hz, 1 H), 8.30 (d, *J*=8.1 Hz, 1 H), 11.62 (s, 1 H); MS: $(M+H)^+$ 160.

Step 2:

Modifications: 14.4 g 5-methyl-*2H*-isoquinolin-1-one used, 10.6 g product obtained (66% yield).

Product:

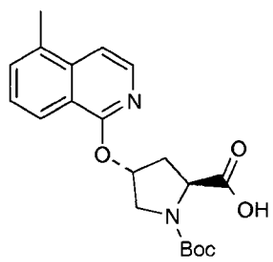


Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.67 (s, 3 H), 7.55 (m, 2 H), 7.70 (dd, *J*=5.9, 1.0 Hz, 1 H), 8.19 (m, 1 H), 8.28 (d, *J*=5.9 Hz, 1 H); MS: $(M+H)^+$ 178.

Step 3:

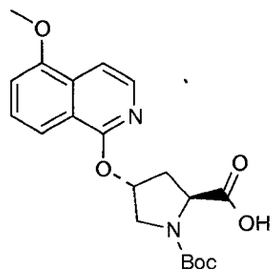
Modifications: 533 mg 1-chloro-5-methyl-isoquinoline used, 1116 mg product obtained (100% yield).

Product:



Data: MS: $(M+H)^+$ 373.

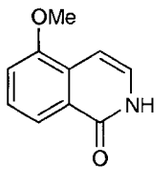
The following intermediates were prepared as described herein and can be incorporated into compounds of Formula 1



Step 1:

Modifications: 10 g 2-methoxy cinnamic acid used, 5.3 g product obtained (53% yield).

Product:

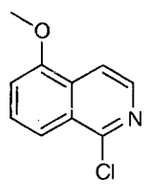


Data: ^{1}H NMR (400 MHz, CD_3OD) δ ppm 3.95 (s, 3 H), 6.94 (d, *J*=7.3 Hz, 1 H), 7.08 (d, *J*=8.1 Hz, 1 H), 7.14 (d, *J*=7.3 Hz, 1 H), 7.43 (t, *J*=8.1 Hz, 1 H), 7.99 (d, *J*=8.1 Hz, 1 H), 10.92 (s, 1 H); MS: $(M+H)^+$ 176.

Step 2:

Modifications: 5.3 g 5-methoxy-*2H*-isoquinolin-1-one used, 5.38 g product obtained (92% yield).

Product:

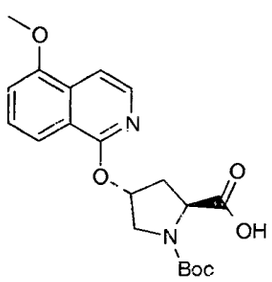


Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.01 (s, 3 H), 7.04 (d, *J*=7.8 Hz, 1 H), 7.57 (t, *J*=8.1 Hz, 1 H), 7.88 (d, *J*=8.6 Hz, 1 H), 7.97 (d, *J*=5.9 Hz, 1 H), 8.25 (d, *J*=5.9 Hz, 1 H); MS: $(M+H)^+$ 194.

Step 3:

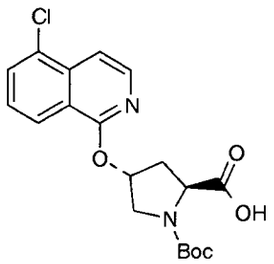
Modifications: 581 mg 1-chloro-5-methoxy-isoquinoline used, 1163 mg product obtained (100% yield).

Product:



Data: MS: $(M+H)^+$ 389.

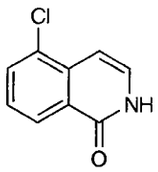
The following intermediates were prepared as described herein and can be incorporated into compounds of Formula 1



Step 1:

Modifications: 25 g 2-chlorocinnamic acid used, 14.6 g product obtained (59% yield).

Product:

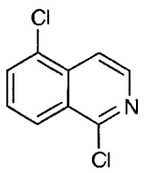


Data: ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.22 (d, *J*=7.3 Hz, 1 H), 7.42 (t, *J*=7.8 Hz, 1 H), 7.73 (d, *J*=7.8 Hz, 1 H), 8.34 (d, *J*=8.1 Hz, 1 H), 10.61 (s, 1 H); MS: $(M+H)^+$ 180.

Step 2:

Modifications: 14.2 g 5-chloro-*2H*-isoquinolin-1-one used, 8.28 g product obtained (53% yield).

Product:

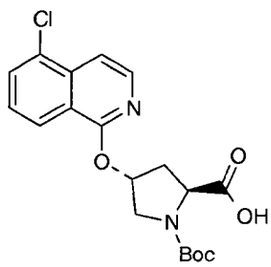


Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.60 (dd, *J*=8. 6, 7.6 Hz, 1 H), 7.83 (m, 1 H), 8.00 (d, *J*=5.9 Hz, 1 H), 8.29 (dt, *J*=8.9, 1.0 Hz, 1 H), 8.38 (d, *J*=5.9 Hz, 1 H); MS: $(M+H)^+$ 198.

Step 3:

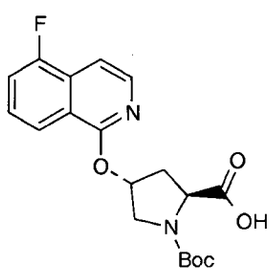
Modifications: 594 mg 1,5-dichloro-isoquinoline used, 1174 mg product obtained (100% yield).

Product:



Data: MS: $(M+H)^+$ 393.

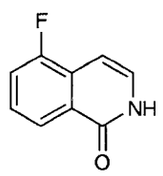
The following intermediates were prepared as described herein and can be incorporated into compounds of Formula 1



Step 1:

Modifications: 16.6 g2-fluorocinnamic acid used, 8.55 g product obtained (51% yield).

Product:

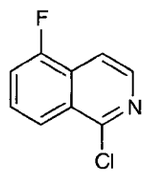


Data: ^{1}H NMR (400 MHz, CD_3COCD_3) δ ppm 6.62 (d, *J*=7.3 Hz, 1 H), 7.32 (d, *J*=7.3 Hz, 1 H), 7.47 (m, 2 H), 8.09 (m, 1 H).

Step 2:

Modifications: 8.4 g 5-fluoro-*2H*-isoquinolin-1-one used, 7.5 g product obtained (80% yield).

Product:

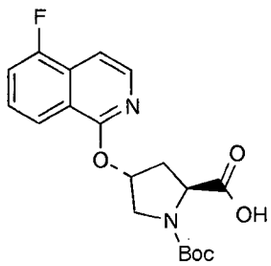


Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.43 (ddd, *J*=9.7, 7.8, 0.9 Hz, 1 H), 7.62 (td, *J*=8.2, 5.4 Hz, 1 H), 7.84 (d, *J*=5.6 Hz, 1 H), 8.14 (d, *J*=8.6 Hz, 1 H), 8.33 (d, *J*=5.9 Hz, 1 H); MS: $(M+H)^+$ 182.

Step 3:

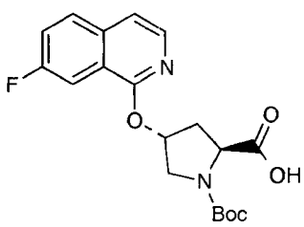
Modifications: 203 mg 1-chloro-5-fluoro-isoquinoline used, 384 mg product obtained (90% yield).

Product:



Data: ^{1}H NMR (400 MHz, CD_3SOCD_3) δ ppm 1.34, 1.36 (2s, 9 H, rotamers), 2.35 (m, 1 H), 2.61 (m, 1 H), 3.65 (d, *J*=12.23 Hz, 1 H), 3.80 (m, 1 H), 4.35 (m, 1 H), 5.70 (s, 1 H), 7.48 (d, *J*=6.11 Hz, 1 H), 7.63 (m, 2 H), 7.99 (m, 1 H), 8.10 (d, *J*=5.87 Hz, 1 H); MS: $(M+Na)^+$ 399.

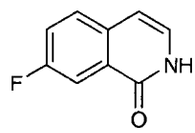
The following intermediates were prepared as described herein and can be incorporated into compounds of Formula 1



Step 1:

Modifications: 16.6 g 4-fluorocinnamic acid used, 8.2 g product obtained (49% yield).

Product:

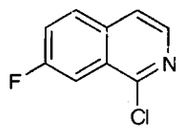


Data: ^{1}H NMR (400 MHz, CD_3COCD_3) δ ppm 6.57 (d, *J*=7.09 Hz, 1 H), 7.21 (d, *J*=7.09 Hz, 1 H), 7.50 (m, 1 H), 7.72 (dd, *J*=8.68, 5.26 Hz, 1 H), 7.90 (dd, *J*=9.54, 2.93 Hz, 1 H).

Step 2:

Modifications: 8.15 g 7-fluoro-2*H*-isoquinolin-1-one used, 7.6 g product obtained (84% yield).

Product:

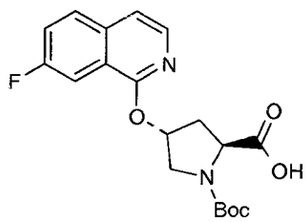


Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.52 (td, *J*=8.6, 2.6 Hz, 1 H), 7.59 (d, *J*=5.6 Hz, 1 H), 7.86 (dd, *J*=9.1, 5.4 Hz, 1 H), 7.95 (dd, *J*=9.5, 2.5 Hz, 1 H), 8.26 (d, *J*=5.6 Hz, 1 H); MS: $(M+H)^+$ 182.

Step 3:

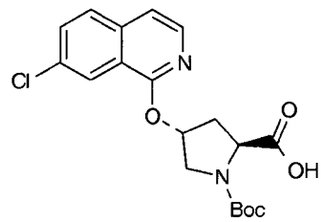
Modifications: 191 mg 1-chloro-7-fluoro-isoquinoline used, 350 mg product obtained (93% yield).

Product:



Data: MS: $(M+Na)^+$ 399.

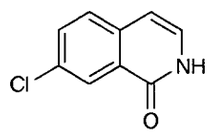
The following intermediates were prepared as described herein and can be incorporated into compounds of Formula 1



Step 1:

Modifications: 9.13 g 4-chlorocinnamic acid used, 4 g product obtained (44% yield).

Product:

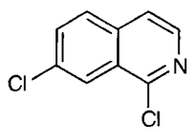


Data: ^{1}H NMR (400 MHz, CD_3SOCD_3) δ ppm 6.58 (d, *J*=7.1 Hz, 1 H), 7.20 (dd, *J*=7.1, 5.9 Hz, 1 H), 7.72 (m, 2 H), 8.10 (m, 1 H).

Step 2:

Modifications: 3.5 g 7-chloro-2*H*-isoquinolin-1-one used, 2.8 g product obtained (72% yield).

Product:

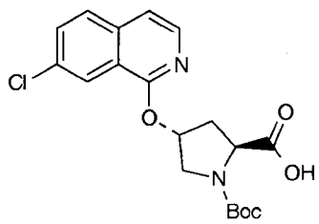


Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.59 (d, *J*=5.5 Hz, 1 H), 7.69 (dd, *J*=8.9, 2.1 Hz, 1 H), 7.80 (d, *J*=8.6 Hz, 1 H), 8.29 (d, *J*=5.5 Hz, 1 H), 8.34 (s, 1 H); MS: $(M+H)^+$ 198.

Step 3:

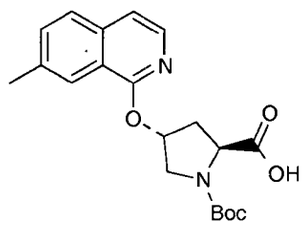
Modifications: 208 mg1,7-dichloro-isoquinoline used, 350 mg product obtained (89% yield).

Product:



Data: MS: $(M+Na)^+$ 415.

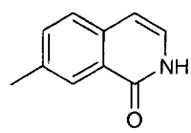
The following intermediates were prepared as described herein and can be incorporated into compounds of Formula 1



Step 1:

Modifications: 25 g 4-methylcinnamic acid used, 15.3 g product obtained (62% yield).

Product:

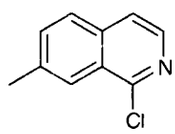


Data: ^{1}H NMR (400 MHz, CD_3OD) δ ppm 2.50 (s, 3 H), 6.54 (d, *J*=7.1 Hz, 1 H), 7.13 (d, *J*=7.1 Hz, 1 H), 7.49 (m, 2 H), 8.22 (s, 1 H), 11.49 (s, 1 H); MS: $(M+H)^+$ 160.

Step 2:

Modifications: 15.3 g 7-methyl-2*H*-isoquinolin-1-one used, 5.15 g product obtained (30% yield).

Product:

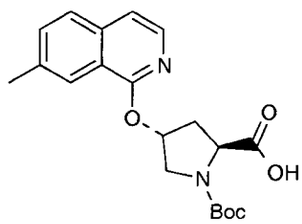


Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.58 (s, 3 H), 7.56 (m, 2 H), 7.73 (d, *J*=8.3 Hz, 1 H), 8.09 (s, 1 H), 8.20 (d, *J*=5.6 Hz, 1 H); MS: $(M+H)^+$ 178.

Step 3:

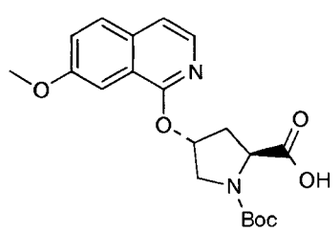
Modifications: 205 mg 1-chloro-7-methyl-isoquinoline used, 350 mg product obtained (89 % yield).

Product:



Data: MS: $(M+H)^+$ 373.

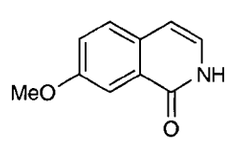
The following intermediates were prepared as described herein and can be incorporated into compounds of Formula 1



Step 1:

Modifications: 33 g using 4-methoxycinnamic acid used, 7 g product obtained (33% yield).

Product:

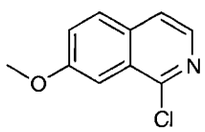


Data: ^{1}H NMR (500 MHz, CD_3COCD_3) δ ppm 3.90 (s, 3 H), 6.49 (d, *J*=7.0 Hz, 1 H), 7.10 (d, *J*=7.3 Hz, 1 H), 7.28 (dd, *J*=8.6, 2.8 Hz, 1 H), 7.57 (d, *J*=8.9 Hz, 1 H), 7.71 (d, *J*=2.8 Hz, 1 H).

Step 2:

Modifications: 4 g 7-methoxy-2*H*-isoquinolin-1-one used, 3 g product obtained (68 % yield).

Product:

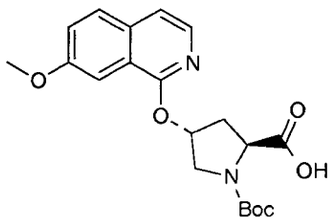


Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.98 (s, 3 H), 7.38 (dd, *J*=8.9, 2.6 Hz, 1 H), 7.52 (m, 2 H), 7.73 (d, *J*=8.8 Hz, 1 H), 8.16 (d, *J*=5.4 Hz, 1 H).

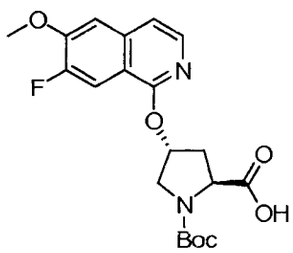
Step 3:

Modifications: 533 mg 1-chloro-7-methoxy-isoquinoline used, 1115 mg product obtained (100 % yield).

Product:



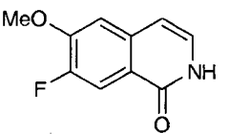
The following intermediates were prepared as described herein and can be incorporated into compounds of Formula 1



Step 1:

Modifications: 19.6 g 4-fluoro-3-methoxycinnamic acid used, 9.5 g product obtained (48% yield).

Product:

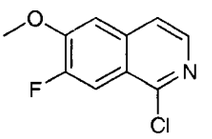


Data: ^{1}H NMR (400 MHz, CD_3COCD_3) δ ppm 4.00 (s, 1 H), 6.49 (d, *J*=7.34 Hz, 1 H), 7.19 (d, *J*=7.09 Hz, 1 H), 7.29 (d, *J*=8.07 Hz, 1 H), 7.86 (d, *J*=11.74 Hz, 1 H).

Step 2:

Modifications: 9 g 7-fluoro-6-methoxy-*2H*-isoquinolin-1-one used, 7 g product obtained (70% yield).

Product:

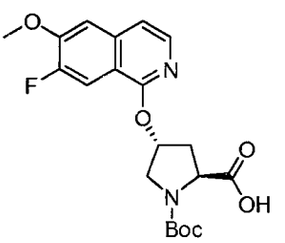


Data: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.04 (s, 3 H), 7.17 (d, *J*=8.07 Hz, 1 H), 7.48 (d, *J*=5.62 Hz, 1 H), 7.94 (d, *J*=11.49 Hz, 1 H), 8.20 (d, *J*=5.62 Hz, 1 H).

Step 3:

Modifications: 222 mg 1-chloro-7-fluoro-6-methoxy-isoquinoline used, 406 mg of desired product obtained.

Desired Product:



The following intermediates were prepared as described herein and can be incorporated into compounds of Formula 1

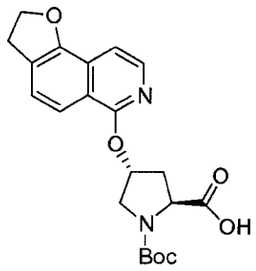
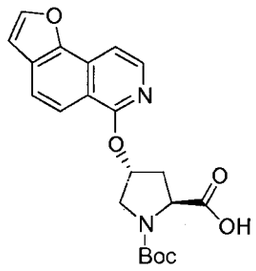
Organizacion y
Digitalizacion CSA Ltda

dl
RCT

Patente de Invención

2/3

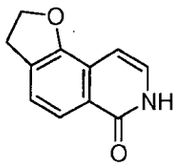
09/47361

Step 1:

Modifications: 3.8 g 3-(2,3-dihydro-benzofuran-7-yl)-acrylic acid used, 2 g product obtained (53% yield).

Product:

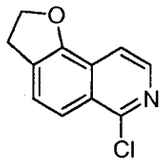


Data: ^{1}H NMR (400 MHz, CD_3OD) δ ppm 3.37 (t, *J*=9.05 Hz, 1 H), 4.73 (t, *J*=9.05 Hz, 2 H), 6.67 (d, *J*=7.09 Hz, 1 H), 7.10 (d, *J*=7.09 Hz, 1 H), 7.37 (d, *J*=8.07 Hz, 1 H), 7.81 (d, *J*=8.07 Hz, 1 H); MS: $(M+H)^+$ 188.

Step 2:

Modifications: 1.87 g 2,3-dihydro-*7H*-furo[2,3-f]isoquinolin-6-one used, 1.84 g product obtained (90% yield).

Product:

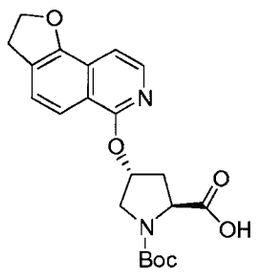


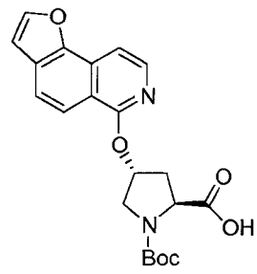
Data: ^{1}H NMR (400 Hz, $CDCl_3$) δ ppm 3.43 (t, *J*=9.05 Hz, 2 H), 4.82 (t, *J*=9.05 Hz, 2 H), 7.52 (d, *J*=8.56 Hz, 1 H), 7.66 (d, *J*=5.62 Hz, 1 H), 7.84 (d, *J*=8.31 Hz, 1 H), 8.19 (d, *J*=5.62 Hz, 1 H); MS $(M+H)^+$ 206.

Step 3:

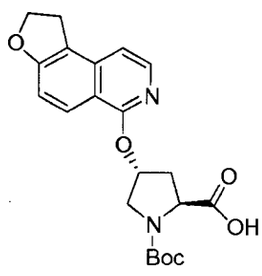
Modifications: 206 mg 6-chloro-2,3-dihydro-furo[2,3-f]isoquinoline used, 300 mg products mixture obtained.

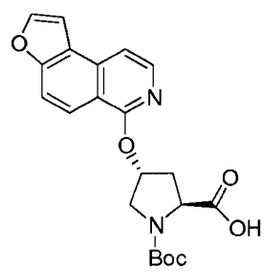
Products:





The following intermediates were prepared as described herein and can be incorporated into compounds of Formula 1

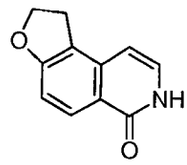




Step 1:

Modifications: 1.14 g 3-(2,3-dihydro-benzofuran-4-yl)-acrylic acid used, 600 mg product obtained (52% yield).

Product:

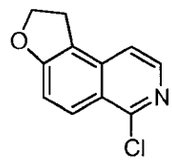


Data: ^{1}H NMR (400 MHz, CD_3OD) δ ppm 3.35 (t, *J*=8.93 Hz, 2 H), 4.74 (t, *J*=8.93 Hz, 2 H), 6.49 (d, *J*=7.09 Hz, 1 H), 6.95 (d, *J*=8.56 Hz, 1 H), 7.25 (d, *J*=7.09 Hz,, 1 H), 8.13 (d, *J*=8.80 Hz, 1 H); MS $(M+H)^+$ 188.

Step 2:

Modifications: 560 mg 1,7-dihydro-2*H*-furo[3,2-f]isoquinolin-6-one used, 380 mg product obtained (48% yield).

Product:

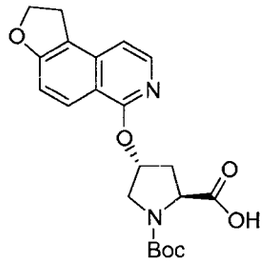


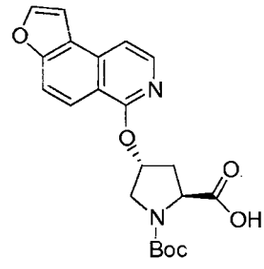
Data: ^{1}H NMR (400 Hz, $CDCl_3$) δ ppm 3.47 (t, *J*=9.05 Hz, 2 H), 4.84 (t, *J*=9.05 Hz, 2 H), 7.24 (d, *J*=8.56 Hz, 1 H), 7.33 (d, *J*=5.87 Hz, 1 H), 8.20 (m, 2 H); MS $(M+H)^+$ 206.

Step 3:

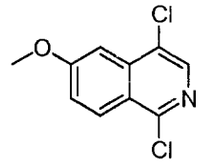
Modifications: 105 mg 6-chloro-1,2-dihydro-furo[3,2-f]isoquinoline used, 390 mg products mixture obtained.

Products:





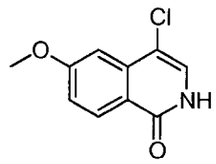
The following intermediates were prepared as described herein and can be incorporated into compounds of Formula 1



Step 1:

Modifications: A mixture of 6-methoxy-2*H*-isoquinolin-1-one (700 mg) and NCS (532 mg) in MeCN (10 mL) was refluxed for 3 h. Filtration gave 600 mg (72%) of the desired product as a solid.

Product:

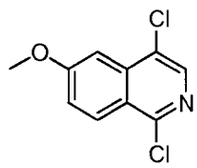


Data: ^{1}H NMR(400 MHz, CD_3OD) δ ppm 3.96 (s, 1 H), 7.19 (dd, *J*=8.80, 2.45 Hz, 1 H), 7.28 (d, *J*=2.45 Hz, 1 H), 7.34 (s, 1 H), 8.25 (d, *J*=9.05 Hz, 1 H); MS: $(M+H)^+$ 210.

Step 2:

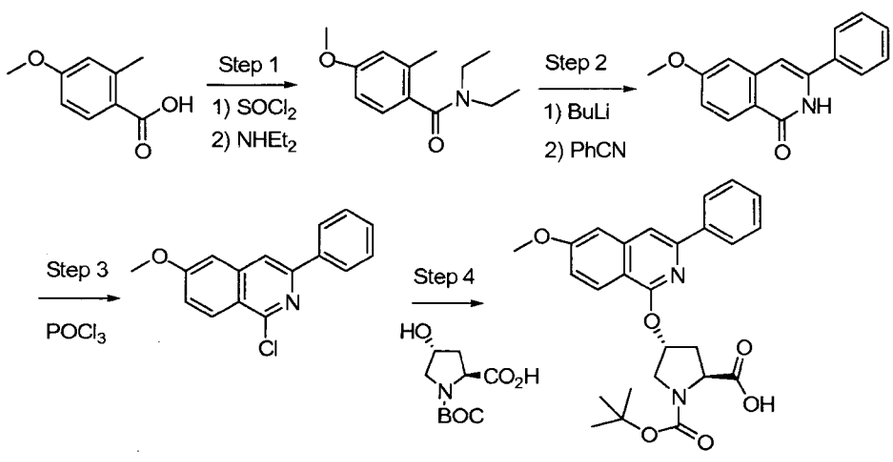
Modifications: 500 mg 4-chloro-6-methoxy-2H-isoquinolin-1-one used, 400 mg product obtained.

Product:



Data: ^{1}H NMR (400 Hz, $CDCl_3$) δ ppm 4.01 (s, 3 H), 7.35 (d, *J*=2.45 Hz, 1 H), 7.41 (d, *J*=2.45 Hz, 1 H), 8.24 (d, *J*=9.29 Hz, 1 H), 8.27 (s, 1 H); MS: $(M+H)^+$ 229.

Method B



000255

Step 1:

A mixture of 4-methoxy-2-methyl-benzoic acid (5.00 g, 30.1 mmol) and thionyl chloride (20.0 g, 0.17 mol) was heated to reflux for 30 min. Removed the volatile in vacuo. After pumping overnight, the viscous oily acid chloride was used as crude for the next reaction without any purification.

To a solution of 4-methoxy-2-methyl-benzoyl chloride in CH_2Cl_2 (60 mL) at 0^0C was added diethylamine dropwise. The formed mixture was allowed to warm up to the ambient temperature for 2 h with stirring. Removed the volatiles in vacuo. The residue was triturated with EtOAc (100 mL) and filtered. The filtrate was washed with 1M HCl , 1M NaOH and brine, dried over $MgSO_4$. Evaporation of the solvent yielded 6.51 g (98%) of the desired product as a viscous oil. MS *m/z* 222 (M^++H).

Step 2:

To a solution of N,N-diethyl-4-methoxy-2-methyl-benzamide (221 mg, 1.0 mmol) in THF (2 mL) at -78^0C was added n-BuLi (0.84 mL of 2.5 M in hexane, 2.10 mmol) dropwise. The formed orange solution was kept at this temperature for additional 30 min before dropwise addition of benzonitrile (103 mg, 1.0 mmol). The final solution was allowed to warm up to the ambient temperature over night with stirring. Quenched with iced 5% citric acid. Filtered, washed with water, dried. Trituration with 2:1 hexane-EtOAc (5 mL) yielded 205 mg (82%) of the desired product as a white solid.

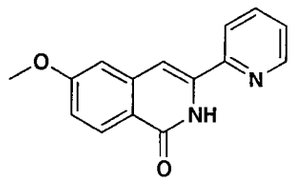
^{1}H NMR (d_6-DMSO) δ 3.89 (s, 3H), 6.84 (s, 1H), 7.05-7.07 (m, 1H), 7.18 (d, *J*=2.5 Hz, 1H), 7.44-7.51 (m, 3H), 7.78 (d, *J*=7.0 Hz, 1H), 8.11 (d, *J*=9.0 Hz, 1H). MS *m/z* 252 (M^++H).

Step 3:

This product, 1-chloro-6-methoxy-3-phenyl-isoquinoline, was prepared by the same method as described above except using 6-methoxy-3-phenyl-2H-isoquinolin-1-one instead.

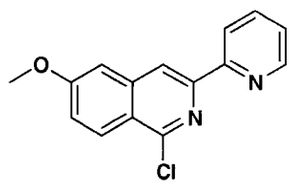
^{1}H NMR ($CDCl_3$) δ 3.97 (s, 3H), 7.12 (d, *J*=2.5 Hz, 1H), 7.23-7.26 (m, 1H), 7.40-7.42 (m, 1H), 7.46-7.50 (m, 2H), 7.89 (s, 1H), 8.08 (d, *J*=7.0 Hz, 2H), 8.21 (d, *J*=9.0 Hz, 1H). MS *m/z* 270, 271 (M^++H).

The following intermediates were prepared as described herein and can be incorporated into compounds of Formula 1



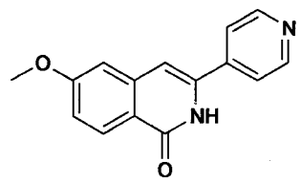
To a solution of N,N-Diethyl-4-methoxy-2-methyl-benzamide (332 mg, 1.5 mmol) in THF (15 mL) at –78°C, t-BuLi (1.7 M solution in pentane, 1.3 mL, 2.25 mmol) was added. The resulting red solution was stirred at –78°C for 10 min, then 2-cyanopyridine (156 mg, 1.5 mmol) was added. The reaction mixture was then warmed to rt and stirred for overnight. The reaction was quenched with saturated NH_4Cl solution and extracted with ethyl acetate twice. The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was purified by Prep. HPLC to give yellowish solid as TFA salt. (85 mg, 15% yield)
^1H NMR (400 MHz, CD_3OD) δ 3.91 (m, 3 H), 7.09 (dd, *J*=9.05, 2.45 Hz, 1 H), 7.17 (d, *J*=2.45 Hz, 1 H), 7.37 (s, 1 H), 7.42 (m, 1 H), 7.92 (m, 1 H), 8.08 (d, *J*=8.07 Hz, 1 H), 8.18 (d, *J*=9.05 Hz, 1 H), 8.65 (d, *J*=4.89 Hz, 1 H). MS m/z 253 (MH^+).

Step 2 (Scheme 3, Step 1):



6-Methoxy-3-pyridin-2-yl-2H-isoquinolin-1-one TFA salt (85 mg, 0.232 mmol) was heated under reflux with $POCl_3$ (3.0 mL) for 2 days. Then $POCl_3$ was distilled off and the residue was quenched with ice. It was then neutralized with 10 N NaOH solution and the brown solid was collected as pure product. (62 mg, 99% yield). MS m/z 271 (MH^+).

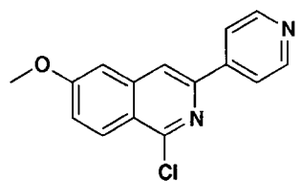
The following intermediates were prepared as described herein and can be incorporated into compounds of Formula 1



To a solution of N,N-Diethyl-4-methoxy-2-methyl-benzamide (332 mg, 1.5 mmol) in THF (15 mL) at –78°C, t-BuLi (1.7 M solution in pentane, 1.3 mL, 2.25 mmol) was added. The resulting red solution was stirred at –78°C for 10 min, then 4-cyanopyridine (164 mg, 1.575 mmol) was added. The reaction mixture was then warmed to rt and stirred for overnight. The reaction was quenched with saturated NH_4Cl solution and the yellow precipitate was collected as pure product. (145 mg, 38% yield)

^1H NMR(CD_3OD, 400 MHz) δ 3.91 (s, 3 H), 7.18 (dd, *J*=8.8 Hz, 2.8 Hz, 1 H), 7.26 (m, 2 H), 8.06 (d, *J*=6.0 Hz, 2H), 8.16 (d, *J*=8.8 Hz, 1H), 8.84 (d, *J*=6.0 Hz, 2H). MS m/z 253 (MH^+).

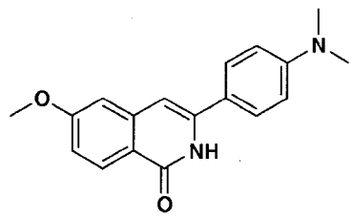
Step 2 (Scheme 3, step 1):



6-Methoxy-3-pyridin-4-yl-2H-isoquinolin-1-one (134 mg, 0.531 mmol) was heated under reflux with $POCl_3$ (6.0 mL) for 5 days. Then $POCl_3$ was distilled off and the residue was quenched with ice. It was then neutralized with saturated $NaHCO_3$ solution and the brown solid was collected as pure product. (125 mg, 87% yield)

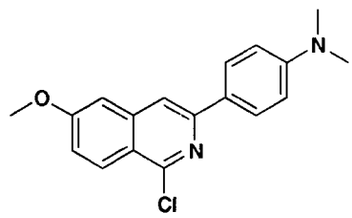
^1H NMR(DMSO-d^6, 400 MHz) δ 3.99 (s, 3 H), 7.53 (dd, *J*=9.04 Hz, 2.44 Hz, 1 H), 7.59 (d, *J*=2.69 Hz, 1 H), 8.26 (d, *J*=9.05 Hz, 1 H), 8.30 (d, *J*=5.38 Hz, 2 H), 8.73 (s, 1 H), 8.85 (d, *J*=6.36 Hz, 2 H). MS m/z 271 (MH^+).

The following intermediates were prepared as described herein and can be incorporated into compounds of Formula 1



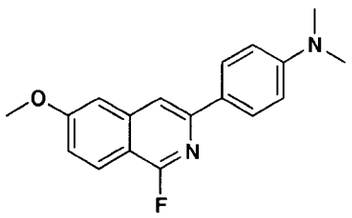
To a solution of N,N-Diethyl-4-methoxy-2-methyl-benzamide (332 mg, 1.5 mmol) in THF (15 mL) at –78°C, t-BuLi (1.7 M solution in pentane, 1.3 mL, 2.25 mmol) was added. The resulting red solution was stirred at –78°C for 10 min, then 4-dimethylamino benzonitrile (219 mg, 1.5 mmol) was added. The reaction mixture was then warmed to rt and stirred for overnight. The reaction was quenched with saturated NH_4Cl solution and the yellow precipitate was collected and triturated with ether to give an off-white solid as pure product. (247 mg, 56% yield)

^{1}H NMR(DMSO-d^6, 400 MHz) δ 2.97 (s, 6 H), 3.87 (s, 3 H), 6.72 (s, 1 H), 6.78 (d, *J*=8.80 Hz, 2 H), 6.97 (dd, *J*=8.80, 2.45 Hz, 1 H), 7.10 (d, *J*=2.45 Hz, 1 H), 7.65 (d, *J*=8.80 Hz, 2 H), 8.05 (d, *J*=8.80 Hz, 1 H), 11.11 (s, 1 H). MS m/z 295 (MH^+).



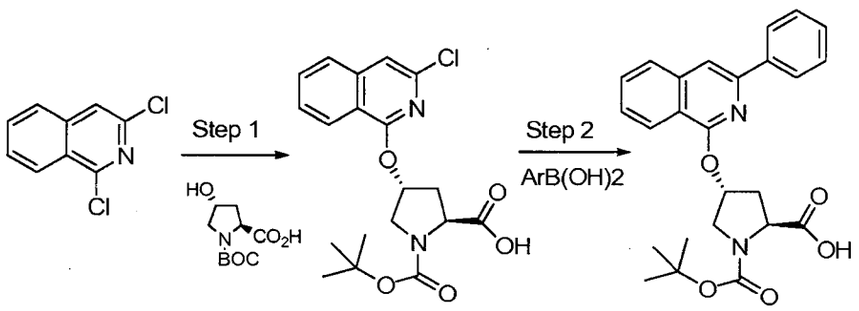
3-(4-Dimethylamino-phenyl)-6-methoxy-2H-isoquinolin-1-one (245 mg, 0.83 mmol) was heated under reflux with $POCl_3$ (10.0 mL) for 2 days. Then $POCl_3$ was distilled off and the residue was quenched with ice. It was then neutralized with 10 N NaOH solution and extracted with ethyl acetate twice. The organic layers were combined and dried (MgSO4). Evaporation of solvent gave an orange solid as product (215 mg, 83% yield)

^{1}H NMR (400 MHz, CD_3OD) δ 3.01 (s, 6 H), 3.96 (s, 3 H), 6.88 (d, *J*=9.05 Hz, 2 H), 7.20 (dd, *J*=9.17, 2.57 Hz, 1 H), 7.28 (d, *J*=2.45 Hz, 1 H), 7.94 (s, 1 H), 7.96 (d, *J*=9.05 Hz, 2 H), 8.13 (d, *J*=9.29 Hz, 1 H). MS m/z 313 (MH^+).



A mixture of [4-(1-Chloro-6-methoxy-isoquinolin-3-yl)-phenyl]-dimethyl-amine (110 mg, 0.35 mmol) and tetrabutyl phosphonium hydrogen difluoride (0.5 g) was heated at 140°C in Smith microwave reactor for 20 min. Then it was added water and extracted with ethyl acetate. The organic layer was separated, washed with water and dried ($MgSO_4$). Evaporation of solvent gave a brownish solid as product. (85 mg, 82% yield). MS m/z 297 (MH^+).

Method C



Step 1:

To a solution of N-BOC-3-(*R*)-hydroxy-L-proline (6.22 g, 26.9 mmol) in DMF (250 mL) at 0°C was added NaH (60%, 3.23 g, 80.8 mmol) by several portions. The formed suspension was stirred at this temperature for 30 min. 1,3-dichloro-isoquinoline (5.33 g, 26.9 mmol) was added as solid in one portion and the final mixture was stirred at the ambient temperature for 12 h. Quenched with iced 5% citric acid (aq), extracted with EtOAC (300 mL). The aqueous phase was extracted with EtOAC again. The combined organic layers were washed with 5% citric acid (aq) and brine respectively, dried over $MgSO_4$, filtered. The filtrate was evaporated in vacuo to dryness to yield 10.53 g (99.8%) of 4-(6-methoxy-isoquinolin-1-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester as an off-white foam. This material was used in the next step reaction as crude without further purification.

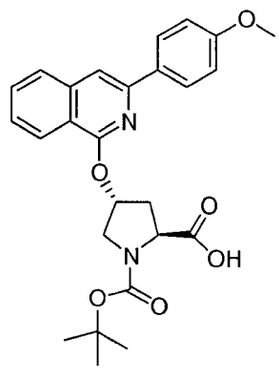
^{1}H NMR (CD_3OD) δ 1.43, 1.44 (rotamers, 9H), 2.39-2.44 (m, 1H), 2.68-2.72 (m, 1H), 3.80-3.90 (m, 2H), 4.44-4.52 (m, 1H), 5.77 (b, 1H), 7.39 (s, 1H), 7.58 (t, *J*=7.3 Hz, 1H), 7.71-7.78 (m, 2H), 8.16 (d, *J*=7.5 Hz, 1H). MS *m/z* 392 (M^++H).

Step 2:

A mixture of of 4-(6-methoxy-isoquinolin-1-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (39 mg, 0.10 mmol), phenylboronic acid (14.6 mg, 0.12 mmol), sodium tert-butoxide (38 mg, 0.40 mmol) and $((t\text{-}Bu)_2POH)_2PdCl_2$ (POPd) (5 mg, 0.01 mmol) in THF (2 mL) was heated to reflux for 4 h. After cooling down, the formed mixture was quenched with 5% citric acid (aq) and extracted with EtOAc (20 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, evaporated. The residue was purified by prep-HPLC to yield 36 mg (83%) of the desired product as an off-white foam.

^{1}H NMR (CD_3OD) δ 1.43, 1.45 (rotamers, 9H), 2.51-2.56 (m, 1H), 2.74-2.82 (m, 1H), 3.88-3.92 (m, 1H), 3.98-4.01 (m, 1H), 4.50-4.57 (m, 1H), 5.95 (b, 1H), 7.36-7.39 (m, 1H), 7.45-7.48 (m, 2H), 7.55 (t, *J*=7.3 Hz, 1H), 7.70 (t, *J*=7.5 Hz, 1H), 7.84-7.89 (m, 2H), 8.14-8.17 (m, 3H), 9.05 (b, 1H). MS *m/z* 435 (M^++H).

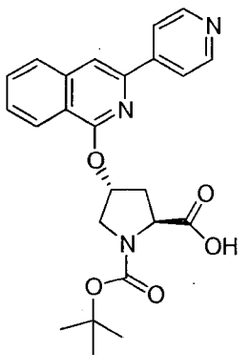
The following intermediates were prepared as described herein and can be incorporated into compounds of Formula 1



Prepared using 4-methoxyphenylboronic acid

^{1}H NMR (CD_3OD) δ 1.40, 1.45 (rotamers, 9H), 2.50-2.55 (m, 1H), 2.73-2.81 (m, 1H), 3.81-3.89 (m, 4H), 3.98-4.01 (m, 1H), 4.50-4.57 (m, 1H), 5.93 (b, 1H), 7.02 (d, *J*=9.0 Hz, 2H), 7.50 (t, *J*=7.3 Hz, 1H), 7.67 (t, *J*=7.5 Hz, 1H), 7.73 (s, 1H), 7.83 (d, *J*=8.5 Hz, 1H), 8.09 (d, *J*=8.5 Hz, 2H), 8.15 (d, *J*=8.0 Hz, 1H). MS *m/z* 465 (M^++H).

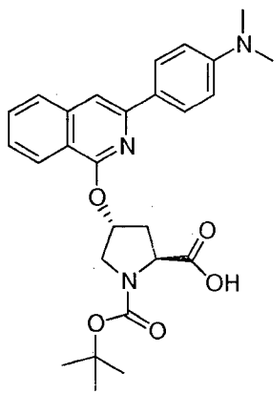
The following intermediate was prepared as described above:



Prepared using 4-pyridylboronic acid

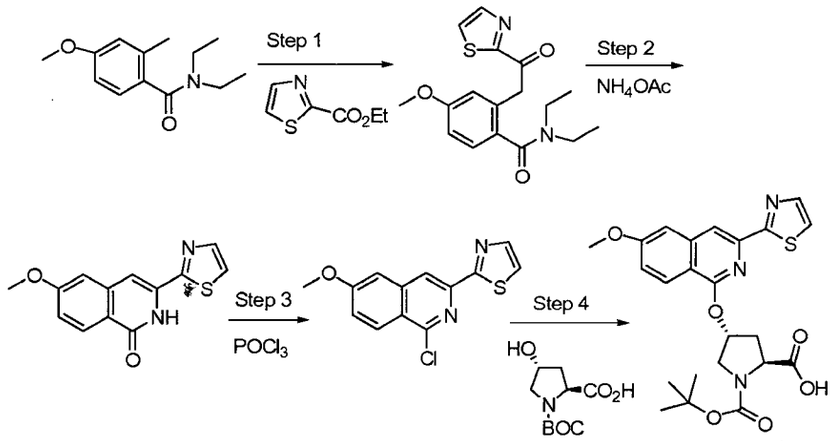
^{1}H NMR (CD_3OD) δ 1.43, 1.46 (rotamers, 9H), 2.53-2.56 (m, 1H), 2.80-2.89 (m, 1H), 3.90-3.93 (m, 1H), 4.00-4.05 (m, 1H), 4.50-4.57 (m, 1H), 6.00, 6.05(rotamers, 1H), 7.80 (t, *J*=7.3 Hz, 1H), 7.87 (t, *J*=7.5 Hz, 1H), 8.08 (d, *J*=8.5 Hz, 1H), 8.32 (d, *J*=8.0 Hz, 1H), 8.49 (s, 1H), 8.84 (d, *J*=6.0 Hz, 2H), 8.84 (d, *J*=6.5 Hz, 2H. MS *m/z* 436 (M^++H).

The following intermediates were prepared as described herein and can be incorporated into compounds of Formula 1



Prepared using 4-N,N-dimethylamino-phenylboronic acid. MS *m/z* 478 (M^++H).

Method D



Step 1:

To a solution of N,N-diethyl-4-methoxy-2-methyl-benzamide (633 mg, 2.9 mmol) in THF (15 mL) at –78°C was added n-BuLi (2.3 mL of 2.5 M in hexane, 5.74 mmol) dropwise. The formed red solution was kept at this temperature for additional 30 min before being cannulated to a solution of thiazole-2-carboxylic acid ethyl ester (A. Medici et al, Tetrahedron Lett. 1983, p2901) (450 mg, 2.9 mmol) in THF (5 mL) at –78°C. The final dark green solution was kept to this temperature for 2 h with stirring. Quenched with sat. NH_4Cl (aq) and extracted with EtOAc (50 mL). The organic layer was washed with sat. NH_4Cl (aq) and brine, dried, purified by flash column chromatography, eluting with 2:1 EtOAc:hexane to provide 405 mg (45%) of the desired product as an off-white viscous oil.

^{1}H NMR ($CDCl_3$) δ 1.08 (t, *J*=7.0 Hz, 6H), 3.22 (b, 2H), 3.44 (b, 2H), 3.79 (s, 3H), 4.59 (s, 2H), 6.79-6.81 (m, 1H), 6.86 (d, *J*=2.5 Hz, 1H), 7.16 (d, *J*=8.5 Hz, 1H), 7.66 (d, *J*=3.0 Hz, 1H), 8.00 (d, *J*=3.0 Hz, 1H).

MS *m/z* 333 (M^++H).

Step 2:

A mixture of N,N-diethyl-4-methoxy-2-(2-oxo-2-thiazol-2-yl-ethyl)-benzamide (405 mg, 1.22 mmol) and NH_4OAc (3.0 g, 38.9 mmol) was heated to 140°C in a sealed tube for 1 h. The melted solution was poured into iced water, filtered, washed the

cake thoroughly with water. The dried brownish solid (240 mg, 76%) was used as crude for the next reaction without further purification. MS *m/z* 259 (M^++H).

Step 3:

This product, 1-chloro-6-methoxy-3-thiazol-2-yl-isoquinoline, was prepared as described above except using 6-methoxy-3-thiazol-2-yl-2H-isoquinolin-1-one instead.

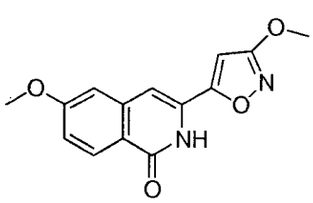
^{1}H NMR ($CDCl_3$) δ 3.97 (s, 3H), 7.16 (d, *J*=4.0 Hz, 1H), 7.27-7.31 (m, 1H), 7.46 (d, *J*=5.0 Hz, 1H), 7.93 (d, *J*=5.5 Hz, 1H), 8.22 (d, *J*=15.5 Hz, 1H), 8.39 (s, 1H). MS *m/z* 277 (M^++H).

Step 4:

This product was prepared by the same method as described above except using 1-chloro-6-methoxy-3-thiazol-2-yl-isoquinoline instead.

^{1}H NMR (CD_3OD) δ 0.97-1.09 (m, 12H), 1.24-1.29 (m, 10H), 1.44-1.46 (m, 1H), 1.87-1.90 (m, 1H), 2.20-2.26 (m, 1H), 2.30-2.36 (m. 1H), 2.65-2.71 (m, 1H), 2.93-2.96 (m, 1H), 3.96 (s, 3H), 4.12-4.27 (m, 2H), 4.38-4.52 (m, 2H), 5.12 (d, *J*=10.5 Hz, 1H), 5.29 (d, *J*=17.5 Hz, 1H), 5.69-5.74 (m, 1H), 5.99 (b, 1H), 7.14 (d, *J*=9.0 Hz, 1H), 7.33 (s, 1H), 7.66 (d, *J*=3.5 Hz, 1H), 7.93 (d, J=3.0 Hz, 1H), 8.05 (s, 1H), 8.11 (d, *J*=9.0 Hz, 1H), 9.14 (b, 1H).
MS *m/z* 797 (M^++H).

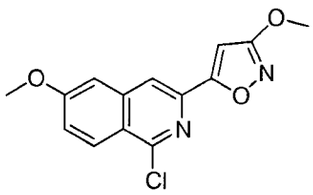
The following intermediates were prepared as described herein and can be incorporated into compounds of Formula 1



6-methoxy-3-(3-methoxy-isoxazol-5-yl)-2H-isoquinolin-1-one was prepared using N,N-diethyl-4-methoxy-2-[2-(3-methoxy-isoxazol-5-yl)-2-oxo-ethyl]-benzamide.

^{1}H NMR (DMSO-d_6) δ 3.89 (s, 3H), 3.97 (s, 3H), 7.01 (s, 1H), 7.14-7.16 (m, 2H), 7.43 (s, 1H), 8.13 (d, *J*=8.5 Hz, 1H).

MS *m/z* 273 (M^++H).

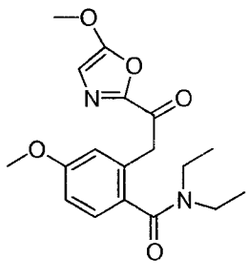


1-chloro-6-methoxy-3-(3-methoxy-isoxazol-5-yl)-isoquinoline was prepared using 6-methoxy-3-(3-methoxy-isoxazol-5-yl)-2H-isoquinolin-1-one

^{1}H NMR ($CDCl_3$) δ 3.97 (s, 3H), 4.04 (s, 3H), 6.60 (s, 1H), 7.17 (d, *J*=2.5 Hz, 1H), 7.31-7.33 (m, 1H), 8.02 (s, 1H), 8.23 (d, *J*=9.0 Hz, 1H).

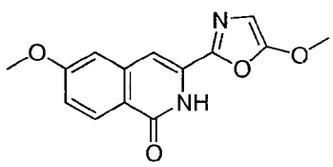
MS *m/z* 291, 293 (M^++H)

The following intermediates were prepared as described herein and can be incorporated into compounds of Formula 1



N,N-diethyl-4-methoxy-2-[2-(5-methoxy-oxazol-2-yl)-2-oxo-ethyl]-benzamide, was prepared using 5-methoxy-oxazole-2-carboxylic acid ethyl ester.

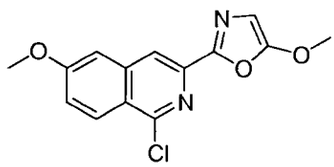
MS *m/z* 347 (M^++H).



6-methoxy-3-(5-methoxy-oxazol-2-yl)-2H-isoquinolin-1-one, was prepared using N,N-diethyl-4-methoxy-2-[2-(5-methoxy-oxazol-2-yl)-2-oxo-ethyl]-benzamide.

^{1}H NMR (DMSO-d_6) δ 3.94 (s, 3H), 4.01 (s, 3H), 6.34 (s, 1H), 6.99 (d, *J*=2.0 Hz, 1H), 7.12-7.14 (m, 1H), 7.25 (s, 1H), 8.32 (d, *J*=9.0 Hz, 1H).

MS *m/z* 274 (M^++H).

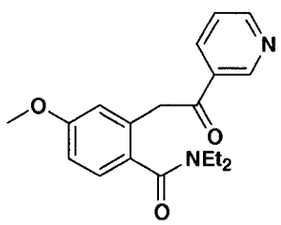


1-chloro-6-methoxy-3-(5-methoxy-oxazol-2-yl)-isoquinoline, was prepared using 6-methoxy-3-(5-methoxy-oxazole-2-yl)-2H-isoquinolin-1-one.

^{1}H NMR ($CDCl_3$) δ 3.96 (s, 3H), 4.00 (s, 3H), 6.34 (s, 1H), 7.12 (d, *J*=2.5 Hz, 1H), 7.28-7.31 (m, 1H), 8.13 (s, 1H), 8.23 (d, *J*=9.0 Hz, 1H).

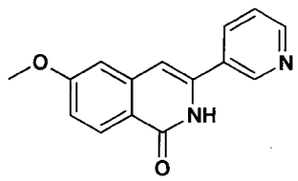
MS *m/z* 291, 293 (M^++H).

The following intermediates were prepared as described herein and can be incorporated into compounds of Formula 1



To a solution of N,N-Diethyl-4-methoxy-2-methyl-benzamide (332 mg, 1.5 mmol) in THF (15 mL) at –78°C, t-BuLi (1.7 M solution in pentane, 2.12 mL, 3.6 mmol) was added. The resulting red solution was stirred at –78°C for 10 min, then methyl nicotinate (206 mg, 1.5 mmol) was added. The reaction mixture was stirred at –78°C for 2h. Then the reaction was quenched with saturated NH_4Cl solution and extracted with ethyl acetate twice. The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was purified by Prep. HPLC to give yellowish thick oil as TFA salt. (124 mg, 19% yield).

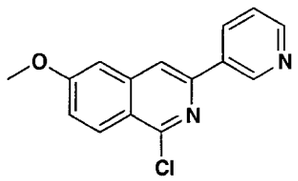
MS m/z 349 ($M+Na^+$).



N,N-Diethyl-4-methoxy-2-(2-oxo-2-pyridin-3-yl-ethyl)-benzamide (120 mg, 0.272 mmol) was heated with ammonium acetate (1 g) for 3 hr. Then it was cooled down and added water. Extracted with ethyl acetate and the organic layer was separated. It was then dried ($MgSO_4$) and concentrated to give a brownish solid as product. (65 mg, 95% yield)

^1H NMR (400 MHz, DMSO-d^6) δ 3.89 (s, 3 H), 6.93 (s, 1 H), 7.10 (dd, *J*=8.80, 2.45 Hz, 1 H), 7.19 (d, *J*=2.45 Hz, 1 H), 7.52 (dd, *J*=7.46, 4.77 Hz, 1 H), 8.15 (m, 2 H), 8.64 (dd, *J*=4.89, 1.47 Hz, 1 H), 8.96 (d, *J*=1.71 Hz, 1 H), 11.51 (s, 1 H).

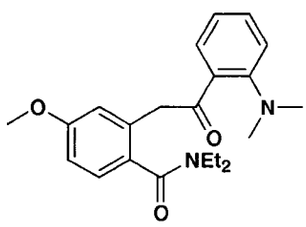
MS m/z 253 (MH^+).



6-Methoxy-3-pyridin-3-yl-2H-isoquinolin-1-one (65 mg, 0.258 mmol) was heated under reflux with $POCl_3$ (2.5 mL) for 7 days. Then $POCl_3$ was distilled off and the residue was quenched with ice. It was then neutralized with 10 N NaOH solution and extracted with ethyl acetate twice. The combined organic layers were dried ($MgSO_4$) and concentrated to give yellow solid as product. (27 mg, 39% yield).

MS m/z 271 (MH^+).

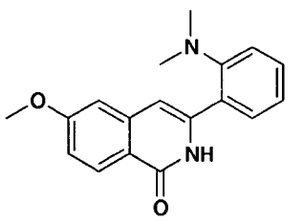
The following intermediates were prepared as described herein and can be incorporated into compounds of Formula 1



To a solution of N,N-Diethyl-4-methoxy-2-methyl-benzamide (332 mg, 1.5 mmol) in THF (15 mL) at –78°C, t-BuLi (1.7 M solution in pentane, 2.2 mL, 3.75 mmol) was added. The resulting red solution was stirred at –78°C for 10 min, then N,N-dimethylanthranilic acid methyl ester (269 mg, 1.5 mmol) was added. The reaction mixture was stirred at –78°C for 2h. Then the reaction was quenched with saturated NH_4Cl solution and extracted with ethyl acetate twice. The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was purified by Prep. HPLC to give yellowish thick oil as product. (256 mg, 46% yield)

^1H NMR (400 MHz, CD_3OD) δ 0.99-1.13 (m, 6 H), 3.23-3.31 (m, 8 H), 3.39 (m, 2 H), 3.82 (s, 3 H), 4.35 (s, 2 H), 6.91 (dd, *J*=8.44, 2.57 Hz, 1 H), 6.99 (d, *J*=2.45 Hz, 1 H), 7.22 (d, *J*=8.56 Hz, 1 H), 7.69 (t, *J*=7.70 Hz, 1 H), 7.84 (m, 1 H), 7.96 (d, *J*=8.31 Hz, 1 H), 8.18 (d, *J*=7.83 Hz, 1 H).

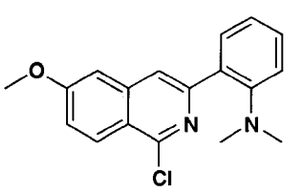
MS m/z 369(MH^+).



2-[2-(2-Dimethylamino-phenyl)-2-oxo-ethyl]-N,N-diethyl-4-methoxy-benzamide (250 mg, 0.678 mmol) was heated with ammonium acetate (1.5 g) for 2 hr. Then it was cooled down and added water. Extracted with ethyl acetate and the organic layer was separated. It was then dried ($MgSO_4$) and concentrated to give a yellowish solid as product. (125 mg, 63% yield)

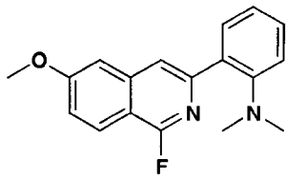
^1H NMR (400 MHz, CD_3OD) δ 2.95 (s, 6 H), 3.92 (s, 3 H), 6.92 (s, 1 H), 7.12 (dd, *J*=8.80, 2.45 Hz, 1 H), 7.16 (d, *J*=2.45 Hz, 1 H), 7.35 (m, 1 H), 7.55 (m, 2 H), 7.63 (d, *J*=7.83 Hz, 1 H), 8.20 (d, *J*=9.05 Hz, 1 H).

MS m/z 295 (MH^+).



3-(2-Dimethylamino-phenyl)-6-methoxy-2H-isoquinolin-1-one (125 mg, 0.425 mmol) was heated under reflux with $POCl_3$ (4.0 mL) for one day. Then $POCl_3$ was distilled off and the residue was quenched with ice. It was then neutralized with 10 N NaOH solution and extracted with ethyl acetate twice. The organic layers were combined and dried ($MgSO_4$). Evaporation of solvent gave a brownish solid as product (82 mg, 62% yield)

MS m/z 313 (MH^+).

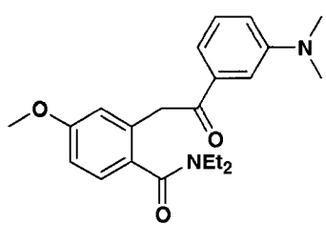


A mixture of [2-(1-Chloro-6-methoxy-isoquinolin-3-yl)-phenyl]-dimethyl-amine (82 mg, 0.262 mmol) and tetrabutyl phosphonium hydrogen difluoride (1.0 g) was heated at 140°C in Smith microwave reactor for 20 min. Then it was added water and extracted with ethyl acetate. The organic layer was separated, washed with water and dried ($MgSO_4$). Evaporation of solvent gave the crude product which was purified by Prep. HPLC to afford a yellowish oil as product. (85 mg)

^1H NMR (400 MHz, CD_3OD) δ 3.41 (s, 6 H), 4.00 (s, 3 H), 7.42 (dd, *J*=9.05, 2.45 Hz, 1 H), 7.53 (s, 1 H), 7.71 (m, 2 H), 7.99 (m, 1 H), 8.16 (m, 2 H), 8.31 (s, 1 H).

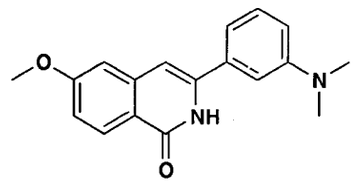
MS m/z 297 (MH^+).

The following intermediates were prepared as described herein and can be incorporated into compounds of Formula 1



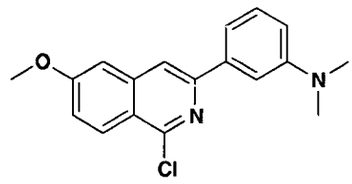
To a solution of N,N-Diethyl-4-methoxy-2-methyl-benzamide (332 mg, 1.5 mmol) in THF (15 mL) at –78°C, t-BuLi (1.7 M solution in pentane, 2.2 mL, 3.75 mmol) was added. The resulting red solution was stirred at –78°C for 10 min, then (3-dimethylamino)benzoic acid methyl ester (269 mg, 1.5 mmol) was added. The

reaction mixture was stirred at –78°C for 2h. Then the reaction was quenched with saturated NH_4Cl solution and extracted with ethyl acetate twice. The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was purified by Prep. HPLC to give yellowish thick oil as TFA salt. (245 mg, 33% yield) 1H NMR (400 MHz, CD_3OD) δ 1.01 (t, *J*=6.85 Hz, 3 H), 1.09 (m, 3 H), 3.11 (s, 6H), 3.21 (m, 2 H), 3.40 (m, 2 H), 3.79 (s, 3 H), 4.39 (s, 2 H), 6.84-6.91 (m, 2 H), 7.19 (d, *J*=8.32 Hz, 1 H), 7.35 (m, 1 H), 7.49 (t, *J*=8.07 Hz, 1 H), 7.66-7.71 (m, 2 H). MS m/z 369(MH^+).

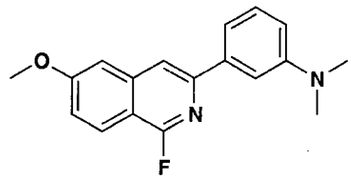


2-[2-(3-Dimethylamino-phenyl)-2-oxo-ethyl]-N,N-diethyl-4-methoxy-benzamide (240 mg, 0.497 mmol) was heated with ammonium acetate (2.0 g) for 2.5 hr. Then it was cooled down and added water. A brownish solid was collected as pure product. (95 mg, 65% yield)

1H NMR (400 MHz, CD_3OD) δ 2.98 (s, 6 H), 3.88 (s, 3 H), 6.74-6.87 (m, 2 H), 7.01-7.07 (m, 3 H), 7.18 (d, *J*=2.44 Hz, 1 H), 7.28 (t, *J*=7.82 Hz, 1 H), 8.10 (d, *J*=8.80 Hz, 1 H). MS m/z 295 (MH^+).



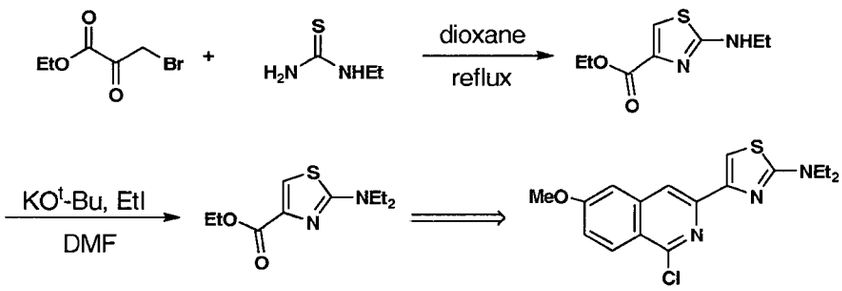
3-(3-Dimethylamino-phenyl)-6-methoxy-2H-isoquinolin-1-one (92 mg, 0.312 mmol) was heated under reflux with $POCl_3$ (3.0 mL) for 2 days. Then $POCl_3$ was distilled off and the residue was quenched with ice. It was then neutralized with saturated $NaHCO_3$ solution and extracted with ethyl acetate twice. The organic layers were combined and dried ($MgSO_4$). Evaporation of solvent gave a brownish thick oil as product. (72 mg, 74% yield). MS m/z 313 (MH^+).



A mixture of [3-(1-Chloro-6-methoxy-isoquinolin-3-yl)-phenyl]-dimethylamine (72 mg, 0.23 mmol) and tetrabutyl phosphonium hydrogen difluoride (0.5 g) was heated at 140°C in Smith microwave reactor for 20 min. Then it was added water and extracted with ethyl acetate. The organic layer was separated, washed with water and dried ($MgSO_4$). Evaporation of solvent gave a brownish oil as product. (58 mg, 85% yield).

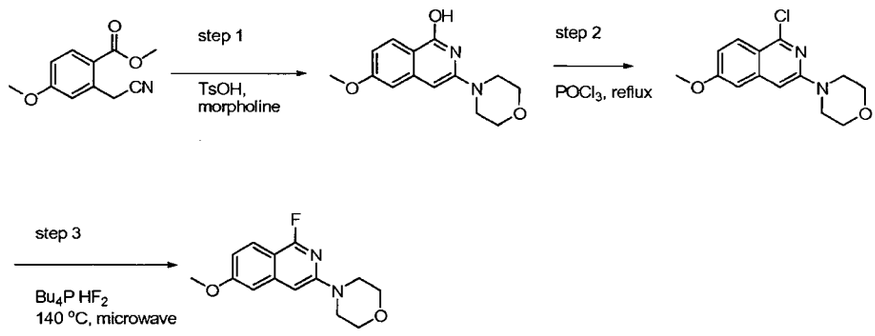
MS m/z 297 (MH^+).

The following intermediates were prepared as described herein and can be incorporated into compounds of Formula 1



Condensation of ethyl bromopyruvate with ethyl thiourea in refluxing dioxane afforded the monoalkylamino thiazole as HBr salt in quantitative yield. Alkylation of 2-ethylamino-thiazole-4-carboxylic acid ethyl ester with EtI in DMF provided 2-diethylamino-thiazole-4-carboxylic acid ethyl ester.

Method E



Step 1:

A suspension of 2-cyanomethyl-4-methoxy-benzoic acid methyl ester (1.9g and TsOH. H_2O (0.15 g, mmol) in morpholine 5 mL) was refluxed for 4 h and removed the solvent in vavuo. The residue was recrystalyzed from EtOAc/hexanes with drops of MeOH to provide the product (0.43 g, 17%). MS *m/z* 266 (M^++1).

Step 2:

A mixture of 6-methoxy-3-morpholin-4-yl-isoquinolin-1-ol (0.298 g, 1.15 mmol) in $POCl_3$ (20 mL) was refluxed for 2 h, removed the solvent in vacuo and cold water was added. The pH was adjustde to >11 by addition of 1.0 N NaOH. The aqueous layer was extracted with EtOAc. The extract was dried ($MgSO_4$), removed the solvent in vacuo to provide the produt (0.299g, 94%). MS *m/z* 279 (M^++1).

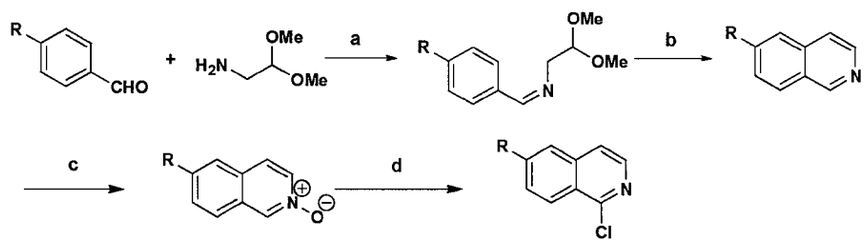
Step 3:

A mixture of 1-Chloro-6-methoxy-3-morpholin-4-yl-isoquinoline (0.050g, 0.18 mmol) and tetrabutyl phosphorium hydrgen difloride (0.8 g, 2.8 mmol) [Synlett ***1992***, (4), 345-6] was heated at 140 °C in microwave for 10 min. the reaction mixture was diluted with EtOAc and filtered through an ISCO 25g precolumn with a layer of silicon gel on the top, removed the solvent to provide the product (0.037 mg, 77%): ^{1}H NMR (CHLOROFORM-D) δ ppm 3.48 (m, 4 H), 3.84 (m, 4 H), 3.89 (s, 3 H), 6.46 (d, *J*=1.22 Hz, 1 H), 6.85 (s, 1 H), 6.90 (dd, *J*=9.16, 2.44 Hz, 1 H), 7.82 (d, *J*=8.85 Hz, 1 H). MS *m/z* 263 (M^++1).

Method F

6-fluoro and 6-alkyl isoquinolines used in the preparation of compounds of Formula 1 were prepared via a Pomeranz-Fritsch synthesis (Typical procedure: Preparation of optically active 8,8-disubstituted 1,1-biisoquinoline, K. Hirao, R. Tsuchiya, Y. Yano, H. Tsue, *Heterocycles* 42(1) 1996, 415-422) as outlined below. The products were converted into the 1-chloro derivatives via N-oxide intermediates.

General Synthetic Scheme



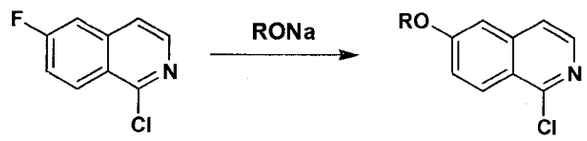
Reagents and reaction conditions: (a) reflux in benzene, azeotropic removal of water; (b) first step: ethyl chloroformate, trimethyl phosphite in THF, second step: titanium tetrachloride in chloroform; (c) MCPBA in CH_2Cl_2; (d) $POCl_3$ in benzene

R	Isoquinoline, Yield	1-Chloride, combined yield
F	20	43
Et	76	65
i-Pr	14	18
t-Bu	47	55

Preparation of 6-isopropoxyl and 6-*tert*-butoxyl isoquinoline intermediates:

Some 6-alkoxy-1-chloro isoquinolines were prepared by a direct, ipso displacement of the 6-fluoro-1-chloroisoquinoline with the corresponding alkoxide metal ions such as potassium *tert*-butoxide (53%) and sodium isopropoxide (54%).

General Synthetic Scheme



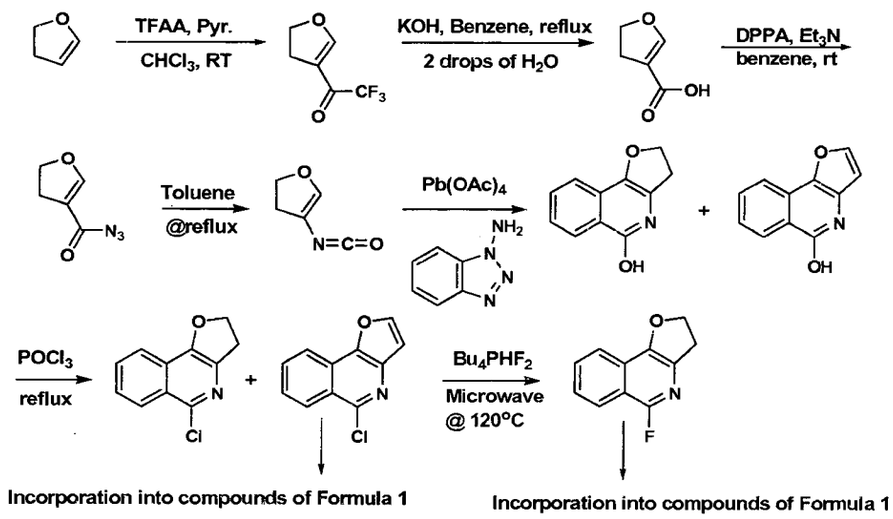
R = alkoxide anions such as *tert*-Bu, iso-Pr

The 6-fluoro-1-chloroisoquinoline was subjected to an aromatic nucleophilic displacement with sodium isopropoxide and potassium *tert*-butoxide in DMF to give the corresponding

6- isopropoxyl (54%): ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.43 (d, *J*=6.11 Hz, 6 H) 4.76 (m, *J*=6.11 Hz, 1 H) 7.08 (d, *J*=2.45 Hz, 1 H) 7.29 (dd, *J*=9.29, 2.45 Hz, 1 H) 7.50 (d, *J*=5.62 Hz, 1 H) 8.18 (d, *J*=5.87 Hz, 1 H) 8.24 (d, *J*=9.29 Hz, 1 H) and 6-*tert*-butoxyl-1-chloro isoquinolines (55%): ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.48 (s, 9 H) 7.31 (m, 2 H) 7.47 (d, J=5.62 Hz, 1 H) 8.18 (d, J=5.62 Hz, 1 H) 8.21 (d, J=9.78 Hz, 1 H) as the major product respectively. These 6-alkoxyl-1-chloro isoquinolines were incorporated into compounds of Formula 1 as described herein.

Method G

General Synthetic Scheme



This synthesis made use of the technologies described, in part, in the following references:

(1) Hojo, Masaru; Masuda, Ryoichi; Sakaguchi, Syuhei; Takagawa, Makoto, *Synthesis* (1986), (12), 1016-17

(2) Rigby, James H.; Holsworth, Daniel D.; James, Kelly. Vinyl Isocyanates In Synthesis. [4 + 2] Cycloaddition Reactions With Benzyne Addends. *Journal Of Organic Chemistry* (1989), 54(17), 4019-20

(3) Uchibori, Y.; Umeno, M.; Yoshiokai, H.; *Heterocycles*, 1992, 34 (8), 1507-1510

Biological Studies

HCV NS3/4A protease complex enzyme assays and cell-based HCV replicon assays were utilized in the present disclosure, and were prepared, conducted and validated as follows:

Generation of recombinant HCV NS3/4A protease complex

HCV NS3 protease complexes, derived from the BMS strain, H77 strain or J4L6S strain, were generated, as described below. These purified recombinant proteins were generated for use in a homogeneous assay (see below) to provide an indication of how effective compounds of the present disclosure would be in inhibiting HCV NS3 proteolytic activity.

Serum from an HCV-infected patient was obtained from Dr. T. Wright, San Francisco Hospital. An engineered full-length cDNA (compliment deoxyribonucleic acid) template of the HCV genome (BMS strain) was constructed from DNA fragments obtained by reverse transcription-PCR (RT-PCR) of serum RNA (ribonucleic acid) and using primers selected on the basis of homology between other genotype 1a strains. From the determination of the entire genome sequence, a genotype 1a was assigned to the HCV isolate according to the classification of Simmonds et al. (See P Simmonds, KA Rose, S Graham, SW Chan, F McOmish, BC Dow, EA Follett, PL Yap and H Marsden, *J. Clin. Microbiol.*, 31(6), 1493-1503 (1993)). The amino acid sequence of the nonstructural region, NS2-5B, was shown to be >97% identical to HCV genotype 1a (H77) and 87% identical to genotype 1b (J4L6S). The infectious clones, H77 (1a genotype) and J4L6S (1b genotype) were obtained from R. Purcell (NIH) and the sequences are published in Genbank (AAB67036, see Yanagi,M., Purcell,R.H., Emerson,S.U. and Bukh,J. *Proc. Natl. Acad. Sci. U.S.A.* 94(16), 8738-8743 (1997); AF054247, see Yanagi,M., St Claire,M., Shapiro,M., Emerson,S.U., Purcell,R.H. and Bukh,J. *Virology* 244 (1), 161-172. (1998)).

The H77 and J4L6S strains were used for production of recombinant NS3/4A protease complexes. DNA encoding the recombinant HCV NS3/4A protease complex (amino acids 1027 to 1711) for these strains was manipulated as described by P. Gallinari et al. (see Gallinari P, Paolini C, Brennan D, Nardi C, Steinkuhler C, De Francesco R. *Biochemistry* 38(17):5620-32, (1999)). Briefly, a three-lysine solubilizing tail was added at the 3'-end of the NS4A coding region. The cysteine in the P1 position of the NS4A-NS4B cleavage site (amino acid 1711) was changed to a glycine to avoid the proteolytic cleavage of the lysine tag. Furthermore, a cysteine to serine mutation was introduced by PCR at amino acid position 1454 to prevent the autolytic cleavage in the NS3 helicase domain. The variant DNA fragment was cloned in the pET21b bacterial expression vector (Novagen) and the NS3/4A complex was expressed in Escherichia. coli strain BL21 (DE3) (Invitrogen) following the protocol described by P. Gallinari et al. (see Gallinari P, Brennan D, Nardi C, Brunetti M, Tomei L, Steinkuhler C, De Francesco R., *J Virol.* 72(8):6758-69 (1998)) with modifications. Briefly, the NS3/4A protease complex expression was induced with 0.5 millimolar (mM) Isopropyl β-D-1-thiogalactopyranoside (IPTG) for 22 hours (h) at 20°C. A typical fermentation (1 Liter (L)) yielded approximately 10 grams (g) of wet cell paste. The cells were resuspended in lysis buffer (10 mL/g) consisting of 25 mM *N*-(2-Hydroxyethyl)Piperazine-*N*'-(2-Ethane Sulfonic acid) (HEPES), pH 7.5, 20% glycerol, 500 mM Sodium Chloride (NaCl), 0.5% Triton X-100, 1 microgram/milliliter ("μg/mL") lysozyme, 5 mM Magnesium Chloride ($MgCl_2$), 1 μg/ml DnaseI, 5mM β-Mercaptoethanol (βME), Protease inhibitor-Ethylenediamine Tetraacetic acid (EDTA) free (Roche), homogenized and incubated for 20 minutes (min) at 4 °C. The homogenate was sonicated and clarified by ultra-centrifugation at 235000 g for 1 hour at 4 °C. Imidazole was added to the supernatant to a final concentration of 15 mM and the pH adjusted to 8.0. The crude protein extract was loaded on a Nickel-Nitrilotriacetic acid (Ni-NTA) column pre-equilibrated with buffer B (25 mM HEPES, pH 8.0, 20% glycerol, 500 mM NaCl, 0.5% Triton X-100, 15 mM imidazole, 5 mM βME). The sample was loaded at a flow rate of 1 mL/min. The column was washed with 15 column volumes of buffer C (same as buffer B except with 0.2% Triton X-100). The protein was eluted with 5 column volumes of buffer D (same as buffer C except with 200 mM Imidazole).

NS3/4A protease complex-containing fractions were pooled and loaded on a desalting column Superdex-S200 pre-equilibrated with buffer D (25 mM HEPES, pH 7.5, 20% glycerol, 300 mM NaCl, 0.2% Triton X-100, 10 mM βME). Sample was loaded at a flow rate of 1 mL/min. NS3/4A protease complex-containing fractions were pooled and concentrated to approximately 0.5 mg/ml. The purity of the NS3/4A protease complexes, derived from the BMS, H77 and J4L6S strains, were judged to be greater than 90% by SDS-PAGE and mass spectrometry analyses. The enzyme was stored at -80 °C, thawed on ice and diluted prior to use in assay buffer.

FRET peptide assay to monitor HCV NS3/4A proteolytic activty

The purpose of this in vitro assay was to measure the inhibition of HCV NS3 protease complexes, derived from the BMS strain, H77 strain or J4L6S strain, as described above, by compounds of the present disclosure. This assay provides an indication of how effective compounds of the present disclosure would be in inhibiting HCV NS3 proteolytic activity.

In order to monitor HCV NS3/4A protease activity, an NS3/4A peptide substrate was used. The substrate was RET S1 (Resonance Energy Transfer Depsipeptide Substrate; AnaSpec, Inc. cat # 22991) (FRET peptide), described by Taliani et al. in Anal. Biochem. 240(2):60-67 (1996). The sequence of this peptide is loosely based on the NS4A/NS4B natural cleavage site for the HCV NS3 protease except there is an ester linkage rather than an amide bond at the cleavage site. The peptide also contains a fluorescence donor, EDANS, near one end of the peptide and an acceptor, DABCYL, near the other end. The fluorescence of the peptide is quenched by intermolecular resonance energy transfer (RET) between the donor and the acceptor, but as the NS3 protease cleaves the peptide the products are released from RET quenching and the fluorescence of the donor becomes apparent.

The peptide substrate was incubated with one of the three recombinant NS3/4A protease complexes, in the absence or presence of a compound of the present disclosure. The inhibitory effects of a compound were determined by monitoring the formation of fluorescent reaction product in real time using a Cytofluor Series 4000.

The reagents were as follow: HEPES and Glycerol (Ultrapure) were obtained from GIBCO-BRL. Dimethyl Sulfoxide (DMSO) was obtained from Sigma. β-

Mercaptoethanol was obtained from Bio Rad.

Assay buffer: 50 mM HEPES, pH 7.5; 0.15 M NaCl; 0.1% Triton; 15% Glycerol; 10 mM βME. Substrate: 2 μM final concentration (from a 2 mM stock solution in DMSO stored at -20°C). HCV NS3/4A protease type 1a (1b), 2-3 nM final concentration (from a 5 μM stock solution in 25 mM HEPES, pH 7.5, 20% glycerol, 300 mM NaCl, 0.2% Triton-X100, 10 mM βME). For compounds with potencies approaching the assay limit, the assay was made more sensitive by adding 50 μg/ml Bovine Serum Albumin (Sigma) to the assay buffer and reducing the end protease concentration to 300 pM.

The assay was performed in a 96-well polystyrene black plate from Falcon. Each well contained 25 μl NS3/4A protease complex in assay buffer, 50 μl of a compound of the present disclosure in 10% DMSO/assay buffer and 25 μl substrate in assay buffer. A control (no compound) was also prepared on the same assay plate. The enzyme complex was mixed with compound or control solution for 1 min before initiating the enzymatic reaction by the addition of substrate. The assay plate was read immediately using the Cytofluor Series 4000 (Perspective Biosystems). The instrument was set to read an emission of 340 nm and excitation of 490 nm at 25 °C. Reactions were generally followed for approximately 15 minutes .

The percent inhibition was calculated with the following equation:

$$100-[(\delta F_{inh}/\delta F_{con})x100]$$

where δF is the change in fluorescence over the linear range of the curve. A non-linear curve fit was applied to the inhibition-concentration data, and the 50% effective concentration (IC_{50}) was calculated by the use of Excel XLfit software using the equation, y=A+((B-A)/(1+((C/x)^D))).

Compounds of the present disclosure, which were tested against more than one type of NS3/4A complex, were found to have similar inhibitory properties though the compounds uniformly demonstrated greater potency against the 1b strains as compared to the 1a strains.

Specificity Assays

The specificity assays were performed to demonstrate the in vitro selectivity of the compounds of the present disclosure in inhibiting HCV NS3/4A protease

complex as compared to other serine or cysteine proteases.

The specificities of compounds of the present disclosure were determined against a variety of serine proteases: human neutrophil elastase (HNE), porcine pancreatic elastase (PPE) and human pancreatic chymotrypsin and one cysteine protease: human liver cathepsin B. In all cases a 96-well plate format protocol using either colorimetric p-nitroaniline (pNA) substrate or fluorometric Amino-Methyl-Coumarin (AMC) specific for each enzyme was used as described previously (PCT Patent Application No. WO 00/09543) with some modifications to the serine protease assays. All enzymes were purchased from Sigma, EMDbiosciences while the substrates were from Bachem, Sigma and EMDbiosciences.

The pNA assay for Chymotrypsin included a 1 h enzyme-inhibitor pre-incubation at room temperature followed by addition of substrate and hydrolysis to ~15% conversion as measured on a Spectramax Pro microplate reader. Compound concentrations varied from 100 to 0.4 μM depending on their potency. Cathepsin B, HNE, and PPE assays each was initiated by addition of substrate to enzyme-inhibitor pre-incubated for 10 min at room temperature and hydrolysis to 15% conversion as measured on cytofluor.

The final conditions for each assay were as follows:

50 mM Tris(hydroxymethyl) aminomethane hydrochloride (Tris-HCl) pH 8, 0.5 M Sodium Sulfate (Na_2SO_4), 50 mM NaCl, 0.1 mM EDTA, 3% DMSO, 0.01% Tween-20 with 100 μM succ-AAPF-pNA and 250 pM Chymotrypsin.

50mM Tris-HCl, pH 8.0, 50 mM NaCl, 0.1mM EDTA, 3% DMSO, 0.02% Tween-20, 5 μM succ-AAPV-AMC and 20 nM HNE or 8 nM PPE;

100 mM NaOAC (Sodium Acetate) pH 5.5, 3% DMSO, 1 mM TCEP (Tris(2-carboxyethyl)phosphine hydrochloride), 5 nM Cathepsin B (enzyme stock activated in buffer containing 20 mM TCEP before use), and 2 μM Z-FR-AMC diluted in H_2O.

The percentage of inhibition was calculated using the formula:

$$[1-((UV_{inh}-UV_{blank})/(UV_{ctl}-UV_{blank}))] \times 100$$

A non-linear curve fit was applied to the inhibition-concentration data, and the 50% effective concentration (IC_{50}) was calculated by the use of Excel XLfit software.

Generation of HCV Replicon

An HCV replicon whole cell system was established as described by Lohmann V, Korner F, Koch J, Herian U, Theilmann L, Bartenschlager R., Science 285(5424):110-3 (1999). This system enabled us to evaluate the effects of our HCV Protease compounds on HCV RNA replication. Briefly, using the HCV strain 1b sequence described in the Lohmann paper (Assession number: AJ238799), an HCV cDNA was synthesized by Operon Technologies, Inc. (Alameda, CA), and the full-length replicon was then assembled in plasmid pGem9zf(+) (Promega, Madison, WI) using standard molecular biology techniques. The replicon consists of (i) the HCV 5' UTR fused to the first 12 amino acids of the capsid protein, (ii) the neomycin phosphotransferase gene (neo), (iii) the IRES from encephalomyocarditis virus (EMCV), and (iv) HCV NS3 to NS5B genes and the HCV 3' UTR. Plasmid DNAs were linearized with ScaI and RNA transcripts were synthesized in vitro using the T7 MegaScript transcription kit (Ambion, Austin, TX) according to manufacturer's directions. In vitro transcripts of the cDNA were transfected into the human hepatoma cell line, HUH-7. Selection for cells constitutively expressing the HCV replicon was achieved in the presence of the selectable marker, neomycin (G418). Resulting cell lines were characterized for positive and negative strand RNA production and protein production over time.

HCV Replicon FRET Assay

The HCV replicon FRET assay was developed to monitor the inhibitory effects of compounds described in the disclosure on HCV viral replication. HUH-7 cells, constitutively expressing the HCV replicon, were grown in Dulbecco's Modified Eagle Media (DMEM) (Gibco-BRL) containing 10% Fetal calf serum (FCS) (Sigma) and 1 mg/ml G418 (Gibco-BRL). Cells were seeded the night before (1.5×10^4 cells/well) in 96-well tissue-culture sterile plates. Compound and no compound controls were prepared in DMEM containing 4% FCS, 1:100

Penicillin/Streptomysin (Gibco-BRL), 1:100 L-glutamine and 5% DMSO in the dilution plate (0.5% DMSO final concentration in the assay). Compound/DMSO mixes were added to the cells and incubated for 4 days at 37 °C. After 4 days, cells were first assessed for cytotoxicity using alamar Blue (Trek Diagnotstic Systems) for a CC_{50} reading. The toxicity of compound (CC_{50}) was determined by adding $1/10^{th}$ volume of alamarBlue to the media incubating the cells. After 4 hours, the fluorescence signal from each well was read, with an excitation wavelength at 530 nm and an emission wavelength of 580 nm, using the Cytofluor Series 4000 (Perspective Biosystems). Plates were then rinsed thoroughly with Phosphate-Buffered Saline (PBS) (3 times 150 µl). The cells were lysed with 25 µl of a lysis assay reagent containing an HCV protease substrate (5X cell Luciferase cell culture lysis reagent (Promega #E153A) diluted to 1X with distilled water, NaCl added to 150 mM final, the FRET peptide substrate (as described for the enzyme assay above) diluted to 10 µM final from a 2 mM stock in 100% DMSO. The plate was then placed into the Cytofluor 4000 instrument which had been set to 340 nm excitation/490 nm emissions, automatic mode for 21 cycles and the plate read in a kinetic mode. EC_{50} determinations were carried out as described for the IC_{50} determinations.

HCV Replicon Luciferase Reporter Assay

As a secondary assay, EC_{50} determinations from the replicon FRET assay were confirmed in a replicon luciferase reporter assay. Utilization of a replicon luciferase reporter assay was first described by Krieger et al (Krieger N, Lohmann V, and Bartenschlager R, *J. Virol.* 75(10):4614-4624 (2001)). The replicon construct described for our FRET assay was modified by inserting cDNA encoding a humanized form of the Renilla luciferase gene and a linker sequence fused directly to the 3'-end of the luciferase gene. This insert was introduced into the replicon construct using an AscI restriction site located in core, directly upstream of the neomycin marker gene. The adaptive mutation at position 1179 (serine to isoleucine) was also introduced (Blight KJ, Kolykhalov, AA, Rice, CM, *Science* 290(5498):1972-1974). A stable cell line constitutively expressing this HCV replicon construct was generated as described above. The luciferase reporter assay

was set up as described for the HCV replicon FRET assay with the following modifications. Following 4 days in a 37 °C/5% CO_2 incubator, cells were analyzed for Renilla Luciferase activity using the Promega Dual-Glo Luciferase Assay System. Media (100 µl) was removed from each well containing cells. To the remaining 50 µl of media, 50 µl of Dual-Glo Luciferase Reagent was added, and plates rocked for 10 min to 2 h at room temperature. Dual-Glo Stop & Glo Reagent (50 µl) was then added to each well, and plates were rocked again for an additional 10 min to 2 h at room temperature. Plates were read on a Packard TopCount NXT using a luminescence program.

The percentage inhibition was calculated using the formula below:

$$\% \text{ control} = \frac{\text{average luciferase signal in experimental wells (+ compound)}}{\text{average luciferase signal in DMSO control wells (- compound)}}$$

The values were graphed and analyzed using XLfit to obtain the EC_{50} value.

Representative compounds of the disclosure were assessed in the HCV enzyme assays, HCV replicon cell assay and/or in several of the outlined specificity assays. For example, Compound 18 was found to have an IC_{50} of 3.4 nanomolar (nM) against the NS3/4A BMS strain in the enzyme assay. Similar potency values were obtained with the published H77 (IC_{50} of 1.2 nM) and J4L6S (IC_{50} of 0.9 nM) strains. The EC_{50} value in the replicon FRET assay was 9 nM and 1.1 nM in the replicon Luciferase assay.

In the specificity assays, the same compound was found to have the following activity: HLE > 1.56 µM; PPE > 1.56 µM; Chymotrypsin > 50 µM; Cathepsin B > 50 µM. These results indicate this family of compounds is highly specific for the NS3 protease and many of these members inhibit HCV replicon replication.

It should be understood that the compounds of the present disclosure may inhibit all genotypes of HCV.

The compounds of the current disclosure were tested and found to have activities in the ranges as follow:

IC_{50} Activity Range (NS3/4A BMS Strain): A is > 0.2 µM; B is 0.02-0.2 µM; C is

0.6-20 nM.

EC_{50} Activity Ranges (for compounds tested): A is > 1 μM; B is 0.1-1 μM; C is 3-100 nM.

Table 2

Compound Number	HCV Protease (IC50)	HCV Pro Replicon (EC50)
409 - first isomer	B	
409 - second isomer	A	
201A	4.00	4.23
201B	B	C
202A	C	C

202B	660.00	1298.00
203A	4.00	1.54
203B	B	C
204 first isomer	C	C
204 second isomer	A	A
205 first isomer	C	C
205 second isomer	A	C

206 first isomer	C	C
206 second isomer	A	A
207 first isomer	C	C
207 second isomer	A	A
208 first isomer	C	C
208 second isomer	A	
209 first isomer	C	C

209 second isomer	A	A
210 first isomer	C	C
210 second isomer	B	B
211 first isomer	C	C
211 second isomer	A	C
212 first isomer	A	B
212 second isomer	C	C

213 first isomer	A	B
213 second isomer	C	C
214 first isomer	C	B
214 second isomer	A	
215B	830.00	5494.00
215A	C	C
216 first isomer	C	C

216 second isomer	A	
217 first isomer	C	C
217 second isomer	A	
218 first isomer	C	C
218 second isomer	A	A
219 first isomer	A	A
219 second isomer	C	C

220 first isomer	C	C
220 second isomer	A	B
221 first isomer	C	B
221 second isomer	B	A
222	C	C
223 first isomer	C	B
223 second isomer	A	A

224 first isomer	C	B
224 second isomer	A	B
226 first isomer	C	C
226 second isomer	A	
227 first isomer	C	C
227 second isomer	A	A
231 first isomer	C	C

231 second isomer	A	A
232 first isomer	C	C
232 second isomer	B	C
233A	B	B
233B	1300.00	2628.00
234 first isomer	B	B

234 second isomer	A	A
235 first isomer	A	
235 second isomer	C	C
236	A	A
237	A	A
238	B	B

239	A	B
240	C	B
241	A	A
1B	289.00	1639.00
1A	C	C
2	B	B
3	C	A

4	B	A
5	B	B
6 first isomer	B	A
6 second isomer	C	B
16	C	C
17	C	C
21	C	C

35	C	C
36	73.00	1424.00
37	C	C
38A	C	C
38B	5000.00	7712.00
200A	C	C
200B	160.00	195.40

242	C	C
243	C	C
22 first isomer	C	C
22 second isomer	C	B
407 first isomer	C	B
407 second isomer	C	B
408 first isomer	C	C

408 second isomer	A	B
410	A	C
411	A	B
7	B	C
8	B	C
9	C	C
10	C	C

11	C	C
12 first isomer	C	C
12 second isomer	B	B
13 first isomer	B	C
13B	1200.00	5740.00
14 first isomer	C	C
14 second isomer	A	B

15 first isomer	C	C
15B	1900.00	3376.00
18	C	C
19 first isomer	C	C
19B	1000.00	1850.00
20 first isomer	C	C
20 second isomer	B	B

23	C	C
24A	26.00	593.20
24 second isomer	A	A
25	C	C
26 first isomer	C	C
26B	1300.00	3189.00
27A	3.00	4.09

27 second isomer	B	C
28 first isomer	C	C
28 second isomer	B	B
29A	C	B
29B	249.00	14890.00
32A	1.00	3.59
32B	A	A

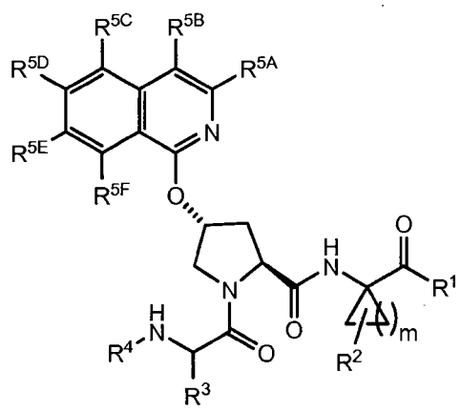
33	2.00	8.19

It will be evident to one skilled in the art that the present disclosure is not limited to the foregoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing examples, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of formula (I)



(I),

or a pharmaceutically acceptable salt thereof, wherein

m is 1, 2, or 3;

R^1 is selected from hydroxy and $-NHSO_2R^6$; wherein R^6 is selected from alkyl, aryl, cycloalkyl, (cycloalkyl)alkyl, heterocyclyl, and $-NR^aR^b$, wherein the alkyl, the cycloalkyl and the cycloalkyl part of the (cycloalkyl)alkyl are optionally substituted with one, two, or three substituents selected from alkenyl, alkoxy, alkoxyalkyl, alkyl, arylalkyl, arylcarbonyl, cyano, cycloalkenyl, (cycloalkyl)alkyl, halo, haloalkoxy, haloalkyl, and (NR^eR^f)carbonyl;

R^2 is selected from hydrogen, alkenyl, alkyl, and cycloalkyl, wherein the alkenyl, alkyl, and cycloalkyl are optionally substituted with halo;

R^3 is selected from alkenyl, alkoxyalkyl, alkoxycarbonylalkyl, alkyl, arylalkyl, carboxyalkyl, cyanoalkyl, cycloalkyl, (cycloalkyl)alkyl, haloalkoxy, haloalkyl, (heterocyclyl)alkyl, hydroxyalkyl, (NR^cR^d)alkyl, and (NR^eR^f)carbonylalkyl;

R^4 is selected from phenyl and a five- or six-membered partially or fully unsaturated ring optionally containing one, two, three, or four heteroatoms selected from nitrogen, oxygen, and sulfur; wherein each of the rings is optionally substituted with one, two, three, or four substitutents independently selected from alkoxy, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfanyl, carboxy, cyano, cycloalkyl, cycloalkyloxy, halo, haloalkyl, haloalkoxy, $-NR^cR^d$, (NR^eR^f)carbonyl,

(NR^eR^f)sulfonyl, and oxo; provided that when R^4 is a six-membered substituted ring all substituents on the ring other than fluoro must be in the meta and/or para positions relative to the ring's point of attachment to the parent molecular moiety;

R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^{5E} and R^{5F} are each independently selected from hydrogen, alkoxy, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, carboxy, cyano, cyanoalkyl, cycloalkyl, halo, haloalkyl, haloalkoxy, heterocyclyl, hydroxy, hydroxyalkyl, nitro,–NR^cR^d, (NR^cR^d)alkyl, (NR^cR^d)alkoxy, (NR^eR^f)carbonyl, and (NR^eR^f)sulfonyl; or

two adjacent R^5 groups, together with the carbon atoms to which they are attached, form a four- to seven-membered partially- or fully-unsaturated ring optionally containing one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the ring is optionally substituted with one, two, or three groups independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, and haloalkyl;

R^a and R^b are independently selected from hydrogen, alkoxy, alkyl, aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, heterocyclyl, and heterocyclylalkyl; or R^a and R^b together with the nitrogen atom to which they are attached form a four to seven-membered monocyclic heterocyclic ring;

R^c and R^d are independently selected from hydrogen, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, arylalkyl, and haloalkyl; and

R^e and R^f are independently selected from hydrogen, alkyl, aryl, arylalkyl, and heterocyclyl; wherein the aryl, the aryl part of the arylalkyl, and the heterocyclyl are optionally substituted with one or two substituents independently selected from alkoxy, alkyl, and halo.

2. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is $–NHSO_2R^6$.

3. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein

m is 1 or 2;

R^1 is $–NHSO_2R^6$; wherein R^6 is selected from alkyl, aryl, cycloalkyl, (cycloalkyl)alkyl, heterocyclyl, and $–NR^aR^b$, wherein the alkyl, the cycloalkyl and

the cycloalkyl part of the (cycloalkyl)alkyl are optionally substituted with one, two, or three substituents selected from alkenyl, alkoxy, alkoxyalkyl, alkyl, arylalkyl, arylcarbonyl, cyano, cycloalkenyl, (cycloalkyl)alkyl, halo, haloalkoxy, haloalkyl, and (NR^eR^f)carbonyl;

R^2 is selected from alkenyl, alkyl, and cycloalkyl, wherein the alkenyl, alkyl, and cycloalkyl are optionally substituted with halo;

R^3 is selected from alkenyl and alkyl;

R^4 is selected from phenyl and a five- or six-membered partially or fully unsaturated ring optionally containing one, two, three, or four heteroatoms selected from nitrogen, oxygen, and sulfur; wherein each of the rings is optionally substituted with one, two, three, or four substitutents independently selected from alkoxy, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylsulfanyl, carboxy, cyano, cycloalkyl, cycloalkyloxy, halo, haloalkyl, haloalkoxy, $-NR^cR^d$, (NR^eR^f)carbonyl, (NR^eR^f)sulfonyl, and oxo; provided that when R^4 is a six-membered substituted ring all substituents on the ring other than fluoro must be in the meta and/or para positions relative to the ring's point of attachment to the parent molecular moiety;

R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^{5E} and R^{5F} are each independently selected from hydrogen, alkoxy, alkoxycarbonyl, alkyl, alkylcarbonyl, aryl, carboxy, cyano, cyanoalkyl, cycloalkyl, halo, haloalkyl, haloalkoxy, heterocyclyl, hydroxy, hydroxyalkyl, nitro,$-NR^cR^d$, (NR^cR^d)alkyl, (NR^cR^d)alkoxy, (NR^eR^f)carbonyl, and (NR^eR^f)sulfonyl; or

two adjacent R^5 groups, together with the carbon atoms to which they are attached, form a four- to seven-membered partially- or fully-unsaturated ring optionally containing one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the ring is optionally substituted with one, two, or three groups independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, and haloalkyl;

R^a and R^b are independently selected from hydrogen, alkoxy, alkyl, aryl, arylalkyl, cycloalkyl, (cycloalkyl)alkyl, heterocyclyl, and heterocyclylalkyl; or R^a and R^b together with the nitrogen atom to which they are attached form a four- to seven-membered monocyclic heterocyclic ring;

R^c and R^d are independently selected from hydrogen, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, arylalkyl, and haloalkyl; and

R^c and R^f are independently selected from hydrogen, alkyl, aryl, arylalkyl, and heterocyclyl; wherein the aryl, the aryl part of the arylalkyl, and the heterocyclyl are optionally substituted with one or two substituents independently selected from alkoxy, alkyl, and halo.

4. A compound of claim 3, or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from unsubstituted cycloalkyl and $-NR^aR^b$.

5. A compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein

m is 1;

R^1 is $-NHSO_2R^6$; wherein R^6 is unsubstituted cycloalkyl;

R^2 is alkenyl;

R^3 is selected from alkenyl and alkyl;

R^4 is selected from phenyl and a five- or six-membered partially or fully unsaturated ring optionally containing one, two, three, or four heteroatoms selected from nitrogen, oxygen, and sulfur; wherein each of the rings is optionally substituted with one, two, or three substitutents independently selected from alkoxy, alkoxycarbonyl, alkyl, alkylcarbonyl, carboxy, cyano, cycloalkyl, cycloalkyloxy, halo, haloalkyl, haloalkoxy, $-NR^cR^d$, (NR^eR^f)carbonyl, (NR^eR^f)sulfonyl, and oxo; provided that when R^4 is a six-membered substituted ring all substituents on the ring other than fluoro must be in the meta and/or para positions relative to the ring's point of attachment to the parent molecular moiety;

R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^{5E} and R^{5F} are each independently selected from hydrogen, alkoxy, aryl, and $-NR^cR^d$; or

two adjacent R^5 groups, together with the carbon atoms to which they are attached, form a six-membered partially- or fully-unsaturated ring optionally containing one or two heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein the ring is optionally substituted with one, two, or three groups independently selected from alkoxy, alkyl, cyano, halo, haloalkoxy, and haloalkyl;

R^c and R^d are independently selected from hydrogen, alkoxycarbonyl, alkyl, alkylcarbonyl, and arylalkyl; and

R^e and R^f are independently selected from hydrogen, alkyl, aryl, and arylalkyl.

6. A compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein R^4 is phenyl optionally substituted with one, two, or three substitutents independently selected from alkoxy, alkoxycarbonyl, alkyl, alkylcarbonyl, carboxy, cyano, cycloalkyl, cycloalkyloxy, halo, haloalkyl, haloalkoxy, $-NR^cR^d$, (NR^eR^f)carbonyl, (NR^eR^f)sulfonyl, and oxo; provided that all substituents on the ring other than fluoro must be in the meta and/or para positions relative to the ring's point of attachment to the parent molecular moiety.

7. A compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein R^4 is a six-membered fully unsaturated ring containing one nitrogen atom; wherein the ring is optionally substituted with one, two, or three substitutents independently selected from alkoxy, alkoxycarbonyl, alkyl, alkylcarbonyl, carboxy, cyano, cycloalkyl, cycloalkyloxy, halo, haloalkyl, haloalkoxy, $-NR^cR^d$, (NR^eR^f)carbonyl, (NR^eR^f)sulfonyl, and oxo; provided that all substituents on the ring other than fluoro must be in the meta and/or para positions relative to the ring's point of attachment to the parent molecular moiety.

8. A compound selected from

N-(4,6-dimethyl-2-pyridinyl)-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

N-(4,6-dimethyl-2-pyridinyl)-D-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

N-(5-(trifluoromethyl)-2-pyridinyl)valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

N-(4,6-dimethoxy-1,3,5-triazin-2-yl)-3-methyl-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

N-(4,6-dimethoxy-1,3,5-triazin-2-yl)valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

N-(4,6-dimethoxy-2-pyrimidinyl)valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

N-(4,6-dimethyl-2-pyrimidinyl)-D-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

N-(4,6-dimethyl-2-pyrimidinyl)-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

N-2-pyridinylvalyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

N-(4-methoxy-2-pyridinyl)valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

N-(4-(trifluoromethyl)-2-pyridinyl)valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

N-(4-methyl-2-pyridinyl)valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

N-(4-cyano-2-pyridinyl)valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

3-methyl-N-2-pyridinyl-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

3-methyl-N-2-pyridinyl-D-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

3-methyl-N-3-pyridinyl-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

3-methyl-N-3-pyridinyl-D-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

N-(4,6-dimethyl-2-pyridinyl)-3-methyl-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

N-(4,6-dimethyl-2-pyridinyl)-3-methyl-D-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

3-methyl-N-phenyl-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

3-methyl-N-phenyl-D-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

N-(4,6-dimethyl-2-pyridinyl)valyl-(4R)-N-((1R,2S)-1-((dimethylsulfamoyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

N-(4,6-dimethyl-2-pyridinyl)valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((3-(dimethylamino)-6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

N-(4,6-dimethyl-2-pyridinyl)-3-methylvalyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((3-(dimethylamino)-6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

3-methyl-N-phenyl-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((3-(dimethylamino)-6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

3-methyl-N-phenyl-D-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((3-(dimethylamino)-6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

3-methyl-N-phenyl-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((3,6-dimethoxy-1-isoquinolinyl)oxy)-L-prolinamide;

3-methyl-N-phenyl-D-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((3,6-dimethoxy-1-isoquinolinyl)oxy)-L-prolinamide;

N-(4,6-dimethyl-2-pyridinyl)valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((3,6-dimethoxy-1-isoquinolinyl)oxy)-L-prolinamide;

N-(4,6-dimethyl-2-pyridinyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(4,6-dimethyl-2-pyridinyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

3-methyl-N-(4-methyl-5-nitro-2-pyridinyl)valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-5-pyrimidinyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-5-pyrimidinyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

3-methyl-N-(5-methyl-3-pyridinyl)valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

3-methyl-N-(6-methyl-3-pyridinyl)-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

3-methyl-N-(6-methyl-3-pyridinyl)-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

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3-methyl-N-(5-(trifluoromethyl)-3-pyridinyl)-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

3-methyl-N-(5-(trifluoromethyl)-3-pyridinyl)-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

3-methyl-N-(6-methyl-2-pyridinyl)-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

3-methyl-N-(6-methyl-2-pyridinyl)-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(2,6-dimethyl-4-pyridinyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(2,6-dimethyl-4-pyridinyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(4,6-dichloro-2-pyridinyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(4,6-dichloro-2-pyridinyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(5-chloro-3-pyridinyl)-3-methylvalyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(4-ethyl-1,3-thiazol-2-yl)-3-methyl-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

N-(5,6-dihydro-4H-1,3-thiazin-2-yl)-3-methyl-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

N-(5,6-dihydro-4H-1,3-thiazin-2-yl)-3-methyl-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-3-(4-(trifluoromethoxy)phenyl)-1-isoquinolinyl)oxy)-L-prolinamide;

3-methyl-N-(6-methyl-2-pyridinyl)-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((3-(dimethylamino)-5-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

3-methyl-N-(6-methyl-2-pyridinyl)-D-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((3-(dimethylamino)-5-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

N-(3-fluorophenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(3-fluorophenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(3-methoxyphenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(3-methoxyphenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

3-methyl-N-(3-(methylcarbamoyl)phenyl)-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

3-methyl-N-(3-(methylcarbamoyl)phenyl)-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(3-cyanophenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(3-cyanophenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(4-(tert-butoxycarbonyl)phenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(4-(tert-butoxycarbonyl)phenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(4-cyanophenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(4-cyanophenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(3-(tert-butylsulfamoyl)phenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(3-(tert-butylsulfamoyl)phenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

3-methyl-N-(3-sulfamoylphenyl)-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

3-methyl-N-(3-sulfamoylphenyl)-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(2,3-difluorophenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(2,3-difluorophenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(4-carboxyphenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(4-carboxyphenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(3-(tert-butoxycarbonyl)phenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(3-(tert-butoxycarbonyl)phenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(3-carboxyphenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(3-carboxyphenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(3-(tert-butylcarbamoyl)phenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(3-(tert-butylcarbamoyl)phenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

3-methyl-N-phenyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

3-methyl-N-phenyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(4-(tert-butylsulfamoyl)phenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(4-(tert-butylsulfamoyl)phenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

3-methyl-N-(4-sulfamoylphenyl)-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

3-methyl-N-(4-sulfamoylphenyl)-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

3-methyl-N-(3-((1-methyl-1-phenylethyl)carbamoyl)phenyl)-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

3-methyl-N-(3-((1-methyl-1-phenylethyl)carbamoyl)phenyl)-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(3-carbamoylphenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(3-carbamoylphenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(3-(dimethylcarbamoyl)phenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(3-(dimethylcarbamoyl)phenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(3-(dimethylsulfamoyl)phenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(3-(dimethylsulfamoyl)phenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(3,4-difluorophenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(3,4-difluorophenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(4-(dimethylcarbamoyl)phenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(4-(dimethylcarbamoyl)phenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

3-methyl-N-(4-((1-methyl-1-phenylethyl)carbamoyl)phenyl)-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

3-methyl-N-(4-((1-methyl-1-phenylethyl)carbamoyl)phenyl)-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(4-(ethylsulfamoyl)phenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(4-(ethylsulfamoyl)phenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(4-(dimethylsulfamoyl)phenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(4-(dimethylsulfamoyl)phenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(4-carbamoylphenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(4-carbamoylphenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

3-methyl-N-(3-(methylsulfamoyl)phenyl)-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

3-methyl-N-(3-(methylsulfamoyl)phenyl)-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(3-(isopropoxycarbonyl)phenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(3-(isopropoxycarbonyl)phenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(3-(methoxycarbonyl)phenyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(3-(methoxycarbonyl)phenyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-1-((2S)-2-((4-ethoxy-1,2,5-thiadiazol-3-yl)amino)butanoyl)-L-prolinamide;

(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-1-((2R)-2-((4-ethoxy-1,2,5-thiadiazol-3-yl)amino)butanoyl)-L-prolinamide;

N-(2-fluorophenyl)-3-methyl-D-valyl-(4R)-4-[(7-chloro-4-methoxy-1-isoquinolinyl)oxy]-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-L-prolinamide;

N-(2-fluorophenyl)-3-methyl-L-valyl-(4R)-4-[(7-chloro-4-methoxy-1-isoquinolinyl)oxy]-N-((1R,2S)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-L-prolinamide;

N-(3,4-difluorophenyl)-3-methyl-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((9-methoxy-4-methyl-3,4-dihydro-2H-[1,4]oxazino[3,2-c]isoquinolin-6-yl)oxy)-L-prolinamide;

N-(3,4-difluorophenyl)-3-methyl-D-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((9-methoxy-4-methyl-3,4-dihydro-2H-[1,4]oxazino[3,2-c]isoquinolin-6-yl)oxy)-L-prolinamide;

N-(6-methoxy-3-pyridinyl)-3-methyl-L-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

N-(6-methoxy-3-pyridinyl)-3-methyl-D-valyl-(4R)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-4-((6-methoxy-1-isoquinolinyl)oxy)-L-prolinamide;

N-(6-methoxy-3-pyridinyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(6-methoxy-3-pyridinyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

N-(6-(difluoromethoxy)-3-pyridinyl)-3-methyl-L-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide; and

N-(6-(difluoromethoxy)-3-pyridinyl)-3-methyl-D-valyl-(4R)-4-((7-chloro-4-methoxy-1-isoquinolinyl)oxy)-N-((1R,2S)-1-((cyclopropylsulfonyl)carbamoyl)-2-vinylcyclopropyl)-L-prolinamide;

or a pharmaceutically acceptable salt thereof.

9. A composition comprising the compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

10. The composition of claim 9 further comprising at least one additional compound having anti-HCV activity.

11. The composition of claim 10 wherein at least one of the additional compounds is an interferon or a ribavirin.

12. The composition of claim 11 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

13. The composition of claim 10 wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

14. The composition of claim 10 wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

15. A method of treating an HCV infection in a patient, comprising administering to the patient a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof.

16. The method of claim 15 further comprising administering at least one additional compounds having anti-HCV activity prior to, after, or simultaneously with the compound of claim 1, or a pharmaceutically acceptable salt thereof.

17. The method of claim 16 wherein at least one of the additional compounds is an interferon or a ribavirin.

18. The method of claim 17 wherein the interferon is selected from interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, and lymphoblastiod interferon tau.

19. The method of claim 16 wherein at least one of the additional compounds is selected from interleukin 2, interleukin 6, interleukin 12, a compound that enhances

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the development of a type 1 helper T cell response, interfering RNA, anti-sense RNA, Imiqimod, ribavirin, an inosine 5'-monophospate dehydrogenase inhibitor, amantadine, and rimantadine.

20. The method of claim 16 wherein at least one of the additional compounds is effective to inhibit the function of a target selected from HCV metalloprotease, HCV serine protease, HCV polymerase, HCV helicase, HCV NS4B protein, HCV entry, HCV assembly, HCV egress, HCV NS5A protein, and IMPDH for the treatment of an HCV infection.

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INHIBIDORES DEL VIRUS DE LA HEPATITIS C

REFERENCIA CRUZADA A SOLICITUDES RELACIONADAS

Esta solicitud reivindica el beneficio de la Solicitud Provisional E.U.A. No. de Serie 60/865,034 presentada el 9 de noviembre de 2006.

La presente invención se dirige generalmente a compuestos antivirales, y se dirige más específicamente a compuestos que inhiben la función de la proteasa NS3 (también referida en la presente como "serina proteasa") codificada por el virus de la hepatitis C (VHC), composiciones que comprenden tales compuestos y métodos para inhibir la función de la proteasa NS3.

El VHC es un patógeno humano principal, que infecta un estimado de 170 millones de personas en el mundo, aproximadamente cinco veces el número infectado por el virus de la inmunodeficiencia humana de tipo 1. Una fracción substancial de estos individuos infectados con VHC desarrollan una enfermedad progresiva del hígado seria, incluyendo cirrosis y carcinoma hepatocelular.

Actualmente, la terapia más efectiva del VHC emplea una combinación del alfa interferón y ribavirina, conduciendo a una eficacia sostenida en 40% de los pacientes. Los resultados clínicos recientes demuestran que el alfa interferón pegilado es superior al alfa interferón sin modificar como monoterapia. Sin embargo,

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aún con los regímenes terapéuticos experimentales que involucran combinaciones del alfa interferón pegilado y la ribavirina, una fracción substancial de los pacientes no tiene una reducción sostenida en la carga viral. Así, hay una necesidad clara y no cubierta para desarrollar terapéuticos efectivos para el tratamiento de la infección por VHC.

El VHC es un virus del ARN de hebra positiva. Con base en la comparación de la secuencia deducida de aminoácidos y la amplia similitud en la región 5' sin traducir, el VHC se ha clasificado como un género separado en la familia Flaviviridae. Todos los miembros de la familia Flaviviridae tienen viriones envueltos que contienen un genoma de ARN de hebra positiva que codifica todas las proteínas conocidas específicas del virus, por medio de la traducción de una estructura de lectura abierta sencilla, sin interrumpir.

Se encuentra una heterogeneidad considerable dentro del nucleótido y de la secuencia codificada de aminoácidos a través del genoma de VHC. Se han caracterizado seis principales genotipos, y se han descrito más de 50 subtipos. Los principales genotipos del VHC difieren en su distribución a nivel mundial, y la importancia clínica en la heterogeneidad genética del VHC permanece elusiva a pesar de diversos estudios sobre el efecto posible de los genotipos en

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la patogénesis y la terapia.

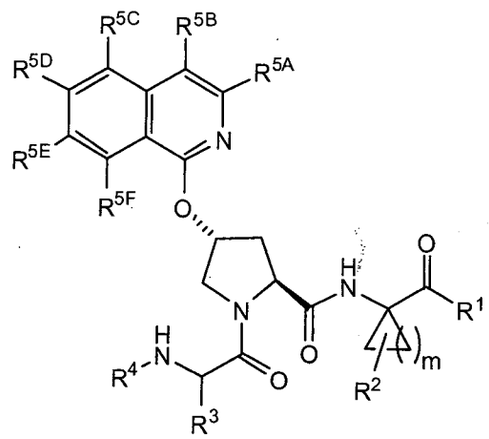
El genoma del ARN del VHC de hebra sencilla, es de aproximadamente 9500 nucleótidos de longitud y tiene una estructura sencilla de lectura abierta (ORF) que codifica una poliproteína grande sencilla de alrededor de 3000 aminoácidos. En las células infectadas, esta poliproteína se desdobla en sitios múltiples por proteasas celulares y virales, para producir las proteínas estructurales y no estructurales (NS). En el caso del VHC, la generación de proteínas maduras no estructurales (NS2, NS3, NS4A, NS4B, NS5A, y NS5B) se efectúa por dos proteasas virales. La primera, se desdobla en la unión NS2-NS3; la segunda es una serina proteasa contenida dentro de la región terminal N del NS3 y media todos los desdoblamientos posteriores en la dirección descendente del NS3, tanto en el sitio cis, en el sitio de desdoblamiento NS3-NS4A, y en trans, para el resto de los sitios NS4A-NS4B, NS4B-NS5A, NS5A-NS5B. La proteína NS4A parece servir a funciones múltiples, actuando como un co-factor para la proteasa NS3 y ayudando posiblemente en la localización de membrana de NS3 y de otros componentes virales de la replicasa. La formación compleja de la proteína NS3 con el NS4A es esencial para el procesamiento de poliproteína eficiente, mejorando el desdoblamiento proteolítico en todos los sitios. La proteína NS3 también muestra una nucleósido trifosfatasa y

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actividades del ARN helicasa. La NS5B es una polimerasa de ARN dependiente del ARN que se involucra en la replicación del VHC.

La presente descripción proporciona compuestos de péptido que pueden inhibir el funcionamiento de la proteasa NS3, por ejemplo, en combinación con la proteasa NS4A. Además, la presente descripción describe la administración de terapia de combinación a un paciente, por ello un compuesto de conformidad con la presente descripción, que es efectivo para inhibir la VHC NS3 proteasa, puede administrarse con uno o dos compuestos adicionales que tienen actividad anti-VHC.

En un primer aspecto la presente descripción proporciona un compuesto de la fórmula (I)



(I)

o una sal farmacéuticamente aceptable del mismo, en donde

m es 1, 2, ó 3;

R^1 se selecciona de hidroxi y $-NHSO_2R^6$; en donde R^6 se selecciona de alquilo, arilo, cicloalquilo, (cicloalquil)alquilo, heterociclilo, y $-NR^aR^b$, en donde el

alquilo, cicloalquilo y la parte cicloalquilo del (cicloalquil)alquilo están opcionalmente substituidos con uno, dos, o tres substituyentes seleccionados de alquenilo, alcoxi, alcoxialquilo, alquilo, arilalquilo, arilcarbonilo, ciano, cicloalquenilo, (cicloalquil)alquilo, halo, haloalcoxi, haloalquilo, y (NR^eR^f)carbonilo;

R^2 se selecciona de hidrógeno, alquenilo, alquilo, y cicloalquilo, en donde el alquenilo, alquilo, y cicloalquilo están opcionalmente substituidos con halo;

R^3 se selecciona de alquenilo, alcoxialquilo, alcoxicarbonilalquilo, alquilo, arilalquilo, carboxialquilo, cianoalquilo, cicloalquilo, (cicloalquil)alquilo, haloalcoxi, haloalquilo, (heterociclil)alquilo, hidroxialquilo, (NR^cR^d)alquilo, y (NR^eR^f)carbonilalquilo;

R^4 se selecciona de fenilo y un anillo parcialmente o completamente insaturado de cinco o seis miembros que contiene opcionalmente uno, dos, tres, o cuatro heteroátomos seleccionados de nitrógeno, oxígeno, y azufre; en donde cada uno de los anillos es opcionalmente substituido con uno, dos, tres, o cuatro substituyentes independientemente seleccionados de alcoxi, alcoxicarbonilo, alquilo, alquilcarbonilo, alquilsulfanilo, carboxi, ciano, cicloalquilo, cicloalquiloxi, halo, haloalquilo, haloalcoxi, $-NR^cR^d$, (NR^eR^f)carbonilo, (NR^eR^f)sulfonilo, y oxo; con la condición de que cuando R^4 es un anillo substituido de seis

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miembros todos los substituyentes en el anillo diferentes a fluoro deberán estar en las posiciones meta y/o para con relación al punto de enlace del anillo a la porción de molécula precursora;

R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^{5E} y R^{5F} son cada uno independientemente seleccionados de hidrógeno, alcoxi, alcoxicarbonilo, alquilo, alquilcarbonilo, arilo, carboxi, ciano, cianoalquilo, cicloalquilo, halo, haloalquilo, haloalcoxi, heterociclilo, hidroxi, hidroxialquilo, nitro, $-NR^cR^d$, (NR^cR^d)alquilo, (NR^cR^d)alcoxi, (NR^eR^f)carbonilo, y (NR^eR^f)sulfonilo; o

dos grupos R^5 adyacentes, junto con los átomos de carbono a los cuales son enlazados, forman un anillo parcialmente o completamente insaturado de cuatro a siete miembros que contiene opcionalmente uno o dos heteroátomos independientemente seleccionados de nitrógeno, oxígeno, y azufre, en donde el anillo está opcionalmente substituido con uno, dos, o tres grupos independientemente seleccionados de alcoxi, alquilo, ciano, halo, haloalcoxi, y haloalquilo;

R^a y R^b son independientemente seleccionados de hidrógeno, alcoxi, alquilo, arilo, arilalquilo, cicloalquilo, (cicloalquil)alquilo, heterociclilo, y heterociclilalquilo; o R^a y R^b junto con el átomo de nitrógeno al cual son enlazados forman un anillo monocíclico heterocíclico de cuatro a siete miembros;

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R^c y R^d son independientemente seleccionados de hidrógeno, alcoxialquilo, alcoxicarbonilo, alquilo, alquilcarbonilo, arilalquilo, y haloalquilo; y

R^e y R^f son independientemente seleccionados de hidrógeno, alquilo, arilo, arilalquilo, y heterociclilo; en donde el arilo, la parte arilo del arilalquilo, y el heterociclilo están opcionalmente substituidos con uno o dos substituyentes independientemente seleccionados de alcoxi, alquilo, y halo.

En una primera modalidad del primer aspecto de la presente descripción se proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable de los mismos, en donde R^1 es $-NHSO_2R^6$.

En una segunda modalidad del primer aspecto de la presente descripción se proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde

m es 1 ó 2;

R^1 es $-NHSO_2R^6$; en donde R^6 se selecciona de alquilo, arilo, cicloalquilo, (cicloalquil)alquilo, heterociclilo, y $-NR^aR^b$, en donde la parte alquilo, cicloalquilo y cicloalquilo del (cicloalquil)alquilo están opcionalmente substituidos con uno, dos, o tres substituyentes seleccionados de alquenilo, alcoxi, alcoxialquilo, alquilo, arilalquilo, arilcarbonilo, ciano, cicloalquenilo, (cicloalquil)alquilo, halo,

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haloalcoxi, haloalquilo, y (NR^eR^f)carbonilo;

R^2 se selecciona de alquenilo, alquilo, y cicloalquilo, en donde el alquenilo, alquilo, y cicloalquilo están opcionalmente substituidos con halo;

R^3 se selecciona de alquenilo y alquilo;

R^4 se selecciona de fenilo y un anillo parcialmente o completamente insaturado de cinco o seis miembros que contiene opcionalmente uno, dos, tres, o cuatro heteroátomos seleccionados de nitrógeno, oxígeno, y azufre; en donde cada uno de los anillos está opcionalmente substituido con uno, dos, tres, o cuatro substituyentes independientemente seleccionados de alcoxi, alcoxicarbonilo, alquilo, alquilcarbonilo, alquilsulfanilo, carboxi, ciano, cicloalquilo, cicloalquiloxi, halo, haloalquilo, haloalcoxi, $-NR^cR^d$, (NR^eR^f)carbonilo, (NR^eR^f)sulfonilo, y oxo; con la condición de que cuando R^4 es un anillo de seis miembros substituido todos los substituyentes en el anillo diferentes a fluoro deberán estar en las posiciones meta y/o para con relación al punto de enlace del anillo a la porción de molécula precursora;

R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^{5E} y R^{5F} son cada uno independientemente seleccionados de hidrógeno, alcoxi, alcoxicarbonilo, alquilo, alquilcarbonilo, arilo, carboxi, ciano, cianoalquilo, cicloalquilo, halo, haloalquilo,

haloalcoxi, heterociclilo, hidroxi, hidroxialquilo, nitro, $-NR^cR^d$, (NR^cR^d)alquilo, (NR^cR^d)alcoxi, (NR^eR^f)carbonilo, y (NR^eR^f)sulfonilo; o

dos grupos R^5 adyacentes, junto con los átomos de carbono a los cuales son enlazados, forman un anillo parcialmente o completamente insaturado de cuatro a siete miembros que contiene opcionalmente uno o dos heteroátomos independientemente seleccionados de nitrógeno, oxígeno, y azufre, en donde el anillo está opcionalmente substituido con uno, dos, o tres grupos independientemente seleccionados de alcoxi, alquilo, ciano, halo, haloalcoxi, y haloalquilo;

R^a y R^b son independientemente seleccionados de hidrógeno, alcoxi, alquilo, arilo, arilalquilo, cicloalquilo, (cicloalquil)alquilo, heterociclilo, y heterociclilalquilo; o R^a y R^b junto con el átomo de nitrógeno al cual son enlazados forman un anillo monocíclico heterocíclico de cuatro a siete miembros;

R^c y R^d son independientemente seleccionados de hidrógeno, alcoxialquilo, alcoxicarbonilo, alquilo, alquilcarbonilo, arilalquilo, y haloalquilo; y

R^e y R^f son independientemente seleccionados de hidrógeno, alquilo, arilo, arilalquilo, y heterociclilo; en donde el arilo, la parte arilo del arilalquilo, y el heterociclilo están opcionalmente substituidos con uno o dos

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substituyentes independientemente seleccionados de alcoxi, alquilo, y halo.

En una tercera modalidad del primer aspecto, la presente descripción proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde R^6 se selecciona de cicloalquilo no sustituido y $-NR^aR^b$.

En un cuarta modalidad del primer aspecto, la presente descripción proporciona un compuesto de la formula (I), o una sal farmacéuticamente aceptable del mismo,

en donde

m es 1;

R^1 es $-NHSO_2R^6$; en donde R^6 es cicloalquilo no sustituido;

R^2 es alquenilo;

R^3 se selecciona de alquenilo y alquilo;

R^4 se selecciona de fenilo y un anillo parcialmente o completamente insaturado de cinco o seis miembros que contiene opcionalmente uno, dos, tres, o cuatro heteroátomos seleccionados de nitrógeno, oxígeno, y azufre; en donde cada uno de los anillos está opcionalmente substituido con uno, dos, o tres substituyentes independientemente seleccionados de alcoxi, alcoxicarbonilo, alquilo, alquilcarbonilo, carboxi, ciano, cicloalquilo, cicloalquiloxi, halo, haloalquilo, haloalcoxi, $-NR^cR^d$, (NR^eR^f)carbonilo, (NR^eR^f)sulfonilo, y oxo; con la condición de que cuando R^4 es

un anillo substituido de seis miembros, todos los substituyentes en el anillo diferentes a fluoro deberán estar en las posiciones meta y/o para con relación al punto de enlace del anillo a la porción de molécula precursora;

R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^{5E} y R^{5F} son cada uno independientemente seleccionados de hidrógeno, alcoxi, arilo, y $-NR^cR^d$; o

dos grupos R^5 adyacentes, junto con los átomos de carbono a los cuales son enlazados, forman un anillo parcialmente o completamente insaturado de seis miembros que contiene opcionalmente uno o dos heteroátomos independientemente seleccionado de nitrógeno, oxígeno, y azufre, en donde el anillo está opcionalmente substituido con uno, dos, o tres grupos independientemente seleccionados de alcoxi, alquilo, ciano, halo, haloalcoxi, y haloalquilo;

R^c y R^d son independientemente seleccionados de hidrógeno, alcoxicarbonilo, alquilo, alquilcarbonilo, y arilalquilo; y

R^e y R^f son independientemente seleccionados de hidrógeno, alquilo, arilo, y arilalquilo.

En una quinta modalidad del primer aspecto, la presente descripción proporciona un compuesto de formula (I), o una sal farmacéuticamente aceptable del mismo,

en donde

m es 1;

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R^1 es $-NHSO_2R^6$; en donde R^6 es cicloalquilo no sustituido;

R^2 es alquenilo;

R^3 se selecciona de alquenilo y alquilo;

R^4 es fenilo opcionalmente substituidos con uno, dos, o tres substituyentes independientemente seleccionados de alcoxi, alcoxicarbonilo, alquilo, alquilcarbonilo, carboxi, ciano, cicloalquilo, cicloalquiloxi, halo, haloalquilo, haloalcoxi, $-NR^cR^d$, (NR^eR^f)carbonilo, (NR^eR^f)sulfonilo, y oxo; con la condición de que todos los substituyentes en el anillo diferentes de fluoro deberán estar en las posiciones meta y/o para con relación al punto de enlace del anillo a la porción de molécula precursora;

R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^{5E} y R^{5F} son cada uno independientemente seleccionados de hidrógeno, alcoxi, arilo, y $-NR^cR^d$; o

dos grupos R^5 adyacentes, junto con los átomos de carbono a los cuales son enlazados, forman un anillo parcialmente o completamente insaturado de seis miembros que contiene opcionalmente uno o dos heteroátomos independientemente seleccionados de nitrógeno, oxígeno, y azufre, en donde el anillo está opcionalmente substituido con uno, dos, o tres grupos independientemente seleccionados de alcoxi, alquilo, ciano, halo, haloalcoxi, y haloalquilo;

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R^c y R^d son independientemente seleccionados de hidrógeno, alcoxicarbonilo, alquilo, alquilcarbonilo, y arilalquilo; y

R^e y R^f son independientemente seleccionados de hidrógeno, alquilo, arilo, y arilalquilo.

En una sexta modalidad del primer aspecto, la presente descripción proporciona un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo,

en donde

m es 1;

R^1 es $-NHSO_2R^6$; en donde R^6 es cicloalquilo no sustituido;

R^2 es alquenilo;

R^3 se selecciona de alquenilo y alquilo;

R^4 es un anillo de seis miembros completamente insaturado que contiene un átomo de nitrógeno; en donde el anillo está opcionalmente substituido con uno, dos, o tres substituyentes independientemente seleccionados de alcoxi, alcoxicarbonilo, alquilo, alquilcarbonilo, carboxi, ciano, cicloalquilo, cicloalquiloxi, halo, haloalquilo, haloalcoxi, $-NR^cR^d$, (NR^eR^f)carbonilo, (NR^eR^f)sulfonilo, y oxo; con la condición de que todos los substituyentes en el anillo diferentes a un fluoro deberán estar en las posiciones meta y/o para con relación al punto de enlace del anillo a la porción de molécula precursora;

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R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^{5E} y R^{5F} son cada uno independientemente seleccionados de hidrógeno, alcoxi, arilo, y $-NR^cR^d$; o

dos grupos R^5 adyacentes, junto con los átomos de carbono a los cuales son enlazados, forman un anillo parcialmente o completamente insaturado de seis miembros que contiene opcionalmente uno o dos heteroátomos independientemente seleccionado de nitrógeno, oxígeno, y azufre, en donde el anillo está opcionalmente substituido con uno, dos, o tres grupos independientemente seleccionados de alcoxi, alquilo, ciano, halo, haloalcoxi, y haloalquilo;

R^c y R^d son independientemente seleccionados de hidrógeno, alcoxicarbonilo, alquilo, alquilcarbonilo, y arilalquilo; y

R^e y R^f son independientemente seleccionados de hidrógeno, alquilo, arilo, y arilalquilo.

En un segundo aspecto la presente descripción proporciona una composición que comprende un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, y un portador farmacéuticamente aceptable. En una primera modalidad del segundo aspecto, la composición comprende además al menos un compuesto adicional que tiene actividad anti-VHC. En una segunda modalidad del segundo aspecto al menos uno de los compuestos adicionales es un interferón o una ribavirina. En una tercera modalidad del segundo aspecto,

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el interferón se selecciona de interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A, e interferón tau linfoblastoide.

En una cuarta modalidad del segundo aspecto la presente descripción proporciona una composición que comprende el compuesto de la fórmula (I), o una sal farmacéuticamente aceptable de la misma, un portador farmacéuticamente aceptable, y al menos un compuesto adicional que tiene actividad anti-VHC; en donde al menos uno de los compuestos adicionales se selecciona de interleucina 2, interleucina 6, interleucina 12, un compuesto que aumenta el desarrollo de una respuesta de célula T auxiliar tipo 1, ARN de interferencia, ARN antisentido, Imiqimod, ribavirina, un inhibidor de 5'-monofosfato deshidrogenasa inosina, amantadina, y rimantadina.

En una quinta modalidad del segundo aspecto la presente descripción proporciona una composición que comprende un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable de la misma, un portador farmacéuticamente aceptable, y al menos un compuesto adicional que tiene actividad anti-VHC; en donde al menos uno de los compuestos adicionales es efectivo para inhibir la función de un objetivo seleccionado de metaloproteasa de VHC, serina proteasa de VHC, polimerasa de VHC, helicasa de VHC, proteína NS4B de VHC, entrada de VHC, ensamble de VHC, salida de VHC, proteína

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NS5A de VHC, e IMPDH para el tratamiento de una infección por VHC.

En un tercer aspecto, la presente descripción proporciona un método de tratamiento de una infección por VHC en un paciente, que comprende administrar al paciente una cantidad terapéuticamente efectiva de un compuesto de la Fórmula (I), o una sal farmacéuticamente aceptable del mismo. En una primera modalidad del tercer aspecto el método comprende además administrar al menos un compuesto adicional que tiene actividad anti-VHC antes de, después o simultáneamente con el compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo. En una segunda modalidad del tercer aspecto al menos uno de los compuestos adicionales es un interferón o una ribavirina. En una cuarta modalidad del tercer aspecto el interferón se selecciona de interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A, y interferón tau linfoblastoide.

En una quinta modalidad del tercer aspecto, la presente descripción proporciona un método para tratar una infección por VHC en un paciente, que comprende administrar al paciente una cantidad terapéuticamente efectiva de un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, y al menos un compuesto adicional que tiene actividad anti-VHC antes de, después o simultáneamente con el compuesto de

la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde al menos uno de los compuestos adicionales se selecciona de interleucina 2, interleucina 6, interleucina 12, un compuesto que mejora el desarrollo de una respuesta de célula T auxiliar tipo 1, ARN de interferencia, ARN antisentido, Imiqimod, ribavirina, un inhibidor de 5'-monofosfato deshidrogenasa inosina, amantadina, y rimantadina.

En una sexta modalidad del tercer aspecto, la presente descripción proporciona un método para tratar una infección por VHC en un paciente, que comprende administrar al paciente una cantidad terapéuticamente efectiva del compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, y al menos un compuesto adicional que tiene actividad anti-VHC antes de, después o simultáneamente con el compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, en donde al menos uno de los compuestos adicionales es efectivo para inhibir la función de un objetivo seleccionado de metaloproteasa de VHC, serina proteasa de VHC, polimerasa de VHC, helicasa de VHC, proteína NS4B de VHC, entrada de VHC, ensamble de VHC, salida de VHC, proteína NS5A de VHC, e IMPDH para el tratamiento de una infección por VHC.

En un cuarto aspecto la presente descripción proporciona una composición que comprende un compuesto de la fórmula (I),

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o una sal farmacéuticamente aceptable del mismo, uno, dos, tres, cuatro, o cinco compuestos adicionales que tienen actividad anti-VHC, y un portador farmacéuticamente aceptable. En una primera modalidad del cuatro aspecto, la composición comprende tres o cuatro compuestos adicionales que tienen actividad anti-VHC. En una segunda modalidad del cuarto aspecto, la composición comprende uno o dos compuestos adicionales que tienen actividad anti-VHC.

En un quinto aspecto, la presente descripción proporciona un método para tratar una infección por VHC en un paciente, que comprende administrar al paciente una cantidad terapéuticamente efectiva de un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo y uno, dos, tres, cuatro, o cinco compuestos adicionales que tienen actividad anti-VHC antes de, después, o simultáneamente con el compuesto de la fórmula (I), o una sal farmacéuticamente aceptable de los mismos. En una primera modalidad del primer aspecto, el método comprende administres tres o cuatro compuestos adicionales que tienen actividad anti-VHC. En una segunda modalidad del primer aspecto, el método comprende administrar uno o dos compuestos adicionales que tienen actividad anti-VHC.

Otros aspectos de la presente descripción pueden incluir combinaciones apropiadas de las modalidades descritas en la presente.

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Aún otras modalidades y aspectos pueden encontrarse en la descripción proporcionada en la presente.

La descripción de la presente descripción aquí deberá construirse en congruencia con las leyes y principios del enlace químico. En algunos casos, puede ser necesario remover un átomo de hidrógeno con objeto de acomodar un substituyente en cualquier ubicación dada.

Se deberá entender que los compuestos abarcados por la presente descripción son aquellos que son adecuadamente estables para uso como agente farmacéutico.

Se pretende que la definición de cualquier substituyente o variable en una ubicación particular en una molécula, sea independiente de sus definiciones en cualquier otro lugar de la molécula. Por ejemplo, cuando n es 2, cada uno de los dos grupos R^5 puede ser el mismo o diferente.

Todas las patentes, solicitudes de patente y referencia de literatura citadas en la especificación se incorporan en la presente para referencia en su totalidad. En el caso de inconsistencias, la presente descripción, incluyendo definiciones, es la que prevalecerá.

Como se usa en la presente especificación, los siguientes términos tienen los significados indicados:

Como se usa en la presente, las formas singulares "un", "uno" y "el" incluye la referencia plural a menos que el contexto claramente dicte lo contrario.

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A menos que se establezca de otra manera, todos los grupos arilo, cicloalquilo y heterociclilo de la presente descripción pueden substituirse como se describe en cada una de sus definiciones respectivas. Por ejemplo, la parte arilo de un grupo arilalquilo puede substituirse como se describe en la definición del término 'arilo'.

En algunos casos, el número de átomos de carbono en cualquier grupo particular se denota antes de recitar el grupo. Por ejemplo, el término "alquilo C_{1-2}" significa un grupo alquilo que contiene uno o dos átomos de carbono. Donde estas designaciones existen, pueden sustituir todas las otras definiciones contenidas en la presente.

Como se usa en la presente, las formas singulares "un", "uno" y "el" incluyen la referencia plural a menos que el contexto claramente dicte lo contrario.

El término "alquenilo", como se usa en la presente, se refiere a un grupo de cadena recta o ramificada de dos hasta seis átomos de carbono que contiene al menos un enlace doble carbono-carbono.

El término "alcoxi", como se usa en la presente, se refiere a un grupo alquilo enlazado a la porción molecular precursora a través de un átomo de oxígeno.

El término "alcoxialquilo", como se usa en la presente, se refiere a un grupo alquilo substituido con uno, dos o tres grupos alcoxi.

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El término "alcoxicarbonilo" como se usa en la presente, se refiere a un grupo alcoxi enlazado a la porción de molécula precursora a través de un grupo carbonilo.

El término "alcoxicarbonilalquilo", como se usa en la presente, se refiere a un grupo alquilo substituido con uno, dos, o tres grupos alcoxicarbonilo.

El término "alquilo", como se usa en la presente, se refiere a un grupo derivado de un hidrocarburo saturado de cadena recta o ramificada que contiene desde uno hasta diez átomos de carbono.

El término "alquilcarbonilo" como se usa en la presente, se refiere a un grupo alquilo enlazado a la porción molecular precursora a través de un grupo carbonilo.

El término "alquilsulfanilo", como se usa en la presente, se refiere a un grupo alquilo enlazado a la porción molecular precursora a través de un átomo de azufre.

El término "arilo", como se usa en la presente, se refiere a un grupo fenilo, o un sistema de anillo fusionado bicíclico en donde uno o más de los anillos es un grupo fenilo. Los sistemas de anillo fusionado bicíclico consisten de un grupo fenilo fusionado a un anillo carbocíclico de cuatro hasta seis miembros aromático o no aromático. Los grupos arilo de la presente invención pueden enlazarse a la porción molecular precursora a través de cualquier átomo de carbono

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sustituible en el grupo. Los ejemplos representativos de grupos arilo incluyen, pero no se limitan a, indanilo, indenilo, naftilo, fenilo, y tetrahidronaftilo. Los grupos arilo de la presente descripción son opcionalmente substituidos con uno, dos, tres, cuatro o cinco substituyentes independientemente seleccionados de alcoxi, alcoxicarbonilo, alquilo, alquilcarbonilo, carboxi, cicloalquilo, cicloalquiloxi, ciano, halo, haloalcoxi, haloalquilo, nitro, $-NR^cR^d$, (NR^cR^d)carbonilo, y oxo.

El término "arilalquilo", como se usa en la presente, se refiere a un grupo alquilo substituido con uno, dos, o tres grupos arilo.

El término "arilcarbonilo", como se usa en la presente, se refiere a un grupo arilo enlazado a la porción molecular precursora a través de un grupo carbonilo.

El término "carbonilo", como se usa en la presente, se refiere a -C(O)-.

El término "carboxi", como se usa en la presente, se refiere a $-CO_2H$.

El término "carboxialquilo", como se usa en la presente, se refiere a un grupo alquilo substituido con uno, dos, o tres grupos carboxi.

El término "ciano", como se usa en la presente, se refiere a -CN.

El término "cianoalquilo", como se usa en la presente,

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se refiere a un grupo alquilo substituido con uno, dos, o tres grupos ciano.

El término "cicloalquenilo", como se usa en la presente, se refiere a un sistema de anillo monocíclico, bicíclico, o tricíclico no aromático, parcialmente insaturado, que tiene tres hasta catorce átomos de carbono y cero heteroátomos. Los ejemplos representativos de grupos cicloalquenilo incluyen, pero no se limitan a, ciclohexenilo, octahidronaftalenilo, y norbornilenilo.

El término "cicloalquilo", como se usa en la presente, se refiere a un sistema de anillo hidrocarburo monocíclico o bicíclico saturado que tiene tres hasta diez átomos de carbono y cero heteroátomos. Los ejemplos representativos de grupos cicloalquilo incluyen, pero no se limitan a, ciclopropilo, ciclobutilo, y ciclopentilo.

El término "(cicloalquil)alquilo", como se usa en la presente, se refiere a un grupo alquilo substituido con uno, dos, o tres grupos cicloalquilo.

El término "cicloalquiloxi", como se usa en la presente, se refiere a un grupo cicloalquilo enlazado a la porción molecular precursora a través de un átomo de oxígeno.

Los términos "halo" y "halógeno," como se usan en la presente, se refieren a F, Cl, Br, e I.

El término "haloalcoxi", como se usa en la presente, se

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refiere a un grupo haloalquilo enlazado a la porción molecular precursora a través de un átomo de oxígeno.

El término "haloalquilo", como se usa en la presente, se refiere a un grupo alquilo substituido por uno, dos, tres o cuatro átomos de halógeno.

El término "heterociclilo", como se usa en la presente, se refiere a un anillo de cinco, seis o siete miembros que contiene uno, dos, tres o cuatro heteroátomos independientemente seleccionados de nitrógeno, oxígeno y azufre. El anillo de cinco miembros tiene cero hasta dos enlaces dobles, y los anillos de seis y siete miembros tiene cero hasta tres enlaces dobles. El término "heterociclilo" también incluye grupos bicíclicos en los cuales el anillo heterociclilo se fusiona a otro grupo heterociclilo monocíclico, o un anillo carbocíclico aromático o no aromático de cuatro hasta seis miembros. Los grupos heterociclilo de la presente descripción pueden enlazarse a la porción molecular precursora a través de un átomo de carbono o átomo de nitrógeno en el grupo. Los ejemplos de grupos heterociclilo incluyen, pero no se limitan a, benzotienilo, furilo, imidazolilo, indolinilo, indolilo, isotiazolilo, isoxazolilo, morfolinilo, oxazolilo, piperazinilo, piperidinilo, pirazolilo, piridinilo, pirrolidinilo, pirrolopiridinilo, pirrolilo, tiazolilo, tienilo, y tiomorfolinilo. Los grupos

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heterociclilo de la presente descripción son opcionalmente substituidos con uno, dos, tres, cuatro, o cinco substituyentes independientemente seleccionados de alcoxi, alcoxicarbonilo, alquilo, alquilcarbonilo, carboxi, cicloalquilo, cicloalquiloxi, ciano, halo, haloalcoxi, haloalquilo, nitro, $-NR^cR^d$, (NR^cR^d)carbonilo, y oxo.

El término "heterociclilalquilo", como se usa en la presente, se refiere a un grupo alquilo substituido con uno, dos, o tres grupos heterociclilo.

El término "hidroxi", como se usa en la presente, se refiere a -OH.

El término "hidroxialquilo," como se usa en la presente, se refiere a un grupo alquilo substituido con uno, dos o tres grupos hidroxi.

El término "nitro," como se usa en la presente, se refiere a $-NO_2$.

El término "$-NR^aR^b$", como se usa en la presente, se refiere a dos grupos, R^a y R^b, los cuales se enlazan a la porción molecular precursora a través de un átomo de nitrógeno. R^a y R^b son independientemente seleccionados de hidrógeno, alcoxi, alquilo, arilo, arilalquilo, cicloalquilo, (cicloalquil)alquilo, heterociclilo, y heterociclilalquilo; o R^a y R^b junto con el átomo de nitrógeno al cual se enlazan forman un anillo heterocíclico monocíclico de cinco o seis miembros.

El término "-NR^cR^d", como se usa en la presente, se refiere a dos grupos, R^c y R^d, los cuales se enlazan a la porción molecular precursora a través de un átomo de nitrógeno. R^c y R^d son independientemente seleccionados de hidrógeno, alcoxicarbonilo, alquilo, y alquilcarbonilo.

El término "(NR^cR^d)alcoxi", como se usa en la presente, se refiere a un grupo (NR^cR^d)alquilo enlazado a la porción molecular precursora a través de un átomo de oxígeno.

El término "(NR^cR^d)alquilo", como se usa en la presente, se refiere a un grupo alquilo substituido con uno, dos o tres grupos -NR^cR^d.

El término "(NR^cR^d)carbonilo", como se usa en la presente, se refiere a un grupo -NR^cR^d enlazado a la porción molecular precursora a través de un grupo carbonilo.

El término "-NR^eR^f", como se usa en la presente, se refiere a dos grupos, R^e y R^f, los cuales se enlazan a la porción molecular precursora a través de un átomo de nitrógeno. R^e y R^f son independientemente seleccionados de hidrógeno, alquilo, arilo y arilalquilo.

El término "(NR^eR^f)carbonilo", como se usa en la presente, se refiere a un grupo -NR^eR^f enlazado a la porción molecular precursora a través de un grupo carbonilo.

El término "(NR^eR^f)carbonilalquilo", como se usa en la presente, se refiere a un grupo (NR^eR^f)carbonilo enlazado a la porción molecular precursora a través de un grupo alquilo.

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El término "(NR^eR^f)sulfonilo", como se usa en la presente, se refiere a un grupo $-NR^eR^f$ enlazado a la porción molecular precursora a través de un grupo sulfonilo.

El término "oxo", como se usa en la presente, se refiere a =O.

El término "sulfonilo", como se usa en la presente, se refiere a $-SO_2-$.

El término "profármaco", como se usa en la presente, representa compuestos que se transforman rápidamente *in vivo* a los compuestos precursores por hidrólisis en la sangre. Los profármacos de la presente descripción incluyen ésteres de grupos hidroxi en la molécula precursora, ésteres de grupos carboxi en la molécula precursora, y amidas de las aminas en la molécula precursora.

Los compuestos de la presente descripción pueden existir como sales farmacéuticamente aceptables. El término "sal farmacéuticamente aceptable", como se usa en la presente, representa sales o formas zwiteriónicas de los compuestos de la presente descripción que son solubles o dispersables en agua o aceite, que son, dentro del alcance del juicio médico sólido, apropiadas para usarse en contacto con los tejidos de pacientes sin una toxicidad, irritación, respuesta alérgica excesiva, u otro problema o complicación correspondientes con una relación beneficio/riesgo razonable, y son efectivos para su uso

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proyectado. Las sales se pueden preparar durante el aislado y purificación final de los compuestos o separadamente al hacer reaccionar una funcionalidad básica apropiada con un ácido apropiado. Las sales de adición ácida representativas incluyen acetato, adipato, alginato, citrato, aspartato, benzoato, bencenosulfonato, bisulfato, butirato, alcanforato, alcanforsulfonato; digluconato, glicerofosfato, hemisulfato, heptanoato, hexanoato, formiato, fumarato, clorohidrato, bromohidrato, yodohidrato, 2-hidroxietansulfonato, lactato, maleato, mesitilensulfonato, metansulfonato, naftilensulfonato, nicotinato, 2-naftalensulfonato, oxalato, palmoato, pectinato, persulfato, 3-fenilproprionato, picrato, pivalato, propionato, succinato, tartrato, tricloroacetato, trifluoroacetato, fosfato, glutamato, bicarbonato, para-toluensulfonato, y undecanoato. Ejemplos de ácidos los cuales se pueden emplear para formar sales de adición farmacéuticamente aceptables incluyen ácidos inorgánicos tales como clorhídrico, bromhídrico, sulfúrico, y fosfórico, y ácidos orgánicos tales como oxálico, maleico, succínico, y cítrico.

Las sales de adición básicas pueden prepararse durante el aislado y purificación final de los compuestos al hacer reaccionar un grupo ácido con una base apropiada tal como el hidróxido, carbonato, o bicarbonato de un catión de

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metal o con amoniaco o una amina primaria, secundaria, o terciaria orgánica. Los cationes de sales farmacéuticamente aceptables incluyen litio, sodio, potasio, calcio, magnesio, y aluminio, así como cationes de amina cuaternaria no tóxica tales como amonio, tetrametilamonio, tetraetilamonio, metilamina, dimetilamina, trimetilamina, trietilamina, dietilamina, etilamina, tributilamina, piridina, N,N-dimetilanilina, N-metilpiperidina, N-metilmorfolina, diciclohexilamina, procaina, dibencilamina, N,N-dibencilfenetilamina, y N,N'-dibenciletilendiamina. Otras aminas orgánicas representativas útiles para la formación de sales de adición básica incluyen etilendiamina, etanolamina, dietanolamina, piperidina, y piperazina.

Como se usa en la presente, el término "actividad anti-VHC" significa que el compuesto es efectivo para tratar el virus VHC.

El término "compuestos de la descripción", y expresiones equivalentes, son un medio que abarca compuestos de la fórmula (I), y enantiómeros, diastereómeros y sales farmacéuticamente aceptables de los mismos. Similarmente, las referencias a compuestos intermedios o intermediarios son un medio para abarcar sus sales donde el contexto así lo permite.

El término "paciente" incluye tanto a los humanos como a otros mamíferos.

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El término "composición farmacéutica" significa una composición que comprende un compuesto de la descripción en combinación con al menos un portador farmacéutico adicional, esto es, adyuvante, excipiente o vehículo, tales como diluyentes, agentes conservadores, rellenadores, agentes reguladores del flujo, agentes desintegrantes, agentes humectantes, agentes emulsificantes, agentes de suspensión, agentes endulzantes, agentes saborizantes, agentes perfumantes, agentes antibacteriales, agentes anti-hongos, agentes lubricantes y agentes dispersantes, dependiendo de la naturaleza del modo de administración y formas de dosificación. Los ingredientes listados en Remington's Pharmaceutical Sciences, 18ª ed., Mack Publishing Company, Easton, PA (1999) por ejemplo, pueden usarse.

La frase "farmacéuticamente aceptable" se emplea en la presente para referirse a aquellos compuestos, materiales, composiciones y/o formas de dosificación que están, dentro del alcance del juicio médico sólido, adecuados para el uso en contacto con los tejidos de pacientes sin toxicidad excesiva, irritación, respuesta alérgica u otros problemas o complicaciones correspondientes con una relación beneficio/riesgo razonable.

El término "cantidad terapéuticamente efectiva" significa la cantidad total de cada componente activo que

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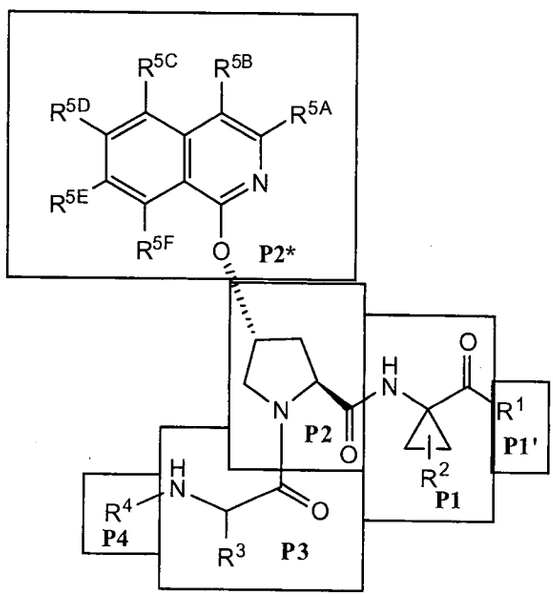
es suficiente para mostrar un beneficio significativo en el paciente, por ejemplo, una reducción sostenida en la carga viral. Cuando se aplica a un ingrediente activo individual, administrado solo, el término se refiere al ingrediente solo. Cuando se aplica a una combinación, el término se refiere a cantidades combinadas de los ingredientes activos que conducen al efecto terapéutico, ya sea administrados en combinación, sucesivamente o simultáneamente.

El término "tratar" y "tratamiento" se refiere a: (i) prevenir que una enfermedad, trastorno o afección se presente en un paciente que puede estar predispuesto a la enfermedad, trastorno y/o afección pero que no ha sido aún diagnosticado como que la tiene; (ii) inhibir la enfermedad, trastorno o afección, es decir, detener su desarrollo; y/o (iii) aliviar la enfermedad, trastorno o afección, es decir, provocar la regresión de la enfermedad, trastorno y/o afección.

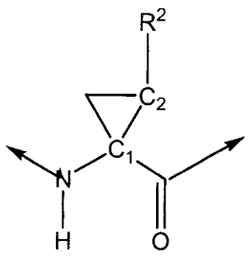
Donde se usan para nombrar compuestos de la presente descripción, las designaciones P1', P1, P2, P2*, P3, y P4, como se usa en la presente, hacen un mapa de las posiciones relativas de los residuos de aminoácido de un inhibidor de proteasa enlazado con relación al enlace del substrato desdoblado del péptido natural. El desdoblamiento se presenta en el substrato natural entre P1 y P1' donde las posiciones sin apóstrofe designan aminoácidos partiendo del extremo de

terminal C del sitio de desdoblamiento natural péptido que se extiende hacia la terminal N; en tanto que, las posiciones con apóstrofe emanadas del extremo de la terminal N del sitio de desdoblamiento se designan y extienden hacia la terminal C. Por ejemplo, P1' se refiere a la primera posición que se aleja del extremo del lado derecho de la terminal C del sitio de desdoblamiento (esto es, primera posición de la terminal N); en tanto que P1 inicia la numeración desde el lado izquierdo del sitio de desdoblamiento de la terminal C, P2: segunda posición de la terminal C, etc.). (Ver Berger A. & Schechter I., Transactions of the Royal Society London series (1970), B257, 249-264].

A continuación se muestran las designaciones para los compuestos de la presente descripción.

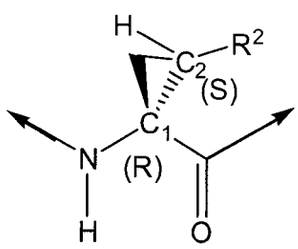


Los centros asimétricos existen en los compuestos de la presente descripción. Por ejemplo, los compuestos pueden incluir el elemento de ciclopropilo P1 de la fórmula

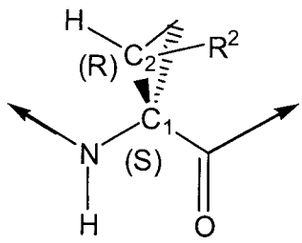


P1

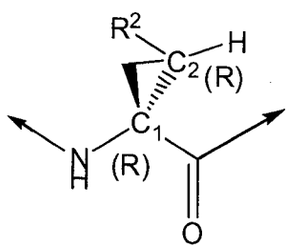
en donde C_1 y C_2 cada uno representan un átomo de carbono asimétrico en las posiciones 1 y 2 del anillo ciclopropilo.



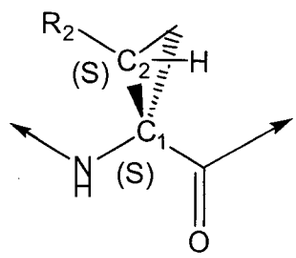
(1R, 2S)
R^2 es syn para carbonilo



(1S, 2R)
R^2 es syn para carbonilo



(1R, 2R)
R^2 es syn para amida



(1S, 2S)
R^2 es syn para amida

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Se entenderá que la descripción abarca todas las formas esteroquímicas, o mezclas de las mismas, que poseen la capacidad para inhibir la proteasa del VHC.

Ciertos compuestos de la presente descripción también pueden existir en formas conformacionales estables diferentes las cuales pueden separarse. La asimetría torsional debido a la rotación restringida alrededor de un enlace sencillo asimétrico, por ejemplo debido a la cadena del anillo u obstrucción estérica, pueden permitir la separación de confórmeros diferentes. La presente descripción incluye cada isómero conformacional de estos compuestos y mezclas de los mismos.

Ciertos compuestos de la presente descripción pueden existir en forma zwitteriónica y la presente descripción incluye cada forma zwitteriónica de estos compuestos y mezclas de los mismos.

Cuando es posible que, para usarse en la terapia, las cantidades terapéuticamente efectivas de un compuesto de la fórmula (I), así como sales farmacéuticamente aceptables de las mismas, puedan administrarse como el químico de entrada, es posible que presentan el ingrediente activo como la composición farmacéutica. En consecuencia, la descripción proporciona además composiciones farmacéuticas, que incluyen cantidades terapéuticamente efectivas de compuestos de la fórmula (I) o sales farmacéuticamente aceptables de los

mismos, y uno o más portadores, diluyentes, o excipientes farmacéuticamente aceptables. Los compuestos de la fórmula (I) y las sales farmacéuticamente aceptables del mismo son como se describen arriba. Los portadores, diluyentes, o excipientes deben ser aceptables en el sentido de que sean compatibles con los otros ingredientes de la formulación y no perjudiciales para el receptor de los mismos. De acuerdo con otro aspecto de la presente descripción, se proporciona también un proceso para la preparación de una formulación farmacéutica que incluye mezclar un compuesto de la fórmula (I), o una sal farmacéuticamente aceptable del mismo, con uno o más portadores, diluyentes o excipientes farmacéuticamente aceptables.

Las formulaciones farmacéuticas pueden estar presentes en formas de dosificación unitarias que contienen una cantidad predeterminada del ingrediente activo por dosis unitaria. Los niveles de dosificación de entre alrededor de 0.01 y alrededor de 250 miligramos por kilogramo ("mg/kg") de peso corporal por día, preferiblemente entre alrededor de 0.05 y alrededor de 100 mg/kg de peso corporal por día de los compuestos de la descripción son típicos en una monoterapia para la prevención y tratamiento de las enfermedades mediadas por VHC. Típicamente, las composiciones farmacéuticas de la descripción se administrarán desde alrededor de 1 hasta alrededor de 5 veces por día o alternativamente, como una

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infusión continua. Tal administración puede ser usada como una terapia aguda o crónica. La cantidad de ingrediente activo que puede ser combinada con los materiales portadores para producir una forma de dosificación sencilla variarán dependiendo de la afección de que se trate, la severidad de la afección, el tiempo de administración, la ruta de administración, la relación de excreción del compuesto empleado, la duración del tratamiento, la edad, género, peso y estado del paciente. Las formulaciones de la dosificación unitaria preferida son aquellas que contienen una dosis diaria o sub-dosis, como se menciona arriba, o una fracción apropiada de la misma, de un ingrediente activo. Generalmente, el tratamiento se inicia con dosificaciones pequeñas sustancialmente menores que la dosis óptima del compuesto. Posteriormente, la dosificación se incrementa mediante pequeños incrementos hasta que se alcanza el efecto óptimo bajo las circunstancias. En general, el compuesto se administra más deseablemente en un nivel de concentración que producirá generalmente resultados efectivos antivirales sin provocar ningún daño o efectos secundarios perjudiciales.

Cuando las composiciones de esta descripción comprenden una combinación de un compuesto de la descripción y uno o más agentes profilácticos o terapéuticos adicionales, tanto el compuesto como el agente adicional se presentan usualmente en niveles de dosificación de entre alrededor de 10 a 150%, y

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más probablemente entre alrededor de 10 y 80% de la dosificación administrada normalmente en un régimen de monoterapia.

Las formulaciones farmacéuticas pueden adaptarse para la administración mediante cualquier ruta apropiada, por ejemplo, mediante la ruta oral (que incluye bucal o sublingual), rectal, nasal, tópica (que incluye bucal, sublingual o transdermal), vaginal o parenteral (que incluye subcutánea, intracutánea, intramuscular, intra-articular, intrasinovial, intraesternal, intratecal, intralesional, intravenosa o inyecciones o infusiones intradermales). Tales formulaciones pueden prepararse mediante cualquier método conocido en el arte de la farmacia, por ejemplo, al poner en asociación el ingrediente activo con los portadores o excipientes.

Las formulaciones farmacéuticas adaptadas para la administración oral pueden ser presentadas como unidades discretas tales como cápsulas o comprimidos, polvos o gránulos, soluciones o suspensiones en líquidos acuosos y no acuosos, espumas comestibles o batidos, o en emulsiones líquidas de aceite en agua o emulsiones de agua en aceite.

Por ejemplo, para la administración oral en la forma de un comprimido o cápsula, el componente del fármaco activo puede ser combinado con un portador inerte farmacéuticamente aceptable no tóxico tal como etanol, glicerol, agua y

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similares. Los polvos se preparan mediante la pulverización del compuesto hasta un tamaño fino adecuado y mezclarlo con un portador farmacéutico similarmente pulverizado tal como un carbohidrato comestible, como por ejemplo, almidón o manitol. Puede también estar presente un saborizante, conservador, dispersante y agente colorante.

Las cápsulas se elaboran preparando una mezcla de polvos como se describe arriba, y se llenan con vainas formadas de gelatina. Los agentes mejoradores de flujo y lubricantes tales como sílice coloidal, talco, estearato de magnesio, estearato de calcio o polietilen glicol sólido pueden agregarse a la mezcla en polvo antes de realizar la operación de relleno. Puede también añadirse un agente desintegrante o de solubilización tal como agar-agar, carbonato de calcio, o carbonato de sodio para mejorar la disponibilidad del medicamento cuando se ingiere la cápsula.

Además, cuando se desee o sea necesario, los aglutinantes adecuados, lubricantes, agentes desintegrantes y agentes colorantes pueden también ser incorporados en la mezcla. Los aglutinantes adecuados incluyen almidón, gelatina, azúcares naturales tales como glucosa o beta-lactosa, edulcorantes de maíz, gomas sintéticas y naturales tales como acacia, tragacanto, o alginato de sodio, carboximetilcelulosa, polietilen glicol y similares. Los lubricantes usados en estas formas de dosificación incluyen

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oleato de sodio, cloruro de sodio y similares. Los desintegradores incluyen, sin limitación, almidón, metil celulosa, agar, betonita, goma de xantano y similares. Los comprimidos se formulan, por ejemplo, mediante la preparación de una mezcla de polvo, granulados o sedimentos añadiendo un lubricante y desintegrante, y comprimir en comprimidos. Una mezcla de polvos se prepara al mezclar el compuesto, pulverizado adecuado, con un diluyente o una base como la descrita arriba, y opcionalmente con un aglutinante tales como carboximetilcelulosa, un alginato, agente de gelificación o polivinil pirrolidona, una solución retardante tal como una parafina, un acelerador de la resorción tal como una sal cuaternaria y/o un agente de absorción tal como bentonita, caolín o fosfato de dicalcio. La mezcla del polvo puede ser granulada mediante un humedecimiento con un aglutinante tal como un jarabe, pasta de almidón, mucílago de acadia o soluciones de materiales poliméricos o celulósicos y forzada a través de un tamiz. Como una alternativa para la granulación, la mezcla del polvo puede realizarse por medio de la máquina para elaborar comprimidos dando como resultado trozos de forma imperfecta fragmentados como gránulos. Los gránulos pueden ser lubricados para prevenir la adherencia a los troqueles que forman el comprimido por medio de la adición de ácido esteárico, una sal de estearato, talco o aceite mineral. La mezcla lubricada se comprime entonces en

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tabletas. Los compuestos de la presente descripción pueden también ser combinados con un portador inerte que fluye libremente y comprimirse en tabletas directamente sin ir a través de las etapas de granulación o sedimentación. Puede proporcionarse un revestimiento protector opaco o transparente que consiste de un revestimiento de sellado con laca, un revestimiento de azúcar o material polimérico y un revestimiento de pulido de cera. Los colorantes pueden añadirse a aquellos revestimientos para distinguir diferentes dosificaciones unitarias.

Los fluidos orales tales como una solución, jarabe y elíxires pueden prepararse en formas de dosificación unitarias tal que una cantidad dada que contenga una cantidad predeterminada del compuesto. Los jarabes pueden prepararse disolviendo el compuesto en una solución acuosa saborizada adecuadamente mientras que los elíxires se preparan a través del uso de un vehículo no tóxico. También pueden añadirse solubilizadores y emulsificadores tales como alcoholes de isoestearilo etoxilados y éteres de polioxietilen sorbitol, conservadores, aditivos de condimentación tales como edulcorantes naturales o aceite de menta, o sacarina u otros edulcorantes artificiales y similares.

Cuando sea apropiado, las formulaciones de dosificación unitarias para la administración oral pueden ser microencapsuladas. La formulación puede también ser preparada

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para prolongar o sostener la liberación mediante por ejemplo, material particulado de revestimiento o incrustación en polímeros, ceras o similares.

Los compuestos de la fórmula (I) y sales farmacéuticamente aceptables de los mismos, pueden también administrarse en la forma de sistemas de suministro de liposomas, tales como vesículas unilaminares pequeñas, vesículas unilaminares grandes y vesículas multilaminares. Los liposomas pueden formarse a partir de una variedad de fosfolípidos tales como colesterol, estearilamina o fosfatidilcolinas.

Los compuestos de la fórmula (I) y las sales farmacéuticamente aceptables de los mismos también pueden suministrarse mediante el uso de anticuerpos monoclonales como portadores individuales en los que se acoplan las moléculas del compuesto. Los compuestos pueden también ser acoplados con polímeros solubles como portadores de fármacos dirigibles. Tales polímeros pueden incluir polivinilpirrolidona, copolímero de pirano, polihidroxipropilmetacrilamidafenol, polihidroxietilaspartamidafenol, o polietilenoxidepolilisina sustituida con residuos de palitoilo. Además, los compuestos pueden ser acoplados a una clase de polímeros biodegradables útiles para obtener una liberación controlada de un fármaco, por ejemplo, ácido poliláctico, poliépsilon caprolactona,

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ácido polihidroxi butírico, poliortoésteres, poliacetales, polidihidropiranos, policianoacrilatos y copolímeros de bloque anfifáticos o reticulados de hidrogeles.

Las formulaciones farmacéuticas adaptadas para la administración transdermal pueden ser presentadas como parches discretos para permanecer en contacto íntimo con la epidermis del receptor durante un periodo de tiempo prolongado. Por ejemplo, el ingrediente activo puede ser suministrado a partir de un parche mediante la iontofóresis como se describe generalmente en Pharmaceutical Research 1986, 3(6), 318.

Las formulaciones farmacéuticas adaptadas para la administración tópica pueden ser formuladas como ungüentos, cremas, suspensiones, lociones, polvos, soluciones, pastas, geles, soluciones de rocíado, aerosoles o aceites.

Para tratamientos del ojo u otros tejidos externos, por ejemplo boca y piel, las formulaciones se aplican preferiblemente como un ungüento o crema tópica. Cuando se formula en un ungüento, el ingrediente activo puede emplearse con una base de ungüento ya sea parafínica o miscible en agua. Alternativamente, el ingrediente activo puede formularse en una crema con una base de crema de aceite en agua o una base de agua en aceite.

Las formulaciones farmacéuticas adaptadas para administraciones tópicas al ojo incluyen gotas para

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ojos en donde el ingrediente activo se disuelve o suspende en un portador apropiado, especialmente un solvente acuoso.

Las formulaciones farmacéuticas adaptadas para la administración tópica en la boca incluyen tabletas, pastillas, y lavados bucales.

Las formulaciones farmacéuticas adaptadas para la administración rectal pueden presentarse como supositorios o como enemas.

Las formulaciones farmacéuticas adaptadas para la administración nasal, en donde el portador es un sólido, incluye un polvo de transporte que tiene un tamaño de partícula, por ejemplo, en el intervalo de 20 hasta 500 micrones, que se administra en la forma en la que se inhala, es decir, mediante la inhalación rápida a través de un pasaje nasal de un recipiente que se mantiene próximo a la nariz. Las formulaciones adecuadas en donde el portador es un líquido, para la administración como un rociador nasal o gotas nasales, incluye soluciones en aceite o acuosas del ingrediente activo.

Las formulaciones farmacéuticas adaptadas para la administración mediante inhalación incluyen polvos o neblinas de partículas finas que pueden ser generadas por medio de varios tipos de aerosoles presurizados de dosis medidas, nebulizadores o insufladores.

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Las formulaciones farmacéuticas adaptadas para la administración vaginal pueden ser presentadas como pesarios, tampones, cremas, geles, pastas, espumas o formulaciones de rocío.

Las formulaciones farmacéuticas adaptadas para la administración parenteral incluyen soluciones de inyecciones estériles acuosas y no acuosas que pueden contener antioxidantes, soluciones amortiguadoras, bacteriostatos y solutos que vuelven la formulación isotónica con la sangre del receptor pretendido; y las suspensiones estériles acuosas y no acuosas que pueden incluir agentes de suspensión y agentes de espesamiento. Las formulaciones pueden estar presentes en contenedores de dosis unitarias y dosis múltiples, por ejemplo, ampolletas y viales sellados, y pueden ser almacenados en una condición secada por congelamiento (liofilizadas) que requiere sólo de la adición del portador líquido estéril, por ejemplo, agua para inyecciones, inmediatamente previo a su uso. Las soluciones de inyecciones extemporáneas y suspensiones pueden estar presentes a partir de polvos estériles, gránulos y comprimidos.

Se entenderá que además de los ingredientes mencionados arriba en particular, las formulaciones pueden incluir otros agentes convencionales en el arte, haciendo referencia al tipo de formulación en cuestión, por ejemplo, aquellas adecuadas para la administración oral pueden incluir agentes saborizantes.

La Tabla 1 a continuación lista algunos ejemplos ilustrativos de los compuestos que pueden ser administrados con los compuestos de esta descripción. Los compuestos de la presente descripción pueden ser administrados con otros compuestos con actividad anti-HCV en combinación con una terapia, ya sea en conjunto o por separado, o combinando los compuestos en una composición.

Tabla 1

Nombre Comercial	*Clase Fisiológica*	*Tipo de Inhibidor u Objetivo*	*Compañía Fuente*
NIM811		Inhibidor de Ciclofilina	Novartis
Zadaxin		Inmunomodulador	Sciclone
Suvus		Azul de metileno	Bioenvision
Actilon (CPG10101)		Agonista TLR9	Coley
Batabulin (T67)	Anticáncer	Agonista de β-tubulina	Tularik Inc., South San Francisco, CA

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Nombre Comercial	*Clase Fisiológica*	*Tipo de Inhibidor u Objetivo*	*Compañía Fuente*
ISIS 14803	Antiviral	antisentido	ISIS Pharmaceuticals Inc, Carlsbad, CA/Elan Phamaceuticals Inc., New York, NY
Summetrel	Antiviral	antiviral	Endo Pharmaceuticals Holdings Inc., Chadds Ford, PA
GS-9132 (ACH-806)	Antiviral	Inhibidor del VHC	Achillion / Gilead
Compuestos y sales de pirazolopiri-midina de WO-2005047288 26 de Mayo de 2005	Antiviral	Inhibidores del VHC	Arrow Therapeutics Ltd.

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Nombre Comercial	*Clase Fisiológica*	*Tipo de Inhibidor u Objetivo*	*Compañía Fuente*
Levovirin	Antiviral	Inhibidor del IMPDH	Ribapharm Inc., Costa Mesa, CA
Merimepodib (VX-497)	Antiviral	Inhibidor del IMPDH	Vertex Pharmaceuticals Inc., Cambridge, MA
XTL-6865 (XTL-002)	Antiviral	anticuerpo monoclonal	XTL Biopharmaceuticals Ltd., Rehovot, Isreal
Telaprevir (VX-950, LY-570310)	Antiviral	Inhibidor de serina proteasa NS3	Vertex Pharmaceuticals Inc., Cambridge, MA/ Eli Lilly y Co. Inc., Indianapolis, IN
HCV-796	Antiviral	Inhibidor de Replicasa NS5B	Wyeth / Viropharma
NM-283	Antiviral	Inhibidor de Replicasa NS5B	Idenix / Novartis

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Nombre Comercial	*Clase Fisiológica*	*Tipo de Inhibidor u Objetivo*	*Compañía Fuente*
GL-59728	Antiviral	Inhibidor de Replicasa NS5B	Gene Labs / Novartis
GL-60667	Antiviral	Inhibidor de Replicasa NS5B	Gene Labs / Novartis
2'C MeA	Antiviral	Inhibidor de Replicasa NS5B	Gilead
PSI 6130	Antiviral	Inhibidor de Replicasa NS5B	Roche
R1626	Antiviral	Inhibidor de Replicasa NS5B	Roche
2'C Metil adenosina	Antiviral	Inhibidor de Replicasa NS5B	Merck
JTK-003	Antiviral	Inhibidor de RdRp	Japan Tobacco Inc., Tokio, Japón
Levovirina	Antiviral	ribavirina	ICN Pharmaceuticals, Costa Mesa, CA
Ribavirina	Antiviral	ribavirina	Schering-Plough Corporation, Kenilworth, NJ

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Nombre Comercial	*Clase Fisiológica*	*Tipo de Inhibidor u Objetivo*	*Compañía Fuente*
Viramidine	Antiviral	Profármaco de Ribavirina	Ribapharm Inc., Costa Mesa, CA
Heptazyme	Antiviral	ribozima	Ribozyme Pharmaceuticals Inc., Boulder, CO
BILN-2061	Antiviral	Inhibidor de serina proteasa	Boehringer Ingelheim Pharma KG, Ingelheim, Alemania
SCH 503034	Antiviral	Inhibidor de serina proteasa	Schering Plough
Zadazim	Modulador inmune	Modulador inmune	SciClone Pharmaceuticals Inc., San Mateo, CA
Ceplene	Inmunomodulador	modulador inmune	Maxim Pharmaceuticals Inc., San Diego, CA

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Nombre Comercial	*Clase Fisiológica*	*Tipo de Inhibidor u Objetivo*	*Compañía Fuente*
CellCept	Inmunodepresor	Inmunodepresor IgG de VHC	F. Hoffmann-La Roche LTD, Basilea, Suiza
Civacir	Inmunodepresor	Inmunodepresor IgG de VHC	Nabi Biopharmaceuticals Inc., Boca Raton, FL
Albuferon-α	Interferón	albúmina IFN-α2b	Human Genome Sciences Inc., Rockville, MD
Infergen A	Interferón	IFN alfacon-1	InterMune Pharmaceuticals Inc., Brisbane, CA
Omega IFN	Interferón	IFN-ω	Intarcia Therapeutics
IFN-β y EMZ701	Interferón	IFN-β y EMZ701	Transition Therapeutics Inc., Ontario, Canadá

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Nombre Comercial	*Clase Fisiológica*	*Tipo de Inhibidor u Objetivo*	*Compañía Fuente*
Rebif	Interferón	IFN-β1a	Serono, Ginebra, Suiza
Roferon A	Interferón	IFN-α2a	F. Hoffmann-La Roche LTD, Basilea, Suiza
Intron A	Interferón	IFN-α2b	Schering-Plough Corporation, Kenilworth, NJ
Intron A y Zadaxin	Interferón	IFN-α2b/α1-timosina	RegeneRx Biopharmiceuticals Inc., Bethesda, MD/ SciClone Pharmaceuticals Inc, San Mateo, CA
Rebetron	Interferón	IFN-α2b/ribaviri-na	Schering-Plough Corporation, Kenilworth, NJ
Actimmune	Interferón	INF-γ	InterMune Inc., Brisbane, CA

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Nombre Comercial	*Clase Fisiológica*	*Tipo de Inhibidor u Objetivo*	*Compañía Fuente*
Interferón-β	Interferón	Interferón-β-1a	Serono
Multiferon	Interferón	IFN de larga duración	Viragen/Valentis
Wellferon	Interferón	IFN-αn1 linfoblastoide	GlaxoSmithKline plc, Uxbridge, RU
Omniferon	Interferón	IFN-α natural	Viragen Inc., Plantation, FL
Pegasys	Interferón	IFN-α2a PEGilado	F. Hoffmann-La Roche LTD, Basilea, Suiza
Pegasys y Ceplene	Interferón	IFN-α2a PEGilado/ modulador inmune	Maxim Pharmaceuticals Inc., San Diego, CA
Pegasys y Ribavirina	Interferón	IFN-α2a PEGilado/ ribavirina	F. Hoffmann-La Roche LTD, Basilea, Suiza

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Nombre Comercial	*Clase Fisiológica*	*Tipo de Inhibidor u Objetivo*	*Compañía Fuente*
PEG-Intron	Interferón	IFN-α2b PEGilado	Schering-Plough Corporation, Kenilworth, NJ
PEG-Intron / Ribavirina	Interferón	IFN-α2b PEGilado/ ribavirina	Schering-Plough Corporation, Kenilworth, NJ
IP-501	Protección de hígado	antifibrótico	Indevus Pharmaceuticals Inc., Lexington, MA
IDN-6556	Protección de hígado	Inhibidor de caspasa	Idun Pharmaceuticals Inc., San Diego, CA
ITMN-191 (R-7227)	Antiviral	Inhibidor de serina proteasa	InterMune Pharmaceuticals Inc., Brisbane, CA
GL-59728	Antiviral	Inhibidor de Replicasa NS5B	Genelabs
ANA-971	Antiviral	Agonista de TLR-7	Anadys
TMC-465350	Antiviral	Inhibidor de serina proteasa	Medivir/Tibotec

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Los compuestos de la descripción también pueden usarse como reactivos de laboratorio. Los compuestos pueden ser instrumentos que proporcionen herramientas de investigación para diseñar ensayos de replicación viral, validación de los sistemas de ensayo para animales y estudios de biología estructural para perfeccionar el conocimiento de los mecanismos de la enfermedad de VHC. Además, los compuestos de la presente descripción son útiles para establecer o determinar el sitio de enlace de otros compuestos antivirales, por ejemplo, mediante la inhibición competitiva.

Los compuestos de esta descripción pueden ser usados también para tratar o prevenir la contaminación viral de los materiales y por lo tanto, reducir el riesgo de una infección viral del personal médico o de laboratorio, o pacientes que están en contacto con tales materiales, por ejemplo, sangre, tejido, instrumentos quirúrgicos y vestimenta, instrumentos de laboratorio y vestimenta, y aparatos y materiales para transfusión o colección sanguínea.

Esta descripción se pretende que abarque los compuestos que tienen la fórmula (I) cuando se preparan por procesos sintéticos o por procesos metabólicos incluyendo aquellos que se presentan en el cuerpo humano o animal (*in vivo*) o procesos que se presentan *in vitro*.

Las abreviaturas usadas en la presente solicitud, incluyendo particularmente en los esquemas de reacción

ilustrativos y ejemplos que siguen, son bien conocidos para aquellos expertos en el arte. Algunas de las abreviaturas usadas son como siguen: 4-DMAP o DMAP para 4-N,N-dimetilaminopiridina; Boc o BOC para terc-butoxicarbonilo; Fmoc para 9-fluorenilmetiloxicarbonilo; CDI para 1,1'-carbonildiimidazol; EDAC o EDC para clorohidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida; THF para tetrahidrofurano; DBU para 1,8-diazabiciclo[5.4.0]undec-7-eno; TFA para ácido trifluoroacético; HATU para fosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio; PyBOP para benzotriazol-1-il-oxi-tris-pirrolidino-fosfoniohexafluorofosfato; Me para metilo; MeI para yoduro de metilo; MOtBu para terc-butóxido de potasio, sodio, o litio; TBME o MTBE para éster metílico de terc-butilo; DMF para N,N-dimetilformamida; DMSO para dimetilsulfóxido; Ph para fenilo; DEAD para dietilazodicarboxilato; POPd para $[(t\text{-}Bu)_2POH]_2PdCl_2$; NaOBu para terc-butóxido de sodio; Oac para acetato; TBMDSCI para cloruro de terc-butildimetilsililo; 1,2-DME para 1,2-dimetoxietano; DMA para N,N-dimetilacetamida; n-BuLi para n-butil-litio; t-BuLi o tBuLi para terc-butil-litio; DPPA para difenilfosforil azida; TBAF para fluoruro de tetrabutilamonio; LiOt-Bu para terc-butóxido de litio; MeOH para metanol; DCM para diclorometano; t-BuOK para terc-butóxido de potasio; DIEA o DIPEA para diisopropiletilamina; MeCN para acetonitrilo; NMM para N-metilmorfolina; DCE para 1,2-dicloroetano; LDA para

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diisopropilamida de litio; DMPU para 1,3-dimetil-3,4,5,6-tetrahidro-2(1H)-pirimidinona; EtOAc para acetato de etilo; y TEA para trietilamina.

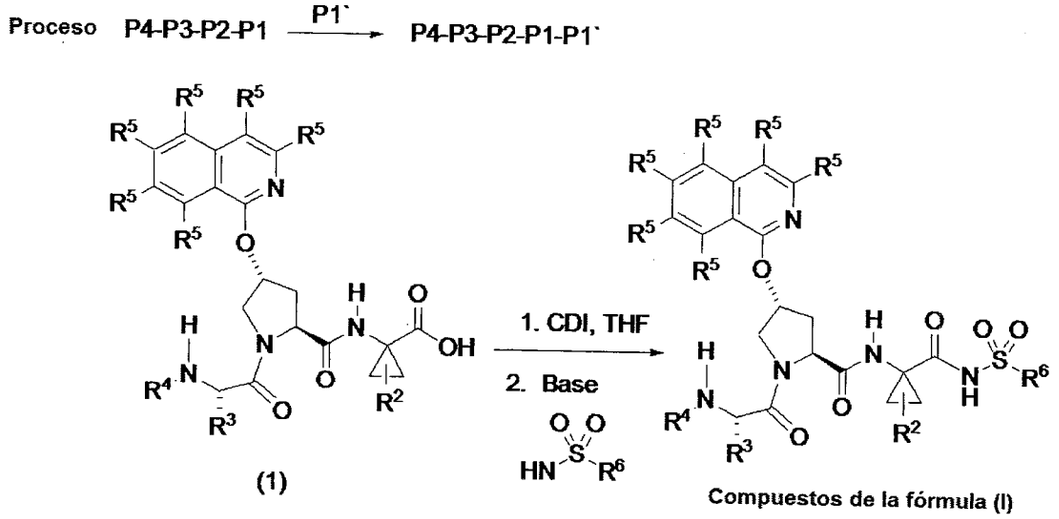
Los materiales de inicio útiles para sintetizar los compuestos de la presente descripción se conocen por aquellos expertos en el arte y pueden fabricarse rápidamente o están comercialmente disponibles.

Los siguientes métodos establecidos enseguida se proporcionan para propósitos ilustrativos y no se pretende que limiten el alcance de las reivindicaciones. Se reconocerá que puede ser necesario preparar tal compuesto en el cual un grupo funcional se protege usando un grupo protector convencional luego para remover el grupo protector para proporcionar el compuesto de la presente descripción. Los detalles que conciernen al uso de grupos protectores de conformidad con la presente descripción se conocen por aquellos expertos en el arte.

El Esquema de Reacción I muestra el proceso general en donde los compuestos de la Fórmula (I) se construyen al acoplar el intermediario de ácido carboxílico tripéptido (1) con una sulfonamida P1'. La reacción de acoplamiento requiere el tratamiento del ácido carboxílico (1) con un reactivo de acoplamiento tal como carbonil diimidazol en un solvente tal como THF, que puede calentarse hasta reflujo, seguido por la adición del derivado formado de (1), a la sulfonamida P1', en un solvente tal como THF o cloruro de metileno en presencia de una base tal como DBU.

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Esquema de reacción I

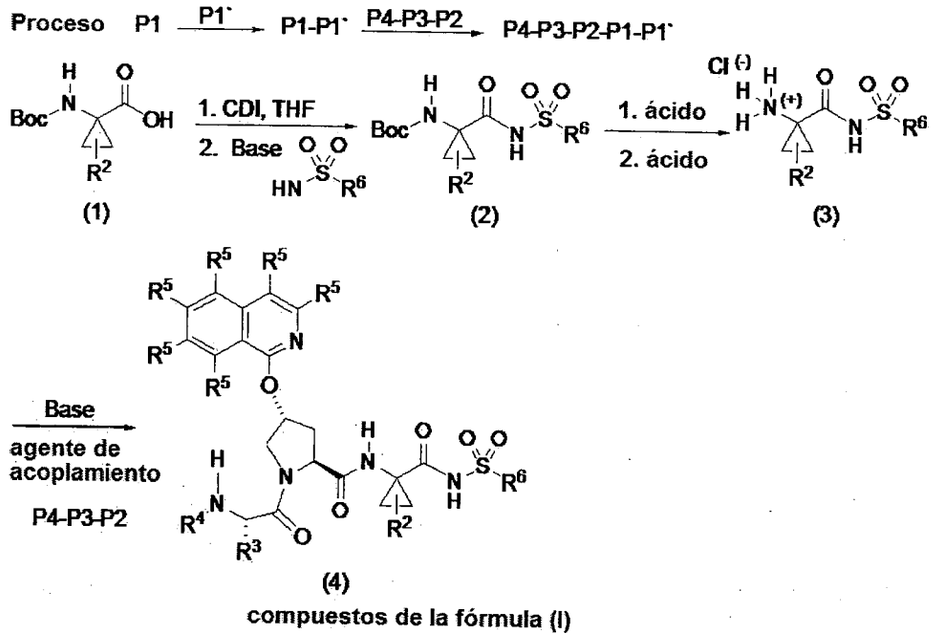


Un proceso alternativo para la construcción de los compuestos de la fórmula (I) se muestra en el esquema de reacción II. En la presente el elemento sulfonamida P1' se acopla al elemento P1 usando el proceso empleado en el esquema de reacción 1. La porción P1-P1' resultante puede luego desprotegerse en su terminal amino. En este ejemplo general un grupo protector Boc se emplea pero alguien experto en el arte deberá reconocer que un número de grupos protectores amino adecuados podría emplearse en este proceso. El grupo protector Boc puede removerse usando ácido tal como ácido trifluoroacético en un solvente tal como dicloroetano para proporcionar la amina desprotegida como la sal TFA. La sal de amina TFA puede emplearse directamente en la reacción se acoplamiento posterior o como una sal de amina TFA alternativa que puede primero convertirse a la sal de amina HCl, y esta sal

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de amina HCl se usa en la reacción de acoplamiento como se muestra en el Esquema de reacción II. El acoplamiento de la sal amina HCl (3) con el carboxilo terminal de un intermediario P4-P3-P2 puede llevarse a cabo usando reactivos de acoplamiento, tal como HATU, en solventes tales como diclorometano para proporcionar los compuestos de la fórmula (I) (4).

Esquema de reacción II

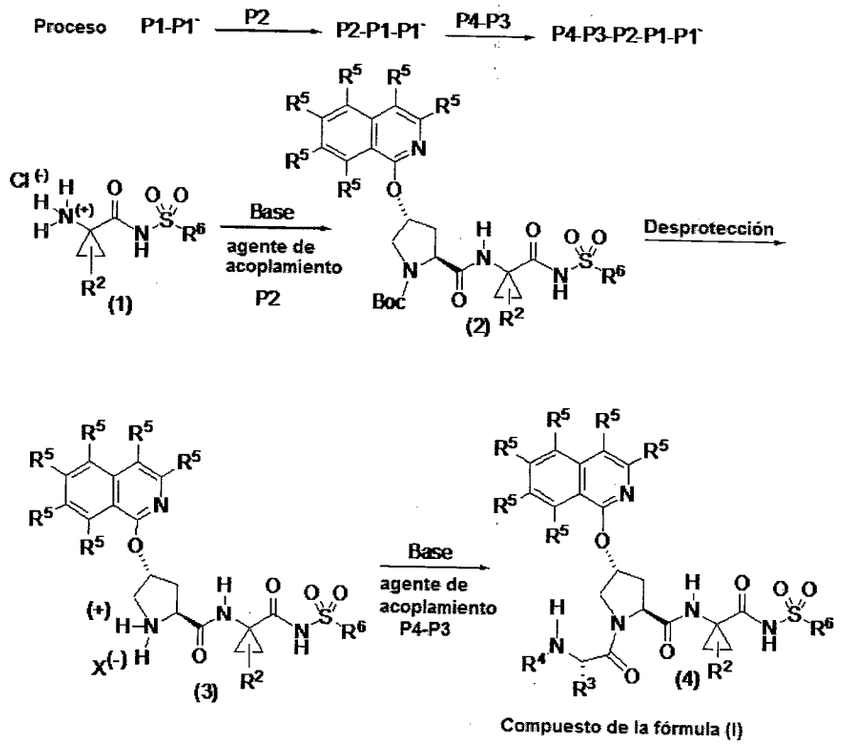


Un proceso alternativo para la construcción de los compuestos de la fórmula (I) se muestra en el esquema de reacción III. En la presente la sal de clorohidrato de la terminal amina P1-P1' (1) se acopla al grupo carboxilo libre del elemento P2 usando agentes de acoplamiento tales como PyBOP, en la presencia de una base tal como diisopropilamina,

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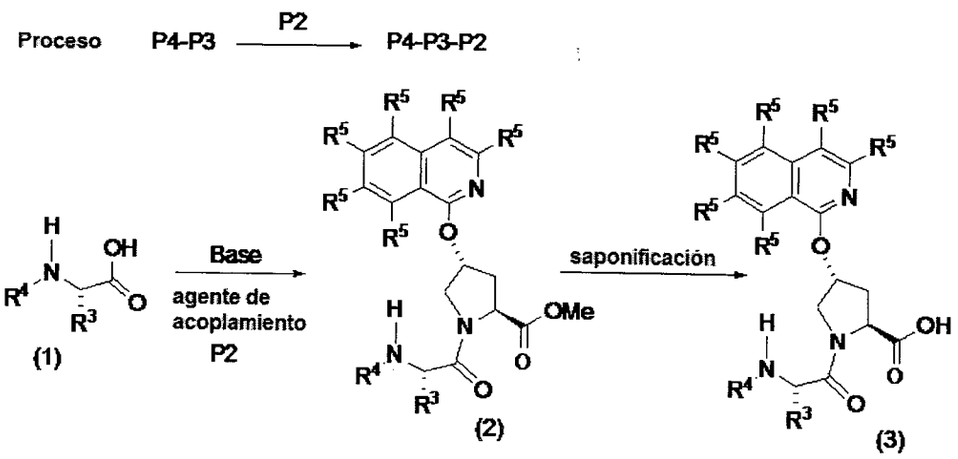
y en un solvente tal como cloruro de metileno. El intermediario P2-P1-P1' resultante puede convertirse a los compuestos de la fórmula (I) en un proceso de dos etapas en donde en la primera etapa se desprotege la terminal amina P2 usando un ácido tal como TFA en un solvente tal como cloruro de metileno. La sal de ácido trifluoroacético resultante puede acoplarse con la terminal carboxilo del elemento P4-P3 usando agentes estándar de acoplamiento tal como PyBop en la presencia de base tal como diisopropil amina, y usando solventes tales como cloruro de metileno para proporcionar los compuestos de la fórmula (I) (4).

Esquema de reacción III



El intermediario P4-P3-P2 utilizado en los esquemas de reacción de arriba puede construirse como se describe previamente con una descripción adicional de este proceso mostrada en el esquema de reacción general IV. La terminal carboxilo libre del intermediario P4-P3 (1), puede acoplarse a la terminal amino del elemento P2 para proporcionar el dipéptido P4-P3-P2 (2). La terminal carboxilo del intermediario P4-P3-P2 puede desprotegerse por saponificación del grupo éster para proporcionar P4-P3-P2 como el ácido carboxílico libre (3). Los intermediarios similares (3) pueden convertirse a los compuestos de la fórmula (I) usando los métodos descritos en la presente.

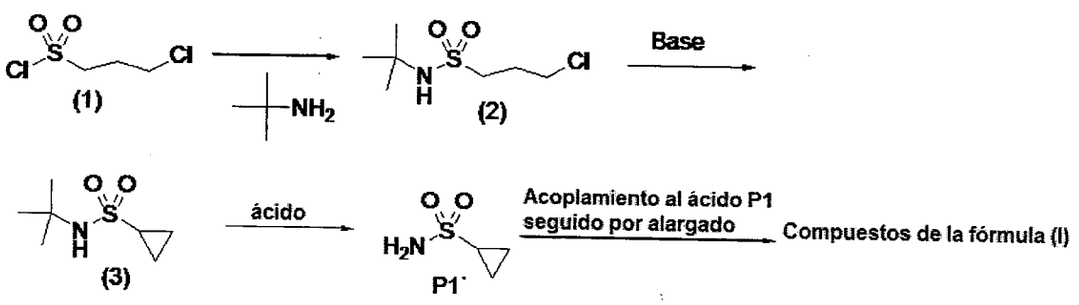
Esquema de reacción IV



En la construcción de los compuestos de la fórmula (I), la terminal P1' se incorpora en las moléculas usando uno de los procesos generales resumidos arriba y descritos en mayor

detalle a continuación. En algunos ejemplos los elementos P1', que son las cicloalquil o alquil sulfonamidas, están comercialmente disponibles o pueden prepararse del cloruro de cicloalquilsulfonilo o alquilo correspondiente por el tratamiento del cloruro de sulfonilo con amonio. Alternativamente, estas sulfonamidas pueden sintetizarse usando los procesos generales resumidos en el esquema de reacción V. El cloruro de 3-cloropropilsulfonilo comercialmente disponible (1) se convierte a una sulfonamida adecuadamente protegida, por ejemplo, por el tratamiento con terc-butil amina. La sulfonamida obtenida (2) luego se convierte a la cicloalquilsulfonamida correspondiente por el tratamiento con dos equivalentes de una base tal como butil-litio en un solvente tal como THF a temperatura baja. La cicloalquilsulfonamida resultante puede desprotegerse por el tratamiento con un ácido para proporcionar la cicloalquilsulfoamida no protegida deseada.

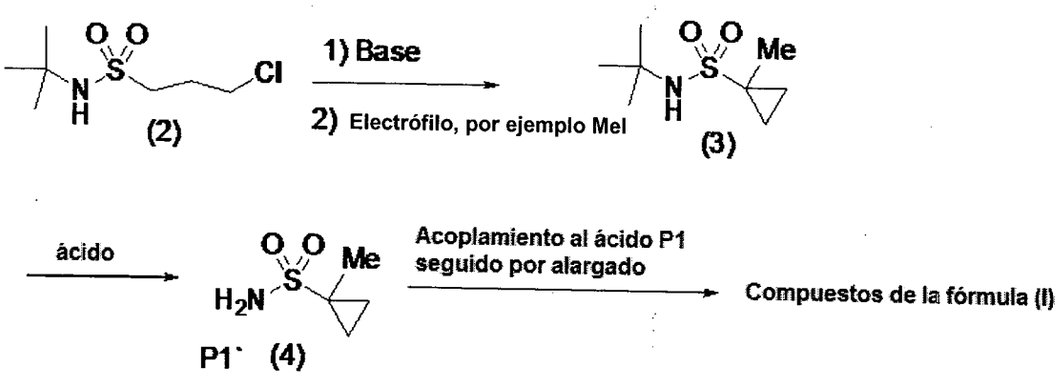
Esquema de reacción V



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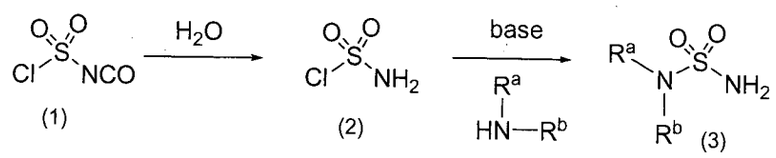
Las cicloalquilsulfonamidas substituidas pueden también incorporarse en los compuestos de la fórmula (I) usando una modificación del procedimiento de arriba. Por ejemplo, el intermediario 2 del Esquema de reacción VI puede tratarse con dos equivalentes de base tal como butil-litio y la mezcla de reacción resultante puede tratarse con un electrófilo tal como yoduro de metilo para proporcionar una cicloalquilsulfonamida substituida (3). Este intermediario (3) puede desprotegerse en la terminal N y el compuesto resultante (4) se utiliza como un intermediario en la preparación de los compuestos de la fórmula (I).

Esquema de reacción VI



Los intermediarios P1' empleados para generar los compuestos de la fórmula (I) son en los mismos casos derivados de derivados de sulfamida. En tales casos los intermediarios de sulfamida son disponibles por diversas rutas sintéticas como, por ejemplo, por la trayectoria resumida en el esquema de reacción VII.

Esquema de reacción VII



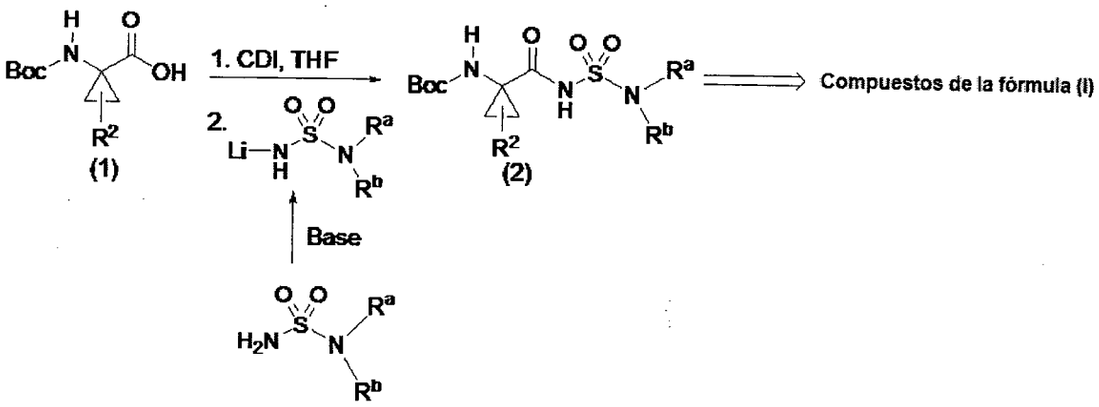
El cloruro de sulfamoilo (2) puede prepararse *in situ* por la adición de agua (por ejemplo, 1 equivalente) hasta isocianato de clorosulfonilo 1 (por ejemplo, 1 equivalente) en un solvente tal como THF mientras se mantiene a una temperatura baja tal como -20°C. La solución resultante luego se permite calentar a 0°C. A esta solución una base, tal como trietilamina anhidro (por ejemplo, 1 equivalente), se agrega seguido por una amina (por ejemplo, 1 equivalente). La mezcla de reacción luego se calienta a temperatura ambiente, se filtra, y el filtrado se concentra para proporcionar las sulfamidas deseadas (3).

Las sulfamidas pueden incorporarse en los compuestos de la fórmula (I) por diversos procesos como, por ejemplo, siguiendo la ruta sintética definida en el esquema de reacción VIII. Un elemento P1 de ácido carboxílico (1) se trata con un agente activo tal como CDI. En un matraz separado, una base fuerte se agrega a una solución de la sulfamida descrita arriba y la mezcla de reacción resultante se agita durante varias horas después de lo cual esta mezcla de reacción se agrega al matraz que contiene el ácido carboxílico activado, para proporcionar derivados de

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acilsulfamida (2). Los intermediarios similares 2 pueden convertirse a los compuestos de la fórmula (I) como se describe en la presente.

Esquema de reacción VIII



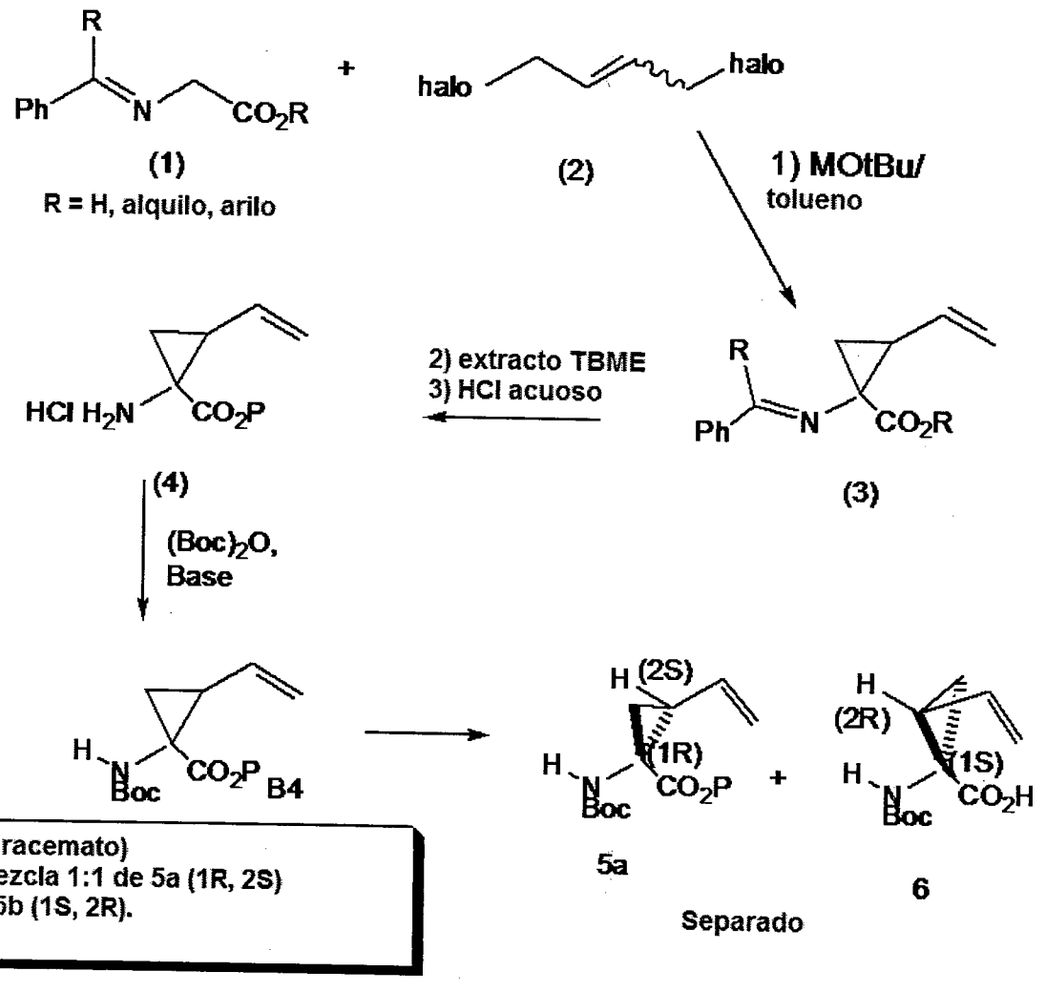
Los elementos P1 utilizados para generar los compuestos de la fórmula (I) están en algunos casos comercialmente disponibles, pero de otra manera se sintetizan usando los métodos descritos en la presente y se incorporan posteriormente en los compuestos de la fórmula (I) usando los métodos descritos en la presente. Los ácidos ciclopropilamino P1 substituidos pueden sintetizarse siguiendo los procesos generales resumidos en el esquema de reacción IX.

El tratamiento de la imina fácilmente sintetizada o comercialmente disponible (1) con 1,4-dihalobuteno (2) en la presencia de una base proporciona la imina resultante (3). La hidrólisis ácida de 3 luego proporciona 4, el cual

tiene un substituyente alilo syn al grupo carboxilo, como un producto mayor. La porción amina de 4 puede protegerse usando un grupo Boc para proporcionar el aminoácido completamente protegido 5. Este intermediario es un racemato el cual puede resolverse por un proceso enzimático en donde la porción éster del 5 se desdobla por una proteasa para proporcionar el ácido carboxílico correspondiente. Sin estar relacionado con alguna teoría particular, se cree que esta reacción es selectiva porque los enantiómeros experimentan la reacción en un intervalo mucho mayor que su imagen de espejo proporcionada para una resolución cinética del racemato intermediario. En los ejemplos citados en la presente, el estereoisómero más preferido para integración en los compuestos de la fórmula (I) es 5a el cual aloja la estereoquímica (1R,2S). En la presencia de la enzima, este enantiómero no tiene desdoblamiento por el éster y por lo tanto este enantiómero, 5a, se recupera de la mezcla de reacción. Sin embargo, el enantiómero menos preferido, 5b, el cual aloja la estereoquímica (1S,2R), experimenta el desdoblamiento por éster, esto es, hidrólisis, para proporcionar el ácido libre 6. Una vez completada esta reacción, el éster 5a puede separarse del producto ácido 6 por métodos de rutina tales como, por ejemplo, métodos de extracción acuosos o cromatografía.

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Esquema de reacción IX

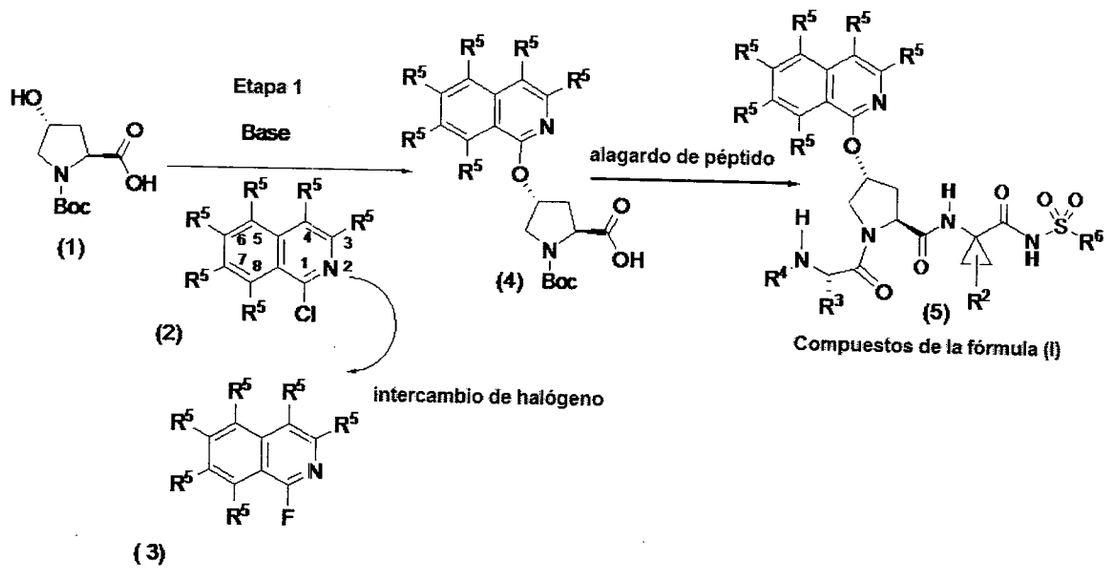


Los procedimientos para elaborar los intermediarios P2 y los compuestos de la fórmula (I) se muestran en los esquemas de reacción a continuación. Se deberá notar que en muchos caso las reacciones se detallan por solamente una posición de un intermediario. Sin embargo, se deberá entender que tales reacciones deberán usarse para impartir modificaciones a otras posiciones dentro de este intermediario. Por otra parte, los intermediarios, condiciones de reacción y métodos

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dados en los ejemplos específicos son ampliamente aplicables a compuestos con otros compañeros de substitución. Tanto los ejemplos generales como específicos son no limitantes.

Esquema de reacción X



El esquema de reacción X muestra el acoplamiento de una porción de C4-hidroxiprolina protegida por N con un heterociclo para formar el intermediario (4) y la modificación posterior del intermediario (4) a un compuesto de la fórmula (I) por el proceso de alargado de péptido como se describe en la presente. Se deberá notar que en la primera etapa, esto es el acoplamiento del grupo C4-hidroxi prolina con el elemento heteroarilo, una base se emplea. Alguien experto en el arte deberá reconocer que este acoplamiento puede usar bases tales como terc-butóxido de potasio, o

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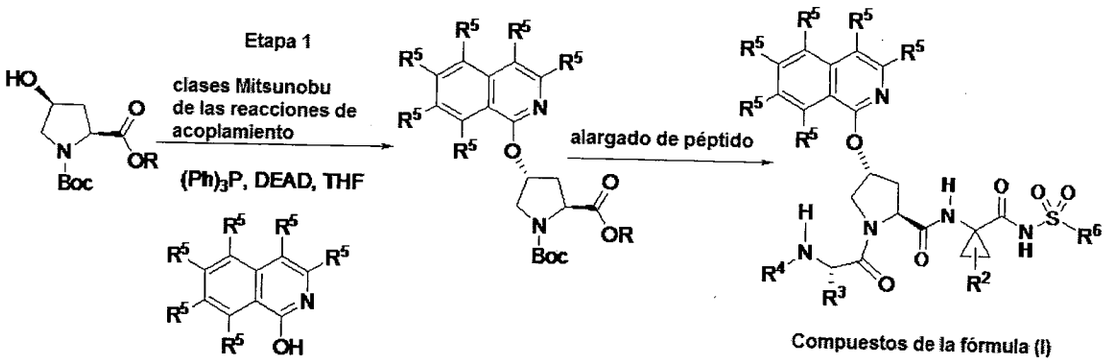
hidruro de sodio, en un solvente tal como DMF o DMSO o THF. Este acoplamiento para el sistema de anillo de isoquinolina se presenta en la posición C1 (numerado por el sistema de anillo mostrado en el intermediario 2 del Esquema de reacción XI) y se dirige por el grupo cloro el cual se desplaza en este proceso. Se deberá notar que los grupos salientes alternativos pueden utilizarse en esta posición (por ejemplo, fluoro) como se muestra en el esquema de reacción. Los intermediarios fluoro (3) están disponibles del compuesto de cloro correspondiente usando procedimientos de la literatura descritos en la presente.

Una alternativa al método descrito arriba por el acoplamiento de la C4-hidroxiprolina al núcleo de isoquinolina se proporciona en la reacción Mitsunobu como se detalla en la etapa 1 del Esquema de reacción XI. En este esquema de reacción general un derivado de C4-hidroxi prolina se acopla a un sistema de anillo de isoquinolina. Esta reacción hace uso de reactivos tales como trifenilfosfina y DEAD (dietilazodicarboxilato) en solventes apróticos tales como THF o dioxano y pueden usarse para la formación de éteres de heteroarilo. Se nota que en el curso de esta reacción de acoplamiento la estereoquímica del centro C4 quiral en el derivado de C4-hidroxiprolina se invierte y por lo tanto es necesario usar el derivado de C4-hidroxiprolina que tiene la estereoquímica (S) en la posición C4 como

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material de partida (como se muestra en el Esquema de reacción XI). Se deberá notar que numerosas modificaciones y mejoras de la reacción Mitsunobu se describen en la literatura, las enseñanzas de las cuales se incorporan en la presente.

Esquema de reacción XI



En los ejemplos en la presente, las isoquinolinas se incorporan en los compuestos finales y específicamente en la región P2 de los compuestos. Alguien experto en el arte deberá reconocer que un número de métodos generales están disponibles para la síntesis de las isoquinolinas. Sin embargo, las isoquinolinas generadas por estos métodos pueden fácilmente incorporarse en los compuestos finales de la fórmula (I) usando los procesos descritos en la presente. Una metodología general para la síntesis de las isoquinolinas se muestra en el esquema de reacción XII, en donde los derivados de ácido cinámico, mostrados en la forma general como la estructura (2), se convierten a 1-cloroisoquinolinas en un

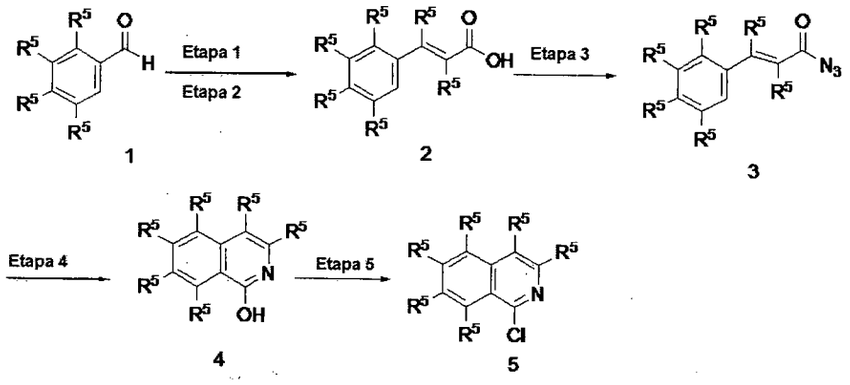
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proceso de cuatro etapas. Las cloroisoquinolinas pueden posteriormente usarse en reacciones de acoplamiento a los derivados de C4-hidroxiprolina como se describe en la presente. La conversión de ácidos cinámicos a cloroquinolinas inicia con el tratamiento del ácido cinámico con un alquilcloroformiato en la presencia de una base. El anhídrido resultante luego se trató con azida de sodio la cual resulta en la formación de una acilazida (3) como se muestra en el esquema de reacción. Los métodos alternativos están disponibles para la formación de acilazidas a partir de ácidos carboxílicos como por ejemplo el ácido carboxílico puede tratarse con difenilfosforilazida (DPPA) en un solvente aprótico tal como cloruro de metileno en la presencia de una base. En la siguiente etapa de la secuencia de reacción la acilazida (3) se convierte a la isoquinolona correspondiente (4) mientras se calienta a unatemperatura de aproximadamente 190°C en un solvente de alto punto de ebullición tal como difenilmetano. Esta reacción es general y proporciona rendimientos moderados a buenos de isoquinolona substituida de los derivados de ácido cinámico correspondientes. Se deberá notar que los derivados del ácido cinámico están comercialmente disponibles o pueden obtenerse del derivado de benzaldehído (1) correspondiente por la condensación directa con ácido malónico o derivados de los mismos y también al emplear una reacción de Wittig. Los intermediarios de

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isoquinolonas (4) del Esquema de reacción XII pueden convertirse a la 1-cloroisoquinolina por el tratamiento con oxicloruro de fósforo. Esta reacción es general y puede aplicarse a las isoquinolonas mostradas en la presente.

Esquema de reacción XII

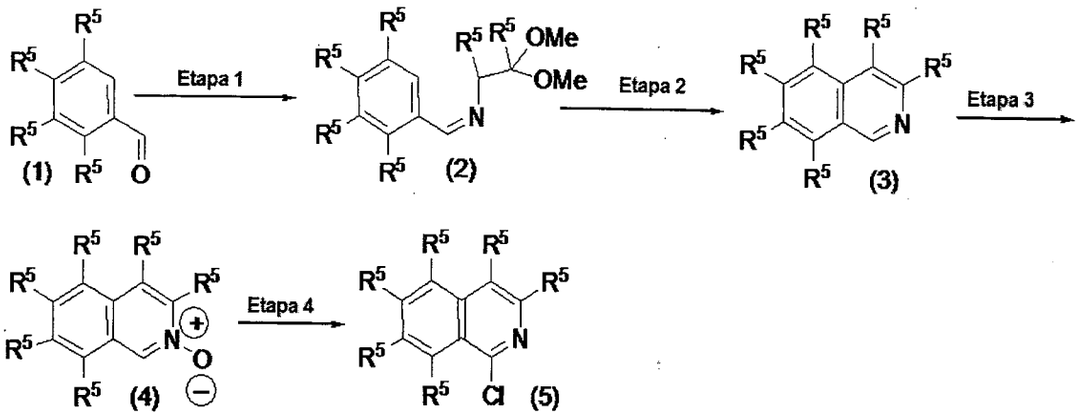


Referencia: N. Briet at al, Tetrahedron, 2002, 5761

Un método alternativo para la síntesis del sistema de anillo de isoquinolina es el procedimiento Pomeranz-Fritsh. Este método general se resume en el Esquema de reacción XIII. Los procesos comienzan con la conversión de un derivado de benzaldehído (1) a una imina funcionalizada (2). La imina luego se convierte al sistema de anillo de isoquinolina por el tratamiento con ácido a temperatura elevada. Esta síntesis de isoquinolina del Esquema de reacción XIII es general, y deberá notarse que este proceso es particularmente útil en producir intermediarios isoquinolina que se substituyen en la posición C8. Los intermediarios de isoquinolinas (3) pueden convertirse a

las 1-cloroquinolinas correspondientes (5) en un proceso de dos etapas como se muestra. La primera etapa en esta secuencia es la formación del N-óxido de isoquinolina (4) por el tratamiento de isoquinolina (3) con ácido meta-cloroperbenzoico en un solvente aprótico tal como diclorometano. El intermediario (4) puede convertirse a la 1-cloroquinolina correspondiente por el tratamiento con oxicloruro de fósforo en cloroformo a reflujo. Nótese que este procesos de dos etapas es general para la formación de cloroisoquinolinas a partir de isoquinolonas.

Esquema de reacción XIII



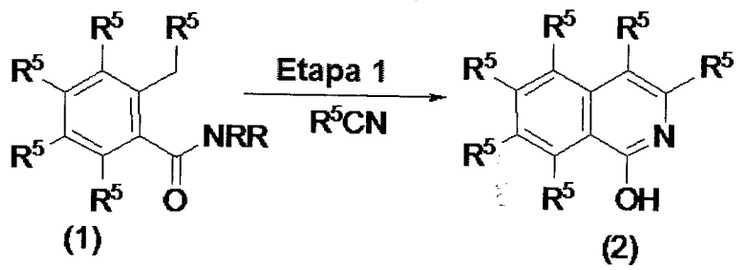
Síntesis Pomeranz-Fritsch
K. Hirao, R. Tsuchiya, Y. Yano, H. Tsue, Heterocycles 42(1) 1996, 415-422

Otro método para la síntesis del sistema de anillo de isoquinolina se muestra en el esquema de reacción XIV. En este proceso un derivado de orto-alquilbenzamida (1) se trata con una base fuerte tal como terc-butil-litio en un solvente tal como THF a temperatura baja. A esta mezcla de

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reacción luego se agrega un derivado de nitrilo, bajo una reacción de adición con el anión derivado de la desprotonación de (1), conduciendo a la formación de (2). Esta reacción es general y puede usarse por la formación de isoquinolinas substituidas. El intermediario (2) del Esquema de reacción XIV puede convertirse a la 1-cloroquinolina correspondiente por los métodos descritos en la presente.

Esquema de reacción XIV

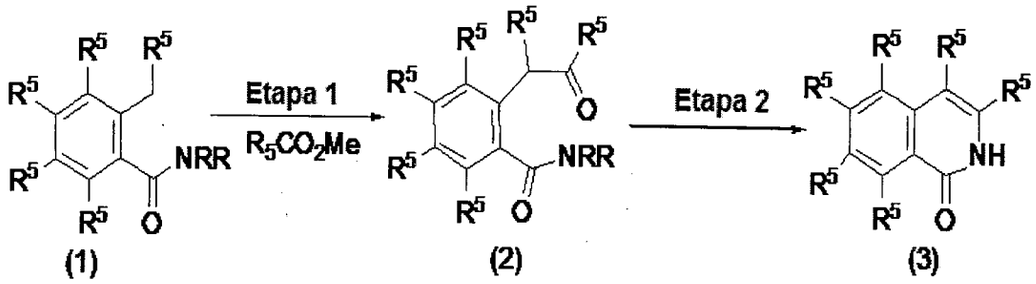


Un método adicional para la síntesis de las isoquinolinas se muestra en el esquema de reacción XV. La desprotonación del intermediario (1) usando terc-butil-litio se describe arriba. En el presente método sin embargo, el anión intermediario se atrapa por un éster, conduciendo a la formación del intermediario (2) como se muestra a continuación. En una reacción posterior, la cetona (2) se condensa con acetato de amonio a temperatura elevada proporcionan la formación de quinolona (3). Esta reacción es general y puede aplicarse

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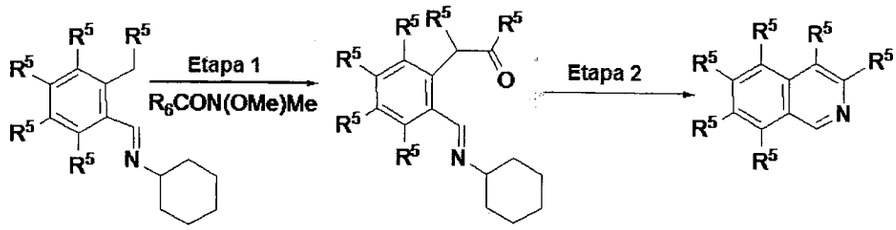
para la construcción de isoquinolonas substituidas las cuales pueden luego convertirse a las 1-cloroisoquinolinas correspondientes como se describen en la presente.

Esquema de reacción XV



Otro método para la construcción de isoquinolinas se encuentra en el Esquema de reacción XVI. En la primera etapa de este proceso un derivado de orto-alquilarilimina tal como (1) se somete a condiciones de desprotonación (sec-butil litio, THF) y el anión resultante se apaga por la adición de un derivado de ácido carboxílico activado tal como una amida Weinreb. La cetoimina resultante (2) puede convertirse a la isoquinolina correspondiente por la condensación con acetato de amonio a temperaturas elevadas. Este método es general y puede usarse para la síntesis de isoquinolinas substituidas. Las isoquinolinas pueden convertirse a la 1-cloroquinolina correspondiente por los métodos descritos en la presente.

Esquema de reacción XVI

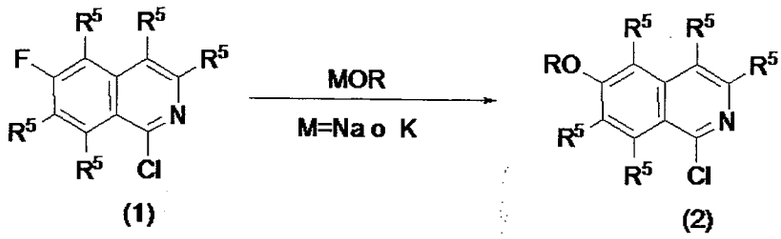


L. Flippin, J. Muchowski, JOC, 1993, 2631-2632

Las isoquinolinas descritas en la presente, y las cuales se incorporan en los compuestos de la fórmula (I), pueden además funcionalizarse. Es obvio para alguien experto en el arte que la funcionalización adicional de los heterociclos puede hacerse ya sea antes o después de la incorporación de estas funcionalidades en los compuestos de la fórmula (I). Los siguientes esquemas de reacción ilustran este punto. Por ejemplo el Esquema de reacción XVII muestra la conversión de una 1-cloro-6-fluoro-isoquinolina a la especie 1-cloro-6-alcoxi-isoquinolina correspondiente, por el tratamiento de (1) con una especie de alcóxido de sodio o potasio en el solvente de alcohol del cual el alcóxido se deriva a temperatura ambiente. En algunos casos puede ser necesario para calentar la reacción para llevarla hasta que se complete. La cloroquinolina puede incorporarse en un compuesto de la fórmula (I) usando el arte descrito en la presente.

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Esquema de reacción XVII

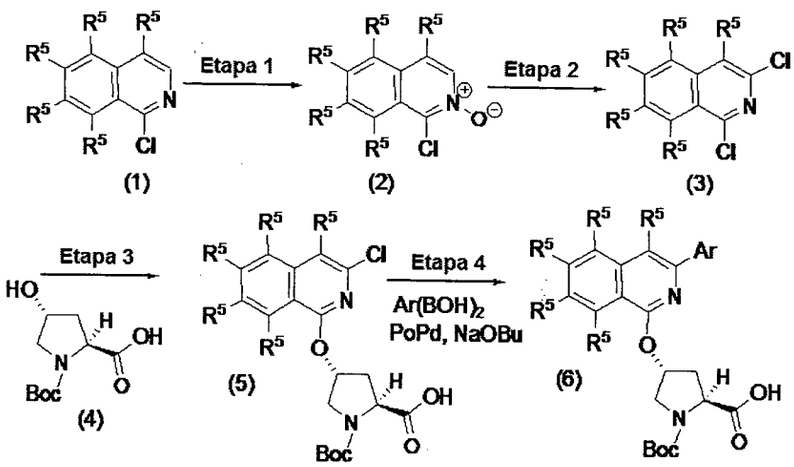


El esquema de reacción XVIII proporciona un ejemplo general para la modificación de isoquinolinas como se define en la presente al emplear reacciones de acoplamiento mediadas por paladio. Los acoplamientos pueden emplearse para funcionalizar un heterociclo en cada posición del sistema de anillo proporcionando el anillo que es activado o funcionalizado adecuadamente, como por ejemplo con un cloruro como se muestra en el esquema de reacción. Esta secuencia comienza con 1-cloroisoquinolina (1) la cual durante el tratamiento con ácido metacloroperbenzoico puede convertirse al N-óxido (2) correspondiente. El intermediario (2) puede convertirse a la 1,3-dicloroisoquinolina correspondiente (3) por el tratamiento con oxicloruro de fósforo en cloroformo a reflujo. El Intermediario (3) puede acoplarse con N-Boc-4-hidroxiprolina por los métodos descritos en la presente para proporcionar el intermediario (5) como se muestra en el esquema de reacción. El Intermediario (5) puede experimentar un acoplamiento de Suzuki con un ácido aril borónico, en la presencia de un reactivo de paladio y una base, y en un

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solvente tal como THF o tolueno o DMF para proporcionar el intermediario de C3-arilisoquinolina (6). Los ácidos heteroarilborónicos pueden también emplearse en estos procesos de acoplamiento mediado por paladio para proporcionar C3-heteroarilisoquinolinas. El Intermediario (6) puede convertirse en los compuestos finales de la fórmula (I) por los métodos descritos en la presente.

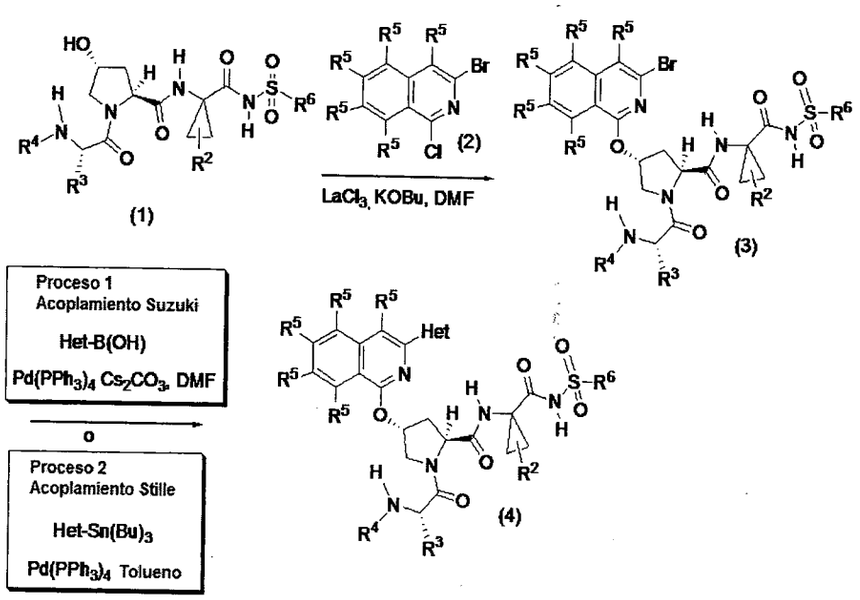
Esquema de reacción XVIII



Los acoplamientos mediados con paladio de los sistemas de isoquinolina con elementos de arilo o heteroarilo pueden también emplearse en una etapa sintética posterior en la construcción de los compuestos de la fórmula (I) como se muestra en el Esquema de reacción XIX. El intermediario detripéptido de acilsulfonamida (1) se acopla a una 1-cloro-3-bromoisoquinolina (2) usando los procesos previamente descritos para proporcionar el intermediario (3). El

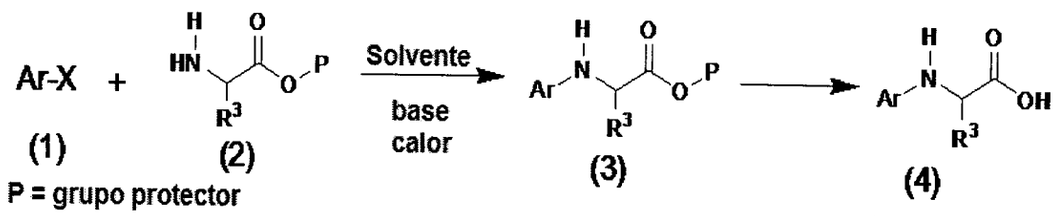
acoplamiento de (1) y (2) es más eficiente en la presencia de un catalizador tal como cloruro de lantano como se describe en la presente. El sistema de anillo de isoquinolina del intermediario (3) puede además funcionalizarse al emplearse ya sea acoplamientos deSuzuki (Proceso 1: se somete (3) a ácidos heteroaril o aril borónicos en la presencia de un catalizador de paladio tal como tetraquistrifenilfosfina paladio y una base tal como carbonato de cesio en solventes tales como DMF) o acoplamientos de Stille (Proceso 2: se somete (3) a heterarilo o derivados de aril estaño en la presencia de un catalizador de paladio tal como tetraquistrifenilfosfina paladio en solventes tales como tolueno).

Esquema de reacción XIX



Los aminoácidos P3 empleados en la presente invención están ya sea comercialmente disponibles o pueden prepararse usando métodos conocidos por aquellos expertos en el arte. Las rutas no limitantes para la preparación del aminoácido P3 incluyen: Ruta 1: substitución aromática nucleofílica de una especie aromática o heteroaromática suficientemente electrofílica (1) con un aminoácido éster (2) como se muestra en el Esquema de reacción XX. Esta reacción luego sigue por un desdoblamiento de éster simple del 3 para proporcionar el aminoácido deseado (4).

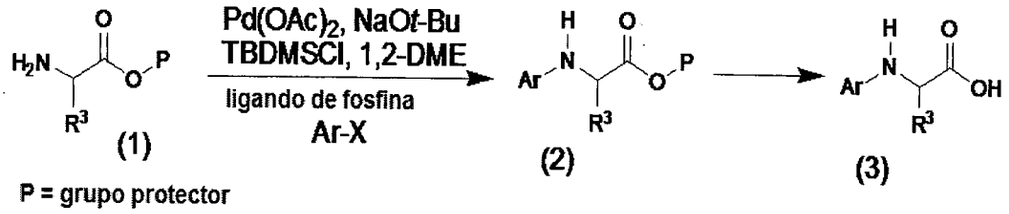
Esquema de reacción XX



Ruta 2: Una reacción tipo Buchwald-Hartwig la cual involucra el acoplamiento del catalizador de paladio en arilo o haluro de heteroarilo enlazado con un aminoácido adecuadamente protegido (1) como se muestra en el Esquema de reacción XXI. La saponificación sencilla del intermediario 2 proporciona el aminoácido deseado (3). (Shen, Q.; Shekhar, S; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2005**, *44*, 1371-1375.):

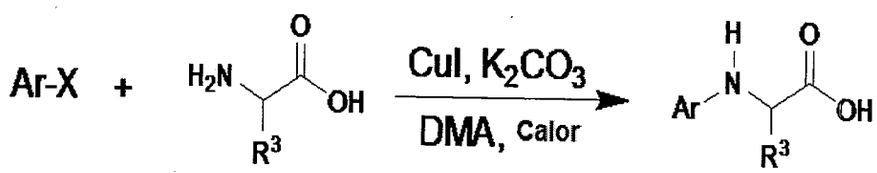
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Esquema de reacción XXI

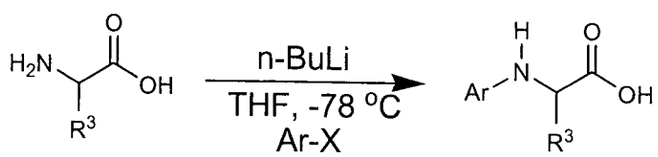


Ruta 3: Un proceso de acoplamiento por el cual un haluro de arilo o heteroarilo y un aminoácido libre se acoplan por medio de un proceso mediado por CuI para dar el arilaminoácido directamente como se muestra en el Esquema de reacción XXII (Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459-12467.)

Esquema de reacción XXII



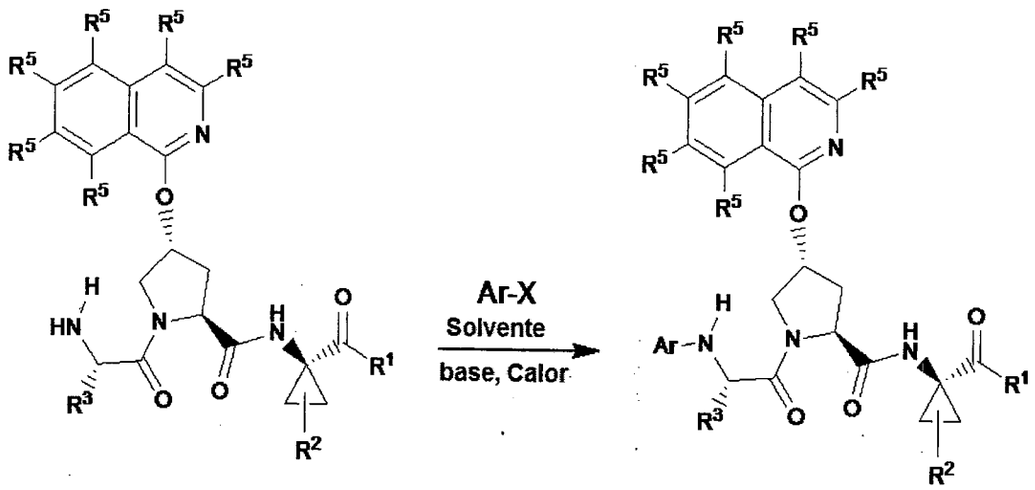
Ruta 4: Un proceso el cual emplea desplazamiento nucleofílico del dianión de un aminoácido libre y un arilo o haluro de heteroarilo, típicamente un fluoruro (similar a Saitton, S.; Kihlberg, J.; Luthman, K. *Tetrahedron* **2004**, *60*, 6113-6120.):



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En algunos casos, como se muestra en el Esquema de reacción XXIII, para tener acceso a los productos de aminoarilo finales puede llevarse a cabo una substitución aromática nucleofílica directa de un anillo de arilo con un tripéptido de núcleo completamente ensamblado que tiene un grupo amino libre en la terminal de la subregión P3.

Esquema de reacción XXIII



EJEMPLOS

La presente descripción se describe ahora en conexión con ciertas modalidades que no se pretende que limiten su alcance. Por el contrario, la presente descripción cubre todas las alternativas, modificaciones y equivalentes como se pueden incluir dentro del alcance de las reivindicaciones. Así, los siguientes ejemplos, los cuales incluyen modalidades específicas, deberán ilustrar una práctica de la presente

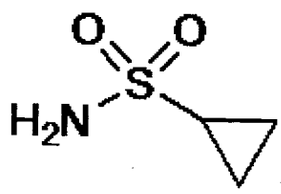
descripción, se entenderá que los ejemplos son para los propósitos de ilustración de ciertas modalidades y se presentan para proporcionar lo que se considera la descripción más útil y fácilmente entendible de sus procedimientos y aspectos conceptuales.

Los porcentajes de la solución expresan una relación peso a volumen, y las relaciones de la solución que expresan una relación volumen a volumen, a menos de que se especifique de otra manera. El espectro de resonancia magnética nuclear (RMN) se registra ya sea en un espectrómetro Bruker 300, 400 ó 500 MHz, los cambio químicos (δ) se reportan en partes por millón. La cromatografía instantánea se lleva a cabo en gel de sílice (SiO_2) de conformidad a las técnicas de cromatografía instantánea Still (J. Org. Chem. 1978,43, 2923).

I. Preparación de los Intermediarios P1`

1. Preparación de ciclopropilsulfonamida

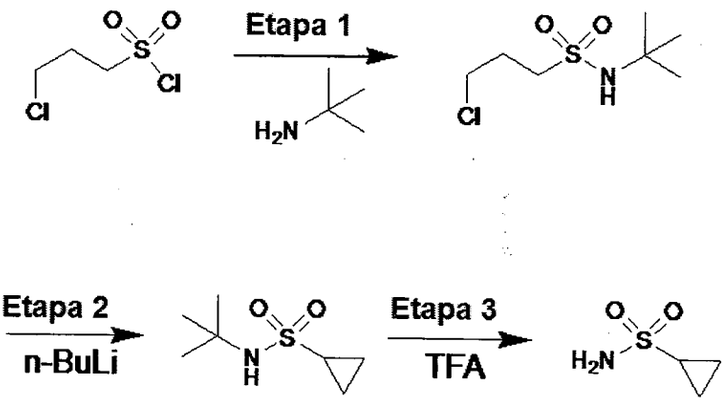
Método 1:



ciclopropilsulfonamida

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Esquema de reacción 1



Etapa 1:

La terc-Butilamina (3.0 mol, 315 mL) se disolvió en THF (2.5 L). La solución se enfrió a -20°C. El cloruro de 3-cloropropansulfonilo (1.5 mol, 182 mL) se agregó lentamente. La mezcla de reacción se permitió calentar a temperatura ambiente y se agitó durante 24 horas. La mezcla se filtró y el filtrado se concentró *in vacuo*. El residuo se disolvió en CH_2Cl_2 (2.0 L). La solución resultante se lavó con HCl 1.0M (1.0 L), agua (1.0 L), y salmuera (1.0 L), se secó sobre Na_2SO_4, se filtró y se concentró *in vacuo* para dar un sólido ligeramente amarillo, el cual se cristalizó a partir de hexano para proporcionar el producto como un sólido blanco (316.0 g, 99%). ^1H RMN ($CDCl_3$) δ 1.38 (s, 9H), 2.30-2.27 (m, 2H), 3.22 (t, *J* = 7.35 Hz, 2H), 3.68 (t, *J* = 6.2 Hz, 2H), 4.35 (a,

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1H).

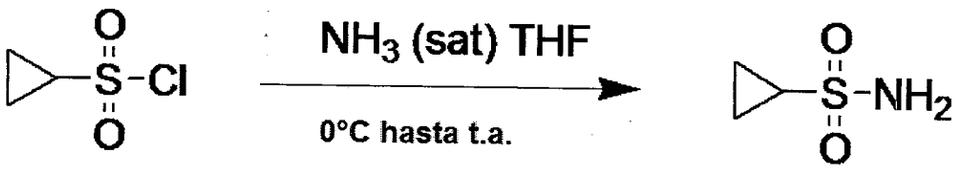
Etapa 2:

A una solución del producto de la Etapa 1 (2.14 g, 10.0 mmol) en THF (100 mL) se agregó n-BuLi (2.5 M en hexano, 8.0 mL, 20.0 mmol) a -78°C. La mezcla de reacción se permitió calentar hasta temperatura ambiente durante un periodo de 1 hora y se concentró *in vacuo*. El residuo se dividió entre acetato de etilo y agua (200 mL cada uno). La fase orgánica separada se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró *in vacuo*. El residuo se recristalizó a partir de hexano para proporcionar el producto deseado como un sólido blanco (1.0 g, 56%). ^{1}H RMN ($CDCl_3$) δ 0.98-1.00 (m, 2H), 1.18-1.19 (m, 2H), 1.39 (s, 9H), 2.48-2.51 (m, 1H), 4.19 (a, 1H).

Etapa 3:

Una solución del producto de la Etapa 2 (110 g, 0.62 mmol) en TFA (500 mL) se agitó a temperatura ambiente durante 16 horas. Los materiales volátiles se removieron *in vacuo*. El residuo se recristalizó a partir de acetato de etilo/hexano (60 mL/240 mL) para proporcionar el producto deseado como un sólido blanco (68.5 g, 91%). ^{1}H RMN (DMSO-d_6) δ 0.84-0.88 (m, 2H), 0.95-0.98 (m, 2H), 2.41-2.58 (m, 1H), 6.56 (a, 2H).

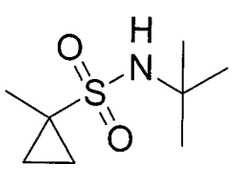
Método 2:



A una solución de 100 mL de THF enfriada a 0°C se burbujeó en amoniaco gaseoso hasta que la saturación se alcanzó. A esta solución se agregó una solución de 5 g (28.45 mmol) de cloruro de ciclopropilsulfonilo (adquirido de Array Biopharma) en 50 mL de THF. La solución se calentó a temperatura ambiente durante la noche y se agitó un día adicional. La mezcla se concentró hasta 1-2 mL del solvente restante y se vació en un tapón de 30 g de SiO_2 (eluido con 30% hasta 60% acetato de etilo/hexanos) para proporcionar 3.45g (100%) de la ciclopropilsulfonamida como un sólido blanco. ^1H RMN (metanol-d_4) δ 0.94-1.07 (m, 4H), 2.52-2.60 (m, 1H); ^{13}C RMN (metanol-d_4) δ 5.92, 33.01.

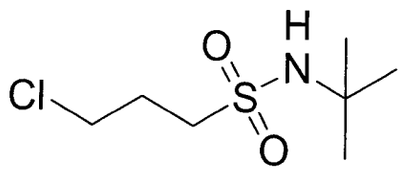
2. Preparación de ciclopropilsulfonamidas C1-substituidas

2a. Preparación de *N-terc*-Butil-(1-metil)ciclopropil-sulfonamida



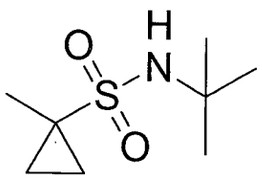
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Etapa 1: Preparación de *N-terc*-Butil-(3-cloro)propilsulfonamida



Preparado como se describe arriba.

Etapa 2: Preparación de *N-terc*-Butil-(1-metil)ciclopropil-sulfonamida

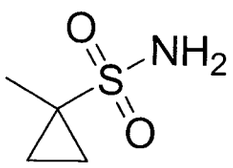


Una solución del producto de la Etapa 1 (4.3 g, 20 mmol) se disolvió en THF seco (100 mL) y se enfrió a -78°C. A esta solución se agregó *n*-butil-litio (17.6 mL, 44 mmol, 2.5M en hexano) lentamente. El baño de hielo seco se removió y la mezcla de reacción se calentó a temperatura ambiente durante un periodo de 1.5 horas. Esta mezcla se enfrió a -78 °C y una solución de *n*-butil-litio (20 mmol, 8 mL, 2.5M en hexano) se agregó. La mezcla de reacción se calentó a temperatura ambiente, se enfrió a -78°C durante un periodo de 2 horas, y se trató con una solución pura de yoduro de metilo (5.68 g, 40 mmol). La mezcla de reacción se calentó a temperatura ambiente durante la noche, luego

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se apagó con NH_4Cl saturado (100 mL) a temperatura ambiente y luego se extrajo con acetato de etilo (100 mL). La fase orgánica se lavó con salmuera (100 mL), se secó ($MgSO_4$), se filtró y se concentró *in vacuo* para proporcionar un aceite amarillo el cual se cristalizó a partir de hexano para proporcionar el producto deseado como un sólido ligeramente amarillo (3.1 g, 81%): ^1H RMN ($CDCl_3$) δ 0.79 (m, 2H), 1.36 (s, 9H), 1.52 (m, 2H), 1.62 (s, 3H), 4.10 (s a, 1H).

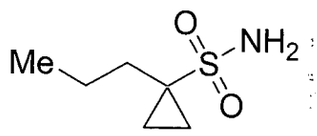
Etapa 3: Preparación de 1-metilciclopropilsulfonamida



Una solución del producto de la Etapa 2 (1.91 g, 10 mmol) se disolvió en TFA (30 mL), y la mezcla de reacción se agitó a temperatura ambiente durante 16 horas. El solvente se removió *in vacuo* para proporcionar un aceite amarillo el cual se cristalizó a partir de acetato de etilo/hexano (1:4, 40 mL) para proporcionar el producto deseado como un sólido blanco (1.25 g, 96%): ^1H RMN ($CDCl_3$) δ 0.84 (m, 2H), 1.41 (m, 2H), 1.58 (s, 3H), 4.65 (s a, 2H). Análisis calculado para $C_4H_9NO_2S$: C, 35.54; H, 6.71; N, 10.36. Encontrado: C, 35.67; H, 6.80; N, 10.40.

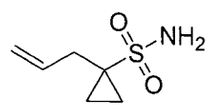
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2b. Preparación de 1-propilciclopropilsulfonamida

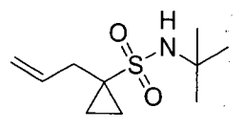


Este compuesto se preparó usando el procedimiento descrito para la preparación de 1-metilciclopropilsulfonamida substituyendo haluro de propilo por yoduro de metilo en la segunda etapa de este proceso.

2c. Preparación de 1-alilciclopropilsulfonamida



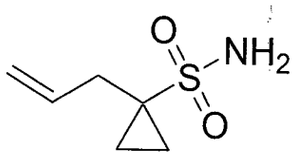
Etapa 1: Preparación de *N-terc*-Butil-(1-alil)ciclopropilsulfonamida



Este compuesto se obtuvo con 97% de rendimiento de conformidad al procedimiento descrito en la síntesis de *N-terc*-Butil-(1-metil)ciclopropilsulfonamida usando 1.25 equivalentes de bromuro de alilo como el electrófilo. El compuesto se usó en la siguiente reacción sin purificación adicional: ^{1}H RMN ($CDCl_3$) δ 0.83 (m, 2H), 1.34 (s, 9H), 1.37 (m, 2H), 2.64 (d, J = 7.3 Hz, 2H), 4.25 (s a, 1H), 5.07-5.10 (m, 2H), 6.70-6.85 (m, 1H).

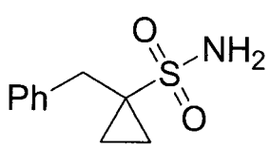
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Etapa 2: Preparación de 1-alilciclopropilsulfonamida

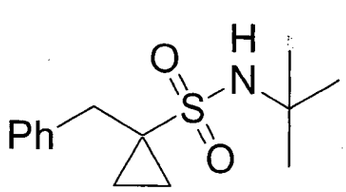


Este compuesto se obtuvo con 40% de rendimiento del producto de la Etapa 1 de conformidad al procedimiento descrito en la síntesis de 1-metilciclopropilsulfonamida. El compuesto se purificó por cromatografía de columna sobre SiO_2 usando 2% metanol en diclorometano como el eluyente: ^1H RMN ($CDCl_3$) δ 0.88 (m, 2H), 1.37 (m, 2H), 2.66 (d, *J*=7.0 Hz, 2H), 4.80 (s, 2H), 5.16 (m, 2H), 5.82 (m, 1H); ^{13}C RMN ($CDCl_3$) δ 11.2, 35.6, 40.7, 119.0, 133.6.

2d. Preparación de 1-Bencilciclopropilsulfonamida



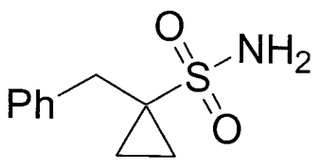
Etapa 1: Preparación de *N-terc*-Butil-(1-Bencil)ciclopropil-sulfonamida.



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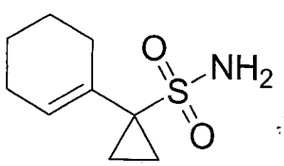
Este compuesto se obtuvo con 60% de rendimiento usando el procedimiento descrito para la síntesis de *N-terc*-Butil-(1-metil)ciclopropilsulfonamida excepto que 1.05 equivalentes de bromuro de bencilo se usaron, seguido por trituración con 10% acetato de etilo en hexano: ^{1}H RMN ($CDCl_3$) δ 0.92 (m, 2H), 1.36 (m, 2H), 1.43 (s, 9H), 3.25 (s, 2H), 4.62 (s a, 1H), 7.29-7.36 (m, 5H).

Etapa 2: Preparación de 1-Bencilciclopropilsulfonamida



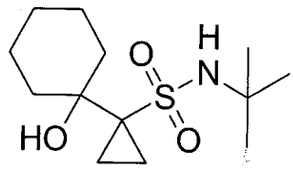
Este compuesto se obtuvo con 66% de rendimiento de (1-Bencil)ciclopropilsulfonamida de *N-terc*-Butilo usando el procedimiento descrito para la síntesis de 1-metilciclopropilsulfonamida, seguido por recristalización de la cantidad mínima de 10% acetato de etilo en hexano: ^{1}H RMN ($CDCl_3$) δ 0.90 (m, 2H), 1.42 (m, 2H), 3.25 (s, 2H), 4.05 (s, 2H), 7.29 (m, 3H), 7.34 (m, 2H); ^{13}C RMN ($CDCl_3$) δ 11.1, 36.8, 41.9, 127.4, 128.8, 129.9, 136.5.

2e. Preparación de 1-(1-ciclohexenil)ciclopropil-sulfonamida



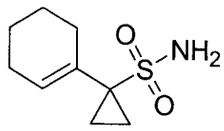
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Etapa 1: Preparación de *N-terc*-Butil-[1-(1-hidroxi)ciclohexil]-ciclopropilsulfonamida



Este compuesto se obtuvo con 84% de rendimiento usado por el procedimiento descrito para la síntesis de *N-terc*-Butil-(1-metil)ciclopropilsul-fonamida excepto que 1.30 equivalentes de ciclohexanona se usaron, seguido por recristalización de la cantidad mínima de 20% acetato de etilo en hexano: ^{1}H RMN ($CDCl_3$) δ 1.05 (m, 4H), 1.26 (m, 2H), 1.37 (s, 9H), 1.57-1.59 (m, 6H), 1.97 (m, 2H), 2.87 (s a, 1H), 4.55 (s a, 1H).

Etapa 2: Preparación de 1-(1-ciclohexenil)ciclopropil-sulfonamida

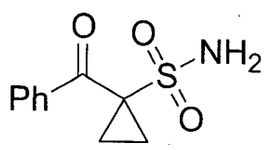


Este compuesto, la 1-(1-ciclohexenil)-ciclopropilsulfonamida se obtuvo con 85% de rendimiento de *N-terc*-Butil-[1-(1-hidroxi)ciclohexil]-ciclopropilsulfonamida usando el procedimiento descrito para la síntesis de 1-metilciclopropilsulfonamida, seguido por recristalización de la cantidad mínima de

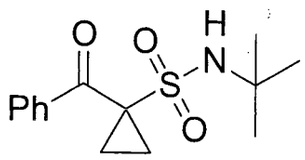
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acetato de etilo y hexano: ^{1}H RMN (DMSO-d_6) δ 0.82 (m, 2H), 1.28 (m, 2H), 1.51 (m, 2H), 1.55 (m, 2H), 2.01 (s, 2H), 2.16 (s, 2H), 5.89 (s, 1H), 6.46 (s, 2H); ^{13}C RMN (DMSO-d_6) δ 11.6, 21.5, 22.3, 25.0, 27.2, 46.9, 131.6, 132.2; EM-BR (ESI): 200 (M^+-1).

2f. Preparación de 1-benzoilciclo-propilsulfonamida



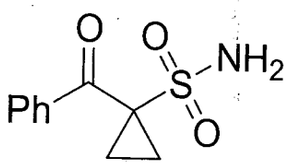
Etapa 1: Preparación de *N-terc*-Butil-(1-benzoil)ciclopropil-sulfonamida



Este compuesto se obtuvo con 66% de rendimiento usando el procedimiento descrito para la síntesis de *N-terc*-Butil-(1-metil)ciclopropilsulfonamida excepto que 1.2 equivalentes de benzoato de metilo se usó como el electrófilo. El compuesto se purificó por cromatografía de columna sobre SiO_2 usando 30% hasta 100% diclorometano en hexano: ^{1}H RMN ($CDCl_3$) δ 1.31 (s, 9H), 1.52 (m, 2H), 1.81 (m, 2H), 4.16 (s a, 1H), 7.46 (m, 2H), 7.57 (m, 1H), 8.05 (d, J = 8.5 Hz, 2H).

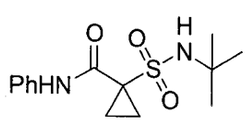
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Etapa 2: Preparación de 1-benzoilciclo-propilsulfonamida



Este compuesto se obtuvo con 87% de rendimiento de *N-terc*-Butil(1-benzoil)ciclopropilsul-fonamida usando el proceso descrito para la síntesis de 1-metilciclopropilsulfonamida, seguido por recristalización de la cantidad mínima de acetato de etilo en hexano: ^{1}H RMN (DMSO-d_6) δ 1.39 (m, 2H), 1.61 (m, 2H), 7.22 (s, 2H), 7.53 (t, *J*=7.6 Hz, 2H), 7.65 (t, *J*=7.6 Hz, 1H), 8.06 (d, *J*=8.2 Hz, 2H); ^{13}C RMN (DMSO-d_6) δ 12.3, 48.4, 128.1, 130.0, 133.4, 135.3, 192.0.

2g. Preparación de *N-terc*-Butil-(1-fenilaminocarboxi)-ciclopropilsulfonamida



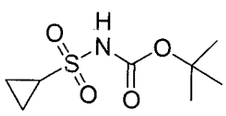
Este compuesto se obtuvo con 42% de rendimiento usando el procedimiento descrito para la síntesis de *N-terc*-Butil-(1-metil)ciclopropilsulfonamida usando 1 equivalente de fenilisocianato, seguido por recristalización de la

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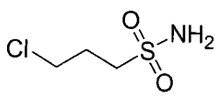
cantidad mínima de acetato de etilo en hexano ^{1}H RMN ($CDCl_3$) δ 1.38 (s, 9H), 1.67-1.71 (m, 4H), 4.30 (s a, 1H), 7.10 (t, J = 7.5 Hz, 1H), 7.34 (t, J = 7.5 Hz, 2H), 7.53 (t, J = 7.5 Hz, 2H).

3. Preparación de ciclopropansulfonamidas C-1 substituidas: El uso de un grupo *N*-Boc protegido

3a. Preparación de carbamato de terc-butilo de ciclopropilsulfonilamina, un intermediario clave en la preparación de ciclopropilsulfonamidas C1-substituidas



Etapa 1: Preparación de 3-cloropropilsulfonamida

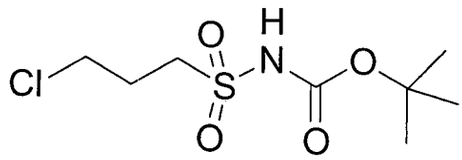


Una solución de cloruro de 3-cloropropansulfonilo (55 g, 310.7 mmol) se disolvió en THF (200 mL) y se agregó gota a gota durante 30 minutos a una solución de NH_4OH (200 mL) a 0°C. La mezcla de reacción se calentó a temperatura ambiente, se agitó 1 hora, y la capa acuosa se extrajo con diclorometano (4 x 500 mL). Los extractos combinados se lavaron con HCl 1N (150 mL), agua (150 mL), se secaron sobre $MgSO_4$, se filtraron y se concentraron *in vacuo*. El sólido sin refinar se recristalizó a partir de la cantidad

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mínima de diclorometano en hexanos para proporcionar el producto deseado como un sólido blanco (45.3 g, 93%). ^{1}H RMN ($CDCl_3$) δ 2.34 (m, 2H), 3.32 (t, *J*=7.3 Hz, 2H), 3.70 (t, *J*=6.2 Hz, 2H), 4.83 (s, 2H); ^{13}C RMN ($CDCl_3$) δ 27.10, 42.63, 52.57.

Etapa 2: Preparación de *terc*-Butilcarbamato de 3-cloropropilsulfonilamina

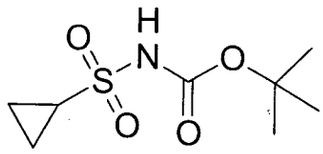


Una solución del producto de la Etapa 1 (30.2 g, 191.5 mmol), trietilamina (30.2 mL, 217.0 mmol), y 4-DMAP (2.40g, 19.6 mmol) en diclorometano (350 mL) a 0°C se trató gota a gota con una solución de di-*terc*-Butildicarbonato (47.2g, 216.9 mmol) en diclorometano (250 mL) durante 30 minutos. La mezcla de reacción se calentó a temperatura ambiente, se agitó 3 horas adicionales, y se lavó con HCl 1N (300 mL), agua (300 mL), y salmuera (300 mL), se secó sobre $MgSO_4$, se filtró y se concentró *in vacuo* para proporcionar el producto sin refinar. Este material se trituró con 70 mL de 5% diclorometano en hexanos para proporcionar el producto deseado como un sólido blanco opaco (47.2 g, 96%): ^{1}H RMN ($CDCl_3$) δ 1.51 (s, 9H), 2.33 (m, 2H), 3.60 (t, *J*=7.3 Hz, 2H),

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3.68 (t, *J*=6.21 Hz, 2H); ^{13}C RMN ($CDCl_3$) δ 26.50, 27.95, 42.37, 50.40, 84.76, 149.53.

Etapa 3: Preparación de carbamato de *terc*-Butilo de ciclopropilsulfonilamina

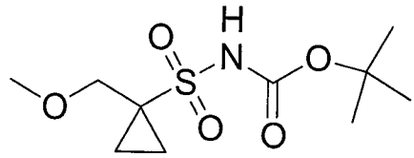


Una solución de *n*-butil-litio (74.7 mL, 119.5 mmol, 1.6M en hexano) se disolvió en THF seco (105 mL) y se enfrió a -78°C bajo una atmósfera de argón. A esta solución se agregó una solución del producto de la Etapa 2 (14 g, 54.3 mmol) en THF seco (105 mL) gota a gota durante 20-30 minutos. El baño de hielo seco se removió y la mezcla de reacción se permitió calentar a temperatura ambiente durante un periodo de 2 horas. La mezcla de reacción se apagó con ácido acético glacial (3.4 mL), se concentró *in vacuo*, y se dividió entre diclorometano (100 mL) y agua (100 mL). La fase orgánica se lavó con salmuera (100 mL), se secó ($MgSO_4$), se filtró y se concentró *in vacuo* para proporcionar el producto deseado como un sólido blanco opaco ceroso (12.08 g, 100%): ^1H RMN ($CDCl_3$) δ 1.10 (m, 2H), 1.34 (m, 2H), 1.50 (s, 9H), 2.88 (m, 1H), 7.43 (s, 1H). ^{13}C RMN ($CDCl_3$) δ 6.21, 28.00, 31.13, 84.07, 149.82.

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3b. Preparación de 1-metoxi-metilciclopropi-sulfonamida

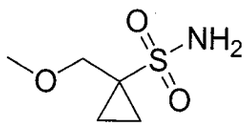
Etapa 1: Preparación de *terc*-Butilcarbamato de 1-metoximetilciclopropilsulfonilamina



A una solución de carbamato de *terc*-Butilo de ciclopropilsulfonilamina (1.0 g, 4.5 mmol) se disolvió en THF (30 mL) se enfrió a -78°C, se agregó *n*-butil-litio (6.4 mL, 10.2 mmol, 1.6M en hexano) y la mezcla de reacción se agitó durante 1 hora. A esta solución se agregó una solución pura de éter clorometil metílico (0.40 mL, 5.24 mmol), y la mezcla se permitió calentar lentamente a temperatura ambiente durante la noche. El pH de la solución se ajustó hasta 3 usando HCl acuoso 1N y luego se extrajo con acetato de etilo (4 x 50 mL porciones). Los extractos combinados se secaron ($MgSO_4$), se filtraron y se concentraron para proporcionar *terc*-Butilcarbamato de 1-metoximetilciclopropilsulfonilamina, como un sólido ceroso (1.20 g, 100%) el cual se tomó directamente en la siguiente reacción sin purificación adicional: ^1H RMN ($CDCl_3$) δ 1.03 (m, 2H), 1.52 (s, 9H), 1.66 (m, 2H), 3.38 (s, 3H), 3.68 (s, 2H), 7.54 (s, 1H); ^{13}C RMN ($CDCl_3$) δ 11.37, 28.29, 40.38, 58.94, 73.43, 83.61, 149.57.

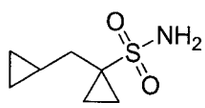
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Etapa 2: Preparación de 1-metoximetilciclopropisulfonamida

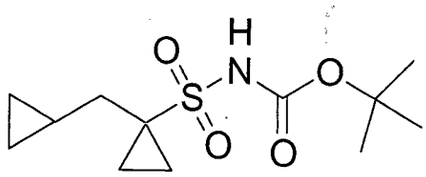


Una solución de *terc*-Butilcarbamato de 1-metoximetilciclopropilsulfonilamina (1.14 g, 4.30 mmol) se disolvió en una solución de 50% TFA/diclorometano (30 mL) y se agitó se agitó a temperatura ambiente durante 16 horas. El solvente se removió *in vacuo* y el residuo se procesó por cromatografía sobre 80g de SiO_2 (eluído con 0% hasta 60% acetato de etilo/hexanos hasta 1-metoximetilciclopropilsulfonamida como un sólido blanco (0.55 g, 77% de rendimiento general sobre dos etapas): ^1H RMN ($CDCl_3$) δ 0.95 (m, 2H), 1.44 (m, 2H), 3.36 (s, 3H), 3.65 (s, 2H), 4.85 (s, 2H); ^{13}C RMN ($CDCl_3$) δ 11.17, 40.87, 59.23, 74.80; LRMS m/z 183 (M^++NH_4).

3c. Preparación de 1-ciclopropilmetilciclopropilsulfonamida



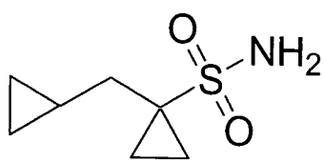
Etapa 1: Preparación de *terc*-Butilcarbamato de 1-ciclopropilmetilciclopropilsulfonilamina



000418

El *terc*-Butilcarbamato de 1-Ciclopropilmetilciclopropilsulfonilamina se obtuvo con 92% de rendimiento de conformidad al procedimiento descrito en la síntesis de *terc*-Butilcarbamato de 1-metoximetilciclopropilsulfonilamina, excepto que 1.10 equivalentes de bromuro de ciclopropilmetilo se usaron como electrófilo. El compuesto se tomó directamente en la siguiente reacción sin purificación: ^{1}H RMN ($CDCl_3$) δ 0.10 (m, 2H), 0.51 (m, 2H), 0.67 (m, 1H), 1.10 (m, 2H), 1.49 (s, 9H), 1.62 (m, 2H), 1.87 (d, *J*=7.0 Hz, 2H).

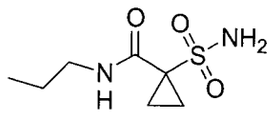
Etapa 2: Preparación de 1-ciclopropilmetil-ciclopropilsulfonamida



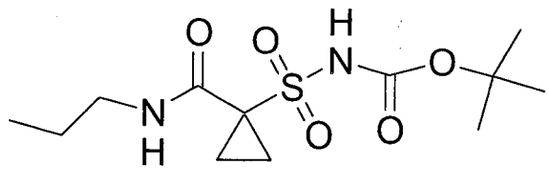
Este compuesto se obtuvo con 65% de rendimiento de *terc*-Butilcarbamato de 1-ciclopropilmetilciclopropilsulfonilamina de conformidad por el procedimiento descrito para la síntesis de 1-metoximetilciclopropilsulfonamida. El compuesto se purificó por cromatografía de columna sobre SiO_2 usando 0% hasta 60% acetato de etilo en hexanos como el eluyente: ^{1}H RMN ($CDCl_3$) δ 0.15 (m, 2H), 0.51 (m, 2H), 1.01 (m, 2H), 1.34 (m, 3H), 1.86 (d, *J*=7.0 Hz, 2H), 4.83 (s, 2H); ^{13}C RMN ($CDCl_3$) δ 4.65, 7.74, 11.26, 35.62, 41.21; LRMS m/z 193 (M^++NH_4).

006419

3d. Preparación de 1-propilcarbamoilciclopropano-sulfonamida

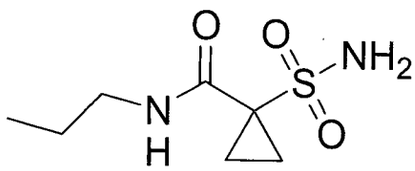


Etapa 1: Preparación de *terc*-Butilcarbamato de 1-propilcarbamoilciclopropanosulfonamida



Este compuesto se obtuvo sin refinar con 100% de rendimiento de conformidad por el procedimiento descrito para la síntesis de *terc*-Butil-carbamato de 1-metoximetilciclopropilsulfonilamina excepto que 1.10 equivalentes de isocianato de *n*-propilo se usó como el electrófilo. El compuesto se tomó directamente en la siguiente reacción sin purificación: ^{1}H RMN ($CDCl_3$) δ 0.10 (m, 2H), 0.51 (m, 2H), 0.67 (m, 1H), 1.10 (m, 2H), 1.49 (s, 9H), 1.62 (m, 2H), 1.87 (d, *J*=7.0 Hz, 2H).

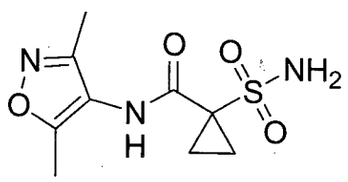
Etapa 2: Preparación de 1-propilcarbamoilciclopropano-sulfonamida



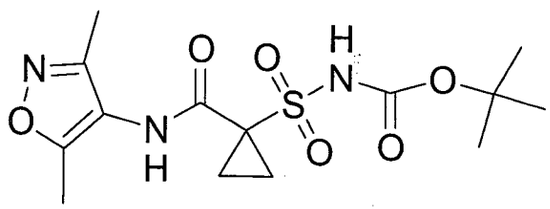
001420

Este compuesto se obtuvo con 50% de rendimiento de *terc*-Butilcarbamato de 1-propilcarbamoilciclopropanosulfonamida de conformidad por el procedimiento descrito para la síntesis de 1-metoximetilciclopropilsulfonamida, excepto que no se procesó por cromatografía porque el material se recristalizó a partir de la cantidad mínima de diclorometano/hexanos: ^{1}H RMN ($CDCl_3$) δ 0.15 (m, 2H), 0.51 (m, 2H), 1.01 (m, 2H), 1.34 (m, 3H), 1.86 (d, *J*=7.0 Hz, 2H), 4.83 (s, 2H); ^{13}C RMN ($CDCl_3$) δ 4.65, 7.74, 11.26, 35.62, 41.21; LRMS m/z 193 (M^++NH_4).

3e. Preparación de 1-(3,5-dimetilisoxazol-4il)carbamoilciclopropanosulfonamida



Etapa 1: Preparación de *terc*-Butilcarbamato de 1-(3,5-dimetilisoxazol-4-il)carbamoilciclopropanosulfonamida

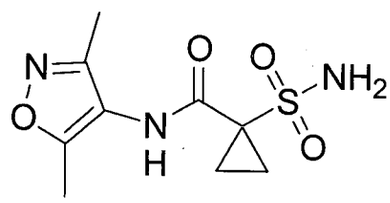


Este compuesto se obtuvo sin refinar con 100 % de

000421

rendimiento de conformidad por el procedimiento descrito para la síntesis de *terc*-Butilcarbamato de 1-metoximetilciclopropilsulfonilamina excepto que 1.20 equivalentes de 3,5-dimetilisoxazol-4-isocianato se usó como el electrófilo. El compuesto se tomó directamente en la siguiente reacción sin purificación.

Etapa 2: Preparación de 1-(3,5-dimetilisoxazol-4il)carbamoilciclopropanosulfonamida

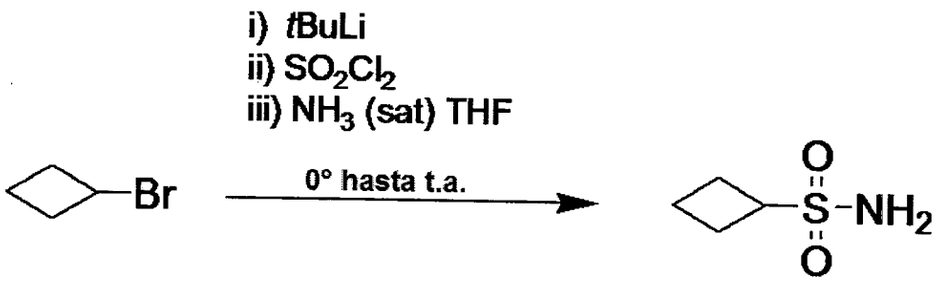


Este compuesto se obtuvo con 50% de rendimiento (580 mg) a partir de 1.62g (4.52 mmol) de *terc*-Butilcarbamato de 1-(3,5-dimetilisoxazol-4-il)carbamoilciclo-propanosulfonamida usando 30 mL (120 mmol) de HCl 4N/dioxanos, se agitó durante la noche, se concentró y se procesó por cromatografía sobre una columna Biotage 40M (eluído con 0% hasta 5% metanol/diclorometano: ^{1}H RMN (metanol-d_4) δ 1.57 (m, 2H), 1.61 (m 2H), 2.15 (s, 3H), 2.30 (s, 3H), 4.84 (s, 3H); ^{13}C RMN (metanol-d_4) δ 9.65, 10.94, 15.01, 46.11, 114.82, 159.45, 165.55, 168.15; LRMS m/z 260 (M^{+}+H).

- 091422

4. Preparación de cicloalquilsulfonamidas a partir de bromuros de cicloalquilo

4a. Preparación de ciclobutilsulfonamida a partir de bromuro de cilobutilo

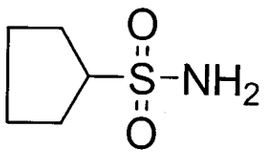


A una solución de 5.0 g (37.0 mmol) de bromuro de ciclobutilo en 30 mL de éter dietílico anhidro (éter dietílico) se enfrió a -78°C se agregó 44 mL (74.8 mmol) de 1.7M terc-butil-litio en pentano. La solución se calentó lentamente a -35°C durante 1.5 horas. Esta mezcla se alimentó por cánula lentamente en una solución de 5.0 g (37.0 mmol) de cloruro de sulfurilo recientemente destilado en 100 mL de hexanos enfriado a -40°C, se calentó a 0°C durante 1 hora y se concentró cuidadosamente *in vacuo*. Esta mezcla se volvió a disolver en éter dietílico, se lavó una vez con algo de agua enfriada en hielo, se secó ($MgSO_4$), se filtró y se concentró cuidadosamente. Esta mezcla se volvió a disolver en 20 mL de THF, se agregó gota a gota hasta 500 mL de NH_3 saturado en THF, y se permitió agitar durante la noche. La mezcla se concentró *in vacuo* hasta un sólido amarillo sin refinar y se

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recristalizó a partir de la cantidad mínima de diclorometano en hexanos con 1-2 gotas de metanol para proporcionar 1.90 g (38%) del producto deseado como un sólido blanco. ^{1}H RMN ($CDCl_3$) δ 1.95-2.06 (m, 2H), 2.30-2.54 (m, 4H), 3.86 (p, J=8 Hz, 1H), 4.75 (s a, 2H); ^{13}C RMN ($CDCl_3$) δ 16.43, 23.93, 56.29. EMAR m/z $(M-H)^-$ calculado para $C_4H_8NSO_2$: 134.0276, encontrado 134.0282.

4b. Preparación de ciclopentil sulfonamida

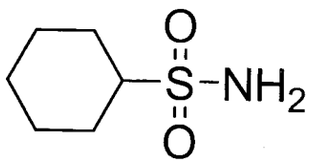


Una solución de 18.5 mL (37.0 mmol) de cloruro de ciclopentil magnesio 2M en éter se agregó gota a gota a una solución de 3.0 mL (37.0 mmol) de cloruro de sulfurilo recientemente destilado (obtenido de Aldrich) en 100 mL de hexanos enfriado a -78°C. La mezcla se calentó a 0°C durante 1 hora y luego se concentró cuidadosamente *in vacuo*. Esta mezcla se volvió a disolver en éter dietílico (200 mL), se lavó una vez con algo de agua enfriada en hielo (200 mL), se secó ($MgSO_4$), se filtró y se concentró cuidadosamente. Esta mezcla se volvió a disolver en 35 mL de THF, se agregó gota a gota hasta 500 mL de NH_3 saturado en THF y se permitió agitar durante la noche. La mezcla se concentró *in*

000424

vacuo hasta un sólido amarillo sin refinar, el residuo se filtró a través de 50g de gel de sílice usando 70% acetato de etilo-hexanos como el eluyente y la solución luego se concentró. El residuo se recristalizó a partir de la cantidad mínima de diclorometano en hexanos con 1-2 gotas de metanol para proporcionar 2.49 g (41%) del producto deseado como un sólido blanco. ^{1}H RMN ($CDCl_3$) δ 1.58-1.72 (m, 2H), 1.74-1.88 (m, 2H), 1.94-2.14 (m, 4H), 3.48-3.59 (m, 1H), 4.80 (s a, 2H); ^{13}C RMN ($CDCl_3$) δ 25.90, 28.33, 63.54; MS m/e 148 $(M-H)^-$.

4c. Preparación de ciclohexil sulfonamida

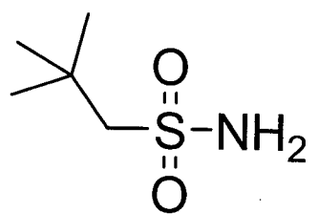


Una solución de 18.5 mL (37.0 mmol) de cloruro de ciclohexilmagnesio 2M (TCI Americas) en éter dietílico se agregó gota a gota a una solución de 3.0 mL (37.0 mmol) cloruro de sulfurilo recientemente destilado en 100 mL de hexanos enfriado a -78°C. La mezcla se calentó a 0°C durante 1 hora y luego se concentró cuidadosamente *in vacuo*. Esta mezcla se volvió a disolver en éter dietílico (200 mL), se lavó una vez con algo de agua enfriada en hielo (200 mL), se secó ($MgSO_4$), se filtró y se concentró cuidadosamente. Esta mezcla se volvió a disolver en 35 mL de THF, se agregó gota a

000425

gota hasta 500 mL de NH_3 saturado en THF y se permitió agitar durante la noche. La mezcla se concentró *in vacuo* hasta un sólido amarillo sin refinar, el residuo se filtró a través de 50g de gel de sílice usando 70% acetato de etilo-hexanos como el eluyente y se concentró. El concentrado se recristalizó a partir de la cantidad mínima de diclorometano en hexanos con 1-2 gotas de metanol para proporcionar 1.66 g (30%) del producto deseado como un sólido blanco: ^{1}H RMN ($CDCl_3$) δ 1.11-1.37 (m, 3H), 1.43-1.56 (m, 2H), 1.67-1.76 (m, 1H), 1.86-1.96 (m, 2H), 2.18-2.28 (m, 2H), 2.91 (tt, *J*=12, 3.5 Hz, 1H), 4.70 (s a, 2H); ^{13}C RMN ($CDCl_3$) δ 25.04, 25.04, 26.56, 62.74; MS m/e 162 $(M-1)^-$.

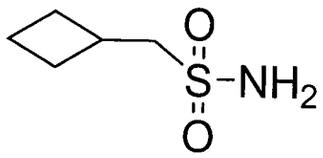
4d. Preparación de neopentilsulfonamida



Siguiendo el procedimiento por la preparación de ciclohexilsulfonamida, 49 mL (37 mmol) de cloruro de neopentilmagnesio 0.75 M (Alfa) en éter dietílico se convirtió a 1.52g (27%) del producto deseado como un sólido blanco. ^{1}H RMN ($CDCl_3$) δ 1.17 (s, 9H), 3.12 (s, 2H), 4.74 (s a, 2H); ^{13}C RMN ($CDCl_3$) δ 29.46, 31.51, 67.38; MS m/e 150 $(M-1)^-$.

000426

4e. Preparación de ciclobutilcarbinilsulfonamida



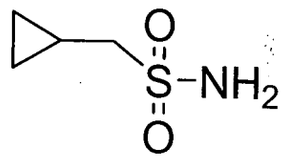
Una solución de 12.3 g (83 mmol) de bromuro de ciclobutilcarbinilo (Aldrich) y 13.7g (91 mmol) de yoduro de sodio en 150 mL de acetona se calentó a reflujo durante la noche y luego se enfrió a temperatura ambiente. Los sólidos inorgánicos se removieron por filtración y la acetona y yoduro de ciclopropilcarbinilo (8.41g, 46%) se removieron por destilación (temperatura ambiente y 150 torr (0.20kg/cm^2) a 80 °C, respectivamente).

Una solución de 4.0 g (21.98 mmol) de yoduro de ciclobutil carbinilo en 30 mL de éter dietílico anhidro se enfrió a -78°C se alimentó por cánula en una solución de 17 mL (21.98 mmol) de sec-butil-litio 1.3M en ciclohexanos y la solución se agitó durante 5 minutos. A esta mezcla se alimentó por cánula una solución de 3.0 g (21.98 mmol) de cloruro de sulfurilo recientemente destilado en 110 mL de hexanos se enfrió a -78°C, la mezcla se calentó a temperatura ambiente durante 1 hora y luego se concentró cuidadosamente *in vacuo*. Esta mezcla se volvió a disolver en éter dietílico, se lavó una vez con algo de agua enfriada en hielo, se secó ($MgSO_4$), se filtró y se concentró cuidadosamente. Esta mezcla

000427

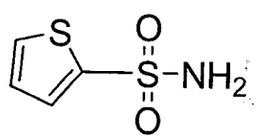
se volvió a disolver en 30 mL de THF, se agregó gota a gota hasta 500 mL de NH_3 saturado en THF y se permitió agitar durante la noche. La mezcla se concentró *in vacuo* hasta un sólido amarillo sin refinar y se recristalizó a partir de la cantidad mínima de diclorometano en hexanos con 1-2 gotas de metanol para proporcionar 1.39 g (42%) del producto deseado como un sólido blanco. ^{1}H RMN ($CDCl_3$) δ 1.81-2.03 (m, 4H), 2.14-2.28 (m, 2H), 2.81-2.92 (m, 1H), 3.22 (d, *J*=7 Hz, 2H), 4.74 (s a, 2H); ^{13}C RMN ($CDCl_3$) δ 19.10, 28.21, 30.64, 60.93. MS m/e 148 $(M-H)^-$.

4f. Preparación de ciclopropilcarbinilsulfonamida



Usando el procedimiento empleado por la preparación de ciclobutilcarbinilsulfonamida, se preparó ciclopropilcarbinilsulfonamida a partir de bromuro de ciclopropilcarbinilo (Aldrich) (ver también *JACS* 1981, p.442-445). ^{1}H RMN ($CDCl_3$) δ 0.39-0.44 (m, 2H), 0.67-0.76 (m, 2H), 1.13-1.27 (m, 1H), 3.03 (d, *J*=7.3 Hz, 2H), 4.74 (s a, 2H); ^{13}C RMN ($CDCl_3$) δ 4.33, 5.61, 59.93; MS m/e 134 (M-1).

4g. Preparación de 2-tiofensulfonamida

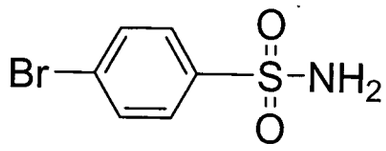


El producto deseado se preparó a partir de cloruro de 2-

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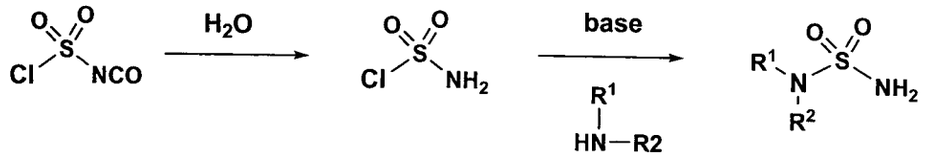
tiofensulfonilo (adquirido de Aldrich) usando el método descrito en *Justus Liebigs Ann. Chem.* **1933**, *501*, p.174-182.

4h. Preparación de 4-bromobencensulfonamida



La 4-Bromofenilsulfonamida se preparó por el tratamiento de cloruro de 4-bromosulfonilo comercialmente disponible con amonio saturado en THF.

5. Procedimiento general para la preparación de sulfamidas

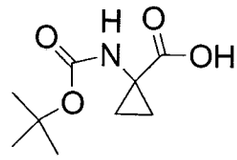


El cloruro de sulfamoilo intermediario se preparó por la adición de agua (1 equiv) en THF a una solución agitada fría (-20 °C) de isocianato de clorosulfonilo (1 equiv) en THF y la solución resultante se permitió calentar a 0°C. A esta solución se agregó trietilamina anhidro (1 equiv) seguido por amina secundaria necesaria (1 equiv). La mezcla de reacción se calentó a temperatura ambiente, luego se filtró y el filtrado se concentró para proporcionar las sulfamidas deseadas.

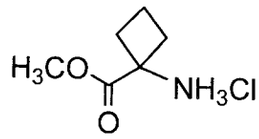
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II Preparación de los Intermediarios P1

5. ácido 1-*terc*-Butoxicarbonilaminociclopropano carboxílico está comercialmente disponible

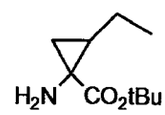


6. Preparación de clorohidrato de éster metílico del ácido 1-aminociclobutanocarboxílico



El ácido 1-Aminociclobutanocarboxílico (100 mg, 0.869 mmol) (Tocris) se disolvió en 10 mL de metanol. El gas HCl se burbujeó durante 2 horas. La mezcla de reacción se agitó durante 18 horas, y luego se concentró *in vacuo* para dar 144 mg de un aceite amarillo. La trituración con 10 mL de éter dietílico proporcionando 100 mg del producto deseado como un sólido blanco. ^{1}H RMN ($CDCl_3$) δ 2.10-2.25 (m, 1H), 2.28-2.42 (m, 1H), 2.64-2.82 (m, 4H), 3.87 (s, 3H), 9.21 (s a, 3H).

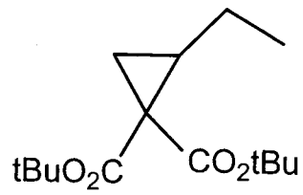
7a. Preparación de éster terc-butílico del ácido (1R,2R)/(1S,2S) 1-amino-2-etilciclopropanocarboxílico (mezcla racémica)



Etilo syn a carboxi

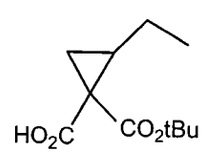
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Etapa 1: Preparación de éster de di-*terc*-Butilo del ácido 2-etilciclopropano-1,1-dicarboxílico, se muestra a continuación



A una suspensión de cloruro de benciltrietilamonio (21.0 g, 92.2 mmol) en una solución NaOH acuoso al 50% (92.4 g en 185 mL H_2O) se agregó 1,2-dibromobutano (30.0 g, 138.9 mmol) y di-*terc*-Butilmalonato (20.0 g, 92.5 mmol). La mezcla de reacción se agitó vigorosamente durante 18 horas a temperatura ambiente y se trató con una mezcla de hielo y agua. El producto sin refinar se extrajo con diclorometano (3x) y se lavó secuencialmente con agua (3x), y salmuera. Los extractos orgánicos se combinaron, se secaron ($MgSO_4$), se filtraron y se concentraron *in vacuo*. El residuo resultante se purificó por cromatografía de columna instantánea (100 g SiO_2, 3% éter dietílico en hexano) para proporcionar el producto deseado (18.3 g, 67.8 mmol, 73% de rendimiento) el cual se usó directamente en la siguiente reacción.

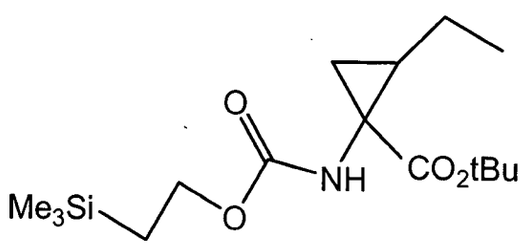
Etapa 2: Preparación de éster terc-butílico del ácido 2-Etilciclopropano-1,1-dicarboxílico, se muestra a continuación



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El producto de la Etapa 1 (18.3 g, 67.8 mmol) se agregó a una suspensión de terc-butóxido de potasio (33.55 g, 299.0 mmol) en éter dietílico seco (500 mL) a 0°C, se trató con H_2O (1.35 mL, 75.0 mmol), y se agitó vigorosamente durante la noche a temperatura ambiente. La mezcla de reacción se vació en una mezcla de hielo y agua y se lavó con éter dietílico (3x). La capa acuosa se ajustó hasta pH ácido con una solución de ácido cítrico acuoso 10% a 0°C y luego se extrajo con acetato de etilo (3x). Las capas orgánicas combinadas se lavaron con agua (2x), salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron *in vacuo* para proporcionar el producto deseado como un aceite amarillo pálido (10 g, 46.8 mmol, 69% de rendimiento).

Etapa 3: Preparación de éster terc-butílico del ácido (1R,2R)/(1S,2S) 2-etil-1-(2-trimetilsilaniletoxicarbonilamino)ciclopropano-carboxílico, se muestra a continuación

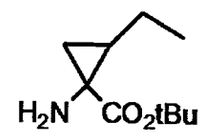


A una suspensión del producto de la Etapa 2 (10 g, 46.8 mmol) y 3g de tamiz molecular 4Å activado recientemente en benceno seco (160 mL) se agregó

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trietilamina (7.50 mL, 53.8 mmol) y DPPA (11 mL, 10.21 mmol). La mezcla de reacción se calentó a reflujo durante 3.5 horas, se trató con 2-trimetilsililetanol (13.5 mL, 94.2 mmol), y se calentó a reflujo durante la noche. La mezcla de reacción se filtró, se diluyó con éter dietílico, se lavó secuencialmente con 10% solución de ácido cítrico acuoso, agua, $NaHCO_3$ acuoso saturado, agua (2x), y salmuera (2x), se secó ($MgSO_4$), se filtró y se concentró *in vacuo*. El residuo se suspendió con 10g de Resina depuradora de poliisocianato Aldrich en 120 mL de diclorometano, se agitó a temperatura ambiente durante la noche, y se filtró para proporcionar el producto deseado (8 g, 24.3 mmol; 52%) como un aceite amarillo pálido: ^1H RMN ($CDCl_3$) δ 0.03 (s, 9H), 0.97 (m, 5H), 1.20 (m a, 1H), 1.45 (s, 9H), 1.40-1.70 (m, 4H), 4.16 (m, 2H), 5.30 (s a, 1H).

Etapa 4: Preparación de éster terc-butílico del ácido (1R,2R)/(1S,2S) 1-amino-2-etilciclopropanocarboxílico (mezcla racémica), se muestra a continuación



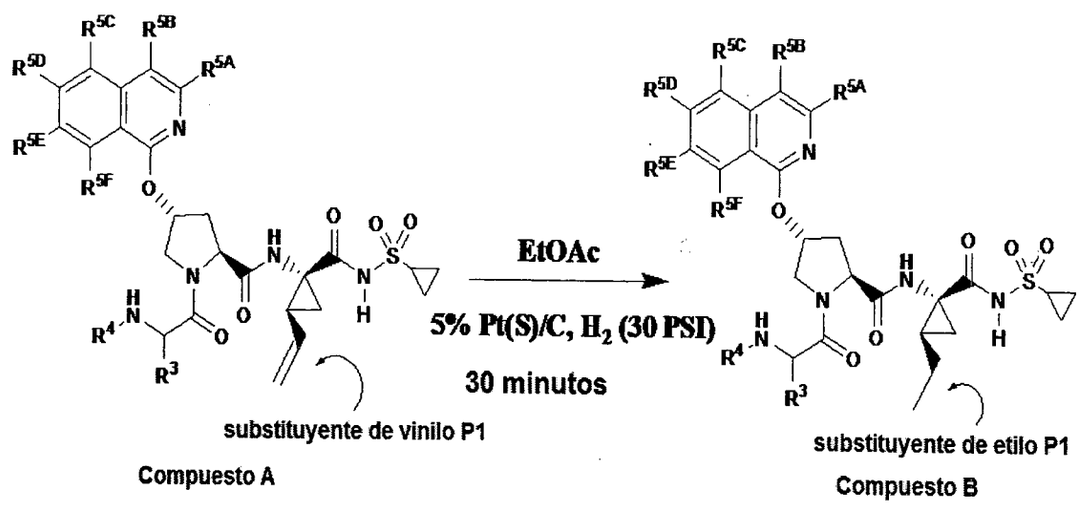
Etilo syn a carboxi

Al producto de la Etapa 3 (3 g, 9 mmol) se agregó una solución TBAF 1.0 M en THF (9.3 mL, 9.3 mmol). La mezcla

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se calentó a reflujo durante 1.5 horas, se enfrió a temperatura ambiente, y se diluyó con 500 mL de acetato de etilo. La solución se lavó sucesivamente con agua (2x100 mL) y salmuera (2x100 mL), se secó ($MgSO_4$), se filtró y se concentró *in vacuo* para proporcionar el producto deseado.

7b. Un método general para la conversión de los compuestos de la fórmula I que porta un substituyente P1 vinilo P1 al análogo P1 saturado correspondiente como se muestra

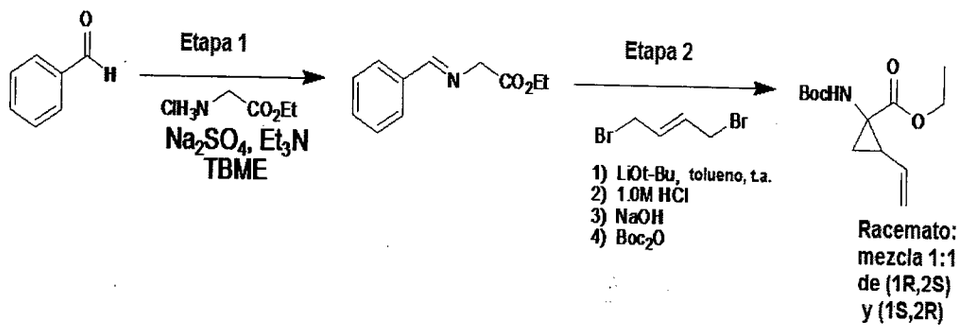


Una suspensión del compuesto A (aproximadamente 100mg) y Pt(S)/C (5%, 10 mg) en aproximadamente 15 mL de EtOAc se hidrogenó, H_2 (2.109 kg/cm^2 (30 PSI)) durante 0.5 h. Después de la filtración a través de un tapón de celite, el filtrado se concentró y se purificó para dar el producto deseado, Compuesto B.

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8. Preparación de éster etílico del ácido (1*R*,2*S*)/(1*S*,2*R*)-1-amino-2-vinilciclopropanocarboxílico:

Esquema de reacción 1



Etapa 1:

El clorohidrato de éster etílico de glicina (304 g, 2.16 moles) se suspendió en éter terc-butilmetílico (1.6 L). El benzaldehído (231 g, 2.16 moles) y sulfato de sodio anhidro (155 g, 1.09 moles) se agregaron, y la mezcla se enfrió a 0°C usando un baño de hielo-agua. Trietilamina (455 mL, 3.26 moles) se agregó gota a gota durante 30 minutos y la mezcla se agitó durante 48 horas a temperatura ambiente. La reacción luego se apagó por la adición de agua enfriada en hielo (1 L) y la capa orgánica se separó. La fase acuosa se extrajo con éter terc-butilmetílico (0.5 L) y las fases orgánicas se combinaron y se lavaron con una mezcla de $NaHCO_3$ acuoso saturado (1 L) y salmuera (1 L). La capa orgánica se secó sobre $MgSO_4$, se filtró y se concentró *in vacuo* para proporcionar 392.4 g del producto de N-bencil imina como un aceite amarillo espeso que se usó directamente en la

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siguiente etapa. ^{1}H RMN ($CDCl_3$, 300 MHz) δ 1.32 (t, *J* = 7.1 Hz, 3H), 4.24 (c, *J* = 7.1 Hz, 2H), 4.41 (d, *J* = 1.1 Hz, 2H), 7.39-7.47 (m, 3H), 7.78-7.81 (m, 2H), 8.31 (s, 1H).

Etapa 2:

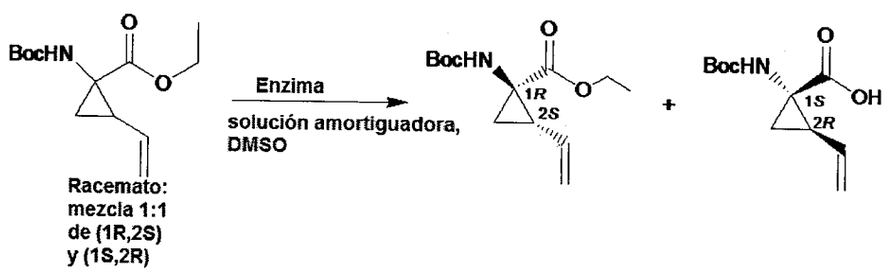
A una suspensión de terc-butóxido de litio (84.1 g, 1.05 mol) en tolueno seco (1.2 L), se agregó gota a gota una mezcla de *N*-Bencil imina de éster de glicina (100 g, 0.526 mol) y *trans*-1,4-dibromo-2-buteno (107 g, 0.500 mol) en tolueno seco (0.6 L) durante 60 minutos. Durante el término de la adición, la mezcla roja oscura se apagó por la adición de agua (1 L) y *éter* terc-butilmetílico (TBME, 1 L). La fase acuosa se separó y luego se extrajo una segunda vez con TBME (1 L). Las fases orgánicas se combinaron, HCl 1.0M (1 L) se agregaron y la mezcla se agitó a temperatura ambiente durante 2 horas. La fase orgánica se separó y luego se extrajo con agua (0.8 L). Las fases acuosas luego se combinaron, se saturaron con sal (700 g), y TBME (1 L) se agregó y la mezcla se enfrió a 0°C. La mezcla agitada luego se hizo básica hasta pH =14 por la adición gota a gota de NaOH 10.0M, la capa orgánica se separó, y la fase acuosa se extrajo con TBME (2 x 500 mL). Los extractos orgánicos se combinaron, se secaron sobre $MgSO_4$, se filtraron y se concentraron hasta un volumen de 1 L. A esta solución de amina libre se agregó Boc_2O o di-*terc*-Butildicarbonato (131 g, 0.600 mol) y la mezcla se agitó

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durante 4 días a temperatura ambiente. El di-*terc*-Butildicarbonato adicional (50 g, 0.23 mol) se agregó a la reacción y la mezcla se puso a reflujo durante 3 horas y luego se permitió enfriar a temperatura ambiente durante la noche. La mezcla de reacción se secó sobre $MgSO_4$, se filtró y se concentró *in vacuo* para proporcionar 80 g del material sin refinar. Este residuo se purificó por cromatografía instantánea (2.5 kg de SiO_2, eluido con 1% hasta 2% CH_3OH/CH_2Cl_2) para proporcionar 57 g (53%) de éster etílico del ácido *N*-Boc-(1*R*,2*S*)/(1*S*,2*R*)-1-amino-2-vinilciclopropano carboxílico como un aceite amarillo el cual se solidificó mientras que está en resposo en el refrigerador: ^1H RMN ($CDCl_3$, 300 MHz) δ 1.26 (t, *J* = 7.1 Hz, 3H), 1.46 (s, 9H), 1.43-1.49 (m, 1H), 1.76-1.82 (m a, 1H), 2.14 (c, *J* = 8.6 Hz, 1H), 4.18 (c, *J* = 7.2 Hz, 2H), 5.12 (dd *J* = 10.3, 1.7 Hz, 1H), 5.25 (s a, 1H), 5.29 (dd, *J* = 17.6, 1.7 Hz, 1H), 5.77 (ddd, *J* = 17.6, 10.3, 8.9 Hz, 1H); MS m/z 254.16 (M-1).

9. Resolución de éster etílico del ácido *N*-Boc-(1*R*,2*S*)/(1*S*,2*R*)-1-amino-2-vinilciclopropano carboxílico

Esquema de reacción 2



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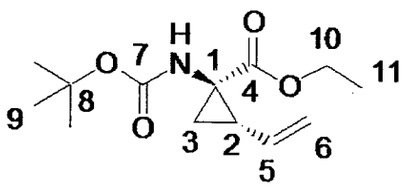
Resolución A

A una solución acuosa de solución amortiguadora de fosfato de sodio (0.1 M, 4.25 litros ("L"), pH 8) alojada en un reactor enchaquetado de 12 Litros, mantenida a 39°C, y agitado a 300 rpm se agregaron 511 gramos de Alcalase 2.4L (alrededor de 425 mL) (Novozymes North America Inc.). Cuando la temperatura de la mezcla alcanzó 39°C, el pH se ajustó hasta 8.0 por la adición de 50% NaOH en agua. Una solución de éster etílico del ácido *N*-Boc-(1R,2S)/(1S,2R)-1-amino-2-vinilciclopropano carboxílico (85g) en 850 mL de DMSO luego se agregó durante un periodo de 40 minutos. La temperatura de reacción luego se mantuvo a 40°C durante 24.5 horas durante este tiempo el pH de la mezcla se ajustó hasta 8.0 en puntos de tiempo de 1.5 horas y 19.5 horas usando 50% NaOH en agua. Después de 24.5 horas, el exceso de enantiómeros del éster se determinó que fue 97.2%, y la reacción se enfrió a temperatura ambiente (26°C) y se agitó durante la noche (16 horas) después de lo cual el exceso de enantiómeros del éster se determinó que fue 100%. El pH de la mezcla de reacción luego se ajustó 8.5 con 50% NaOH y la mezcla resultante se extrajo con MTBE (2 x 2 L). El extracto MTBE combinado luego se lavó con 5% $NaHCO_3$ (3 x 100 mL), agua (3 x 100 mL), y se concentró *in vacuo* para dar el éster etílico del ácido *N*-Boc-(1R,2S)/-1-amino-2-vinilciclopropano carboxílico enantioméricamente puro como un sólido amarillo claro (42.55

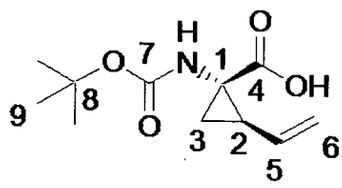
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g; pureza: 97% @ 210 nm, que no contiene ácido; 100% exceso enantiomérico ("ee").

La capa acuosa del proceso de extracción luego se acidificó hasta pH 2 con 50% H_2SO_4 y luego se extrajo con MTBE (2 x 2 L). El extracto MTBE se lavó con agua (3 x 100 mL) y se concentró para dar el ácido como un sólido amarillo claro (42.74 g; pureza: 99% @ 210 nm, que no contiene éster).



1R,2S-éster



1S,2R-ácido

	éster	ácido
Espectro de masa de alta resolución	(+) ESI, $C_{13}H_{22}NO_4$, $[M+H]^+$, calculado 256.1549, encontrado 256.1542	(-) ESI, $C_{11}H_{16}NO_4$, $[M-H]^-$, calculado 226.1079, encontrado 226.1089
RMN giro químico observado Solvente: $CDCl_3$ (protón δ 7.24 ppm, C-13 δ 77.0 ppm) Bruker DRX-500C: protón 500.032 MHz, carbono 125.746 MHz		

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Posición	Protón (modelo) ppm	C-13 ppm	Protón (modelo) ppm	C-13 ppm
1	----	40.9	----	40.7
2	2.10 (c, *J* = 9.0 Hz)	34.1	2.17 (c, *J* = 9.0 Hz)	35.0
3a	1.76 (amp)	23.2	1.79 (amp)	23.4
3b	1.46 (amp)		1.51, (amp)	
4	----	170.8	----	175.8
5	5.74 (ddd, *J* = 9.0, 10.0, 17.0 Hz)	133.7	5.75 (m)	133.4
6a	5.25 (d, *J* = 17.0 Hz)	117.6	5.28 (d, *J* = 17.0 Hz)	118.1
6b	5.08 (dd, *J* = 10.0, 1.5 Hz)		5.12 (d, *J* = 10.5 Hz)	
7	----	155.8	----	156.2
8	----	80.0	----	80.6
9	1.43 (s)	28.3	1.43 (s)	28.3
10	4.16 (m)	61.3	----	----
11	1.23 (t, *J* = 7.5 Hz)	14.2	----	----

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Resolución B

A la solución amortiguadora 0.5 mL 100 mM Heps·Na (pH 8.5) en una cavidad de una placa de 24 cavidades (capacidad: 10 mL/cavidad), 0.1 mL de Savinase 16.0L (proteasa de Bacillus clausii) (Novozymes North America Inc.) y una solución de éster etílico del ácido *N*-Boc-(1R,2S)/(1S,2R)-1-amino-2-vinilciclopropano carboxílico racémico (10 mg) en 0.1 mL de DMSO se agregaron. La placa se selló y se incubó a 250 rpm a 40°C. Después de 18 horas, el exceso de enantiómeros del éster se determinó que fue 44.3% como sigue: 0.1 mL de la mezcla de reacción se removió y se mezcló bien con 1 mL etanol; después de la centrifugación, 10 microlitro ("µL") del sobrenadante se analizó con el HPLC quiral. A la mezcla de reacción restante, 0.1 mL de DMSO se agregó, y la placa se incubó durante 3 días adicionales a 250 rpm a 40°C, después de lo cual 4 mL de etanol se agregó a la cavidad. Después de la centrifugación, 10 µL del sobrenadante se analizó con el HPLC quiral y el exceso de enantiómeros del éster se determinó que fue 100%.

Resolución C

A la solución amortiguadora 0.5 mL 100 mM Heps·Na (pH 8.5) en una cavidad de una placa de 24 cavidades

(capacidad: 10 mL/cavidad), 0.1 mL de Esperasa 8.0L, (proteasa de Bacillus halodurans) (Novozymes North America Inc.) y una solución del éster etílico del ácido *N*-Boc-(1R,2S)/(1S,2R)-1-amino-2-vinilciclopropano carboxílico racémico (10 mg) en 0.1 mL de se agregó DMSO. La placa se selló y se incubó a 250 rpm a 40°C. Después de 18 horas, el exceso de enantiómeros del éster se determinó que fue 39.6% como sigue: 0.1 mL de la mezcla de reacción se removió y se mezcló bien con 1 mL etanol; después de la centrifugación, 10 µL del sobrenadante se analizó con HPLC quiral. A la mezcla de reacción restante, 0.1 mL de DMSO se agregó, y la placa se incubó durante 3 días adicionales a 250 rpm a 40°C, después de lo cual 4 mL de etanol se agregó a la cavidad. Después de la centrifugación, 10 µL del sobrenadante se analizó con el HPLC quiral y el exceso de enantiómeros del éster se determinó que fue 100%.

Las muestras de análisis se llevaron a cabo en la siguiente manera:

1) Preparación de muestra: Alrededor de 0.5 mL de la mezcla de reacción se mezcló bien con 10 volumen de etanol. Después de la centrifugación, 10 µL del sobrenadante se inyectó en la columna HPLC.

2) Determinación de conversión:

Columna: YMC ODS A, 4.6 x 50 mm, S-5 µm

Solvente: A, 1 mM HCl en agua; B, CH_3CN

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Gradiente: 30% B durante 1 min; 30% hasta 45% B durante 0.5 min; 45% B durante 1.5 min; 45% hasta 30% B durante 0.5 minutos.

Relación de flujo: 2 mL/min

Detección UV: 210 nm

Tiempo de retención: ácido, 1.2 min; éster, 2.8 minutos.

3) La determinación del exceso de enantiómeros para el éster:

Columna: CHIRACEL OD-RH, 4.6 x 150 mm, S-5 μm

Fase móvil: CH_3CN/50 mM $HClO_4$ en agua (67/33)

Relación de flujo: 0.75 mL/min.

Detección UV: 210 nm.

Tiempo de retención:

ácido (1S,2R)-1-amino-2-vinilciclopropano carboxílico 5.2 min;

Racemato éster etílico del ácido (1R,2S)/(1S,2R)-1-amino-2-vinilciclopropano carboxílico 18.5 minutos y 20.0 min;

Éster etílico del ácido (1R,2S)-1-amino-2-vinilciclopropano carboxílico 18.5 minutos.

Resolución D

5 L de solución amortiguadora de fosfato de sodio 0.3 M (pH 8) se mantuvo a 38°C en un reactor enchaquetado de 20 Litros, agitado a 130 rpm. Cuatro litros de Alcalase 2.4L (Novozymes North America Inc.) y 1 litro de agua DI se

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agregaron al reactor. Cuando la temperatura de la mezcla se acerca a 38°C, el pH se ajustó hasta 7.8 con NaOH 10 N. Una solución del éster etílico del ácido *N*-Boc-(1R,2S)/(1S,2R)-1-amino-2-vinilciclopropano carboxílico (500 gramos) en 5 litros de DMSO se agregó al reactor durante un periodo de 1 hora por medio de un embudo de adición. La temperatura de reacción luego se ajustó hasta 48°C. Después de 21 horas, el exceso de enantiómeros del éster alcanzó 99.3%. El calentamiento se detuvo 24 horas y la reacción se enfrió lentamente a temperatura ambiente (alrededor de 25°C) y se agitó durante la noche. El pH de la mezcla de reacción se ajustó hasta 8.5 con NaOH 10 N y la mezcla se extrajo con MTBE (2 x 4 L). El extracto MTBE combinado se lavó con 5% $NaHCO_3$ (3 x 400 mL) y agua (3 x 400 mL), y se concentró para dar el éster etílico del ácido *N*-Boc-(1R,2S)/-1-amino-2-vinilciclopropano carboxílico enantioméricamente puro como un cristal amarillo claro (259 g; pureza: 96.9% @ 210 nm, que no contiene ácido; 100%ee).

Resolución E

10 L de solución amortiguadora de fosfato de sodio 0.1 M (pH 8) se mantuvo a 40°C en un reactor enchaquetado de 20 Litros, se agitó a 360 rpm. 1.5 litros de Alcalase 2.4L (Novozymes North America Inc.) se agregó al reactor. Cuando la temperatura de la mezcla se acercó a 38°C, el pH se ajustó hasta 8.0 con NaOH 10 N. Una solución de éster etílico del

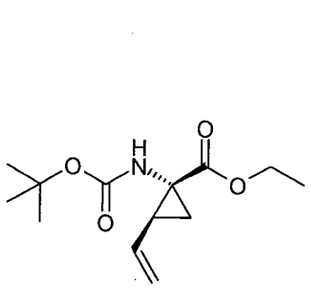
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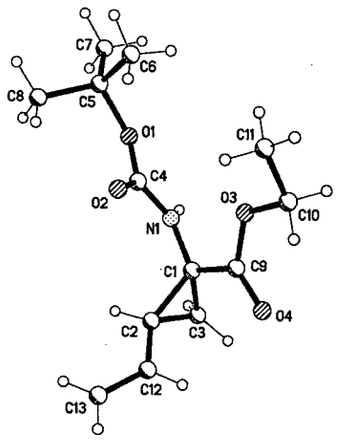
ácido *N*-Boc-(1R,2S)/(1S,2R)-1-amino-2-vinilciclopropano racémico (200 gramos) en 2 litros DMSO se agregó al reactor durante un periodo de 1 hora por medio de un embudo de adición. La temperatura de reacción luego se ajustó hasta 40°C. Después de 3 horas, el pH se ajustó hasta 8.0 con NaOH 10 N. Después de 21 horas, la reacción se enfrió hasta 25°C, el pH de la mezcla de reacción se ajustó hasta 8.5 con NaOH 10 N y la mezcla se extrajo con MTBE (2 x 5 L). El extracto MTBE combinado se lavó con 5% $NaHCO_3$ (3 x 500 mL) y agua (3 x 200 mL), y se concentró para dar 110 gramos de aceite amarillo. El aceite se colocó a temperatura ambiente bajo alojamiento al vacío y dio el éster etílico del ácido *N*-Boc-(1R,2S)/-1-amino-2-vinilciclopropano carboxílico enantioméricamente puro como un cristal de varillas largas incoloras (101 g; pureza: 97.9% @ 210 nm, que no contiene ácido; 100%ee).

La estructura de cristal del éster etílico del ácido *N*-Boc-(1R,2S)/-1-amino-2-vinilciclopropano carboxílico enantioméricamente puro se caracterizó por análisis de cristal sencillo (rayos X NB#: 52795-093, código de referencia: 634592N1). La configuración absoluta no establece la carencia de un centro quiral conocido o átomo(s) más pesado. Una estructura de cadena a lo largo del eje a cristalográfico se forma por medio del enlace de hidrógeno intermolecular entre el grupo amida y el átomo de oxígeno de carbonilo (N...O 3.159 Å).

000445

La estructura del éster etílico del ácido N-Boc-(1R,2S)-1-amino-2-vinilciclopropano carboxílico:





Datos del cristal:	Experimental:
Fórmula química: C13H21N1O4	<u>Cristalización</u>
Sistema de cristal: Ortorómbico	Fuente de cristal: MTBE
Grupo de espacio: $P2_12_12_1$	Descripción de cristal: Varilla incolora
a = 5.2902(1) Å α=90°	Tamaño de cristal (mm): 0.12 X 0.26 X 0.30
b = 13.8946(2) Å β=90°	*<u>Colección de datos</u>*
c = 19.9768(3) Å γ=90°	Temperatura (K): 293
V = 1468.40(4) Å^3	θ_{max} (°): 65.2 (Cu Kα)
Z = 4 d_x = 1.155 g cm^{-3}	No. de reflexiones medidas: 7518

000446

No. de reflexiones para los parámetros de la rejilla: 6817	No. de reflexiones independiente: 2390 (R_{int} = 0.0776)
intervalo θ para los parámetros de la rejilla (°): 2.2-65.2	No. de reflexiones observadas ($I \geq 2\sigma$: 2284
Coeficiente de absorción (mm^{-1}): 0.700	Corrección de absorción (T_{min}-T_{max}): 0.688-1.000

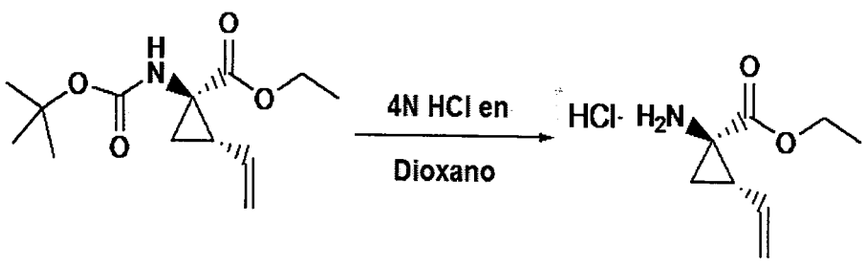
Resolución F

5 L de la solución amortiguadora borato de sodio 0.2 M (pH 9) se mantuvo a 45°C en un reactor enchaquetado de 20 Litros, y se agitó a 400 rpm. Tres litros de agua DI y cuatro litros de Savinase 16L, tipo EX (Novozymes North America Inc.) se agregaron al reactor. Cuando la temperatura de la mezcla se acercó a 45°C, el pH se ajustó hasta 8.5 con NaOH 10 N. Una solución de éster etílico del ácido *N*-Boc-(1R,2S)/(1S,2R)-1-amino-2-vinilciclopropano carboxílico racémico (200 gramos) en 2 litros DMSO se agregó al reactor durante un periodo de 40 minutos, por medio de un embudo de adición. La temperatura de reacción luego se ajustó hasta 48°C. Después de 2 horas, el pH se ajustó hasta pH 9.0 con NaOH 10 N. A 18 horas, el exceso de enantiómeros del éster alcanzó 72%, el pH se ajustó hasta 9.0 con NaOH 10 N. A 24 horas, la temperatura se redujo a 35°C. A 42 horas, la

000447

temperatura se elevó a 48°C y el pH se ajustó hasta 9.0 con NaOH 10 N. El calentamiento se detuvo 48 horas y la reacción se enfrió lentamente a temperatura ambiente (alrededor de 25°C) y se agitó durante la noche. A 66 horas, el pH de la mezcla de reacción fue 8.6. La mezcla se extrajo con MTBE (2 x 4 L). El extracto MTBE combinado se lavó con 5% $NaHCO_3$ (6 x 300 mL) y agua (3 x 300 mL), y se concentró para dar éster etílico del ácido *N*-Boc-(1R,2S)/-1-amino-2-vinilciclopropano carboxílico enantioméricamente puro como cristal amarillo claro (101A g; pureza: 95.9% @ 210 nm, que no contiene ácido; 98.6%ee).

10. Preparación de clorhidrato de éster etílico del ácido (1R,2S)-1-amino-2-vinilciclopropano carboxílico quiral

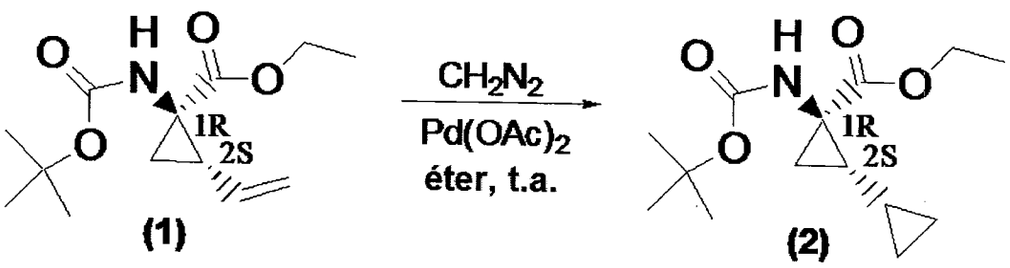


El éster etílico del ácido (1R,2S) *N*-Boc-1-amino-2-vinilciclopropano carboxílico (8.5 g, 33.3 mmol) se agitó bajo una atmósfera de nitrógeno con 200 mL de HCl 4N/dioxano (Aldrich) a temperatura ambiente durante 3 horas. El solvente se removió bajo presión reducida manteniendo la temperatura de bajo de 40°C. Esto dio 6.57 g (~100%) de clorohidrato de éster

000448

etílico del ácido (1R,2S)-1-amino-2-vinilciclopropano carboxílico como un sólido color canela claro. ^{1}H RMN (300 MHz, CD_3OD) δ 1.31 (t, *J*=7.0 Hz, 3H), 1.69-1.82 (m, 2H), 2.38 (c, *J*=8.8 Hz, 1H), 4.29 (c, *J*=7.0 Hz, 2H), 5.22 (d, *J*=10.3 Hz, 1H), 5.40 (d, *J*=17.2 Hz, 1H), 5.69-5.81 (m, 1H). MS m/z 156 (M^++1).

11. Preparación de éster etílico del ácido *N*-Boc-(1R,2S)-1-amino-2-ciclopropilciclopropano carboxílico



Una solución de ácido *N*-Boc-(1R,2S)-1-amino-2-vinilciclopropano carboxílico (255 mg, 1.0 mmol) en éter dietílico (10 mL) se trató con acetato de paladio (5 mg, 0.022 mmol). La solución anaranjada/roja se colocó bajo una atmósfera de nitrógeno. Un exceso de diazometano en éter dietílico se agregó gota a gota durante el curso de 1 hora. La solución resultante se agitó a temperatura ambiente durante 18 horas. El exceso de diazometano se removió usando una corriente de nitrógeno y la solución resultante se concentró por evaporación rotatoria para dar el producto sin refinar. La cromatografía instantánea

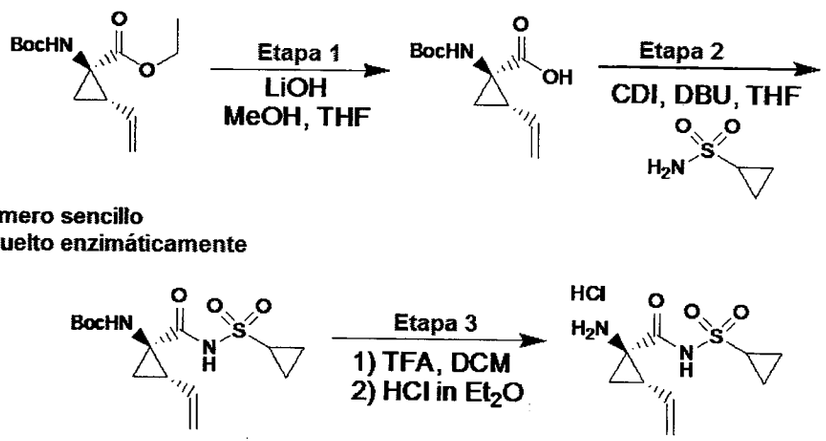
000449

(10% acetato de etilo/hexano) proporcionando 210 mg (78%) de éster etílico del ácido (1R,2S)-*N*-Boc-1-amino-2-ciclopropilciclopropano carboxílico como un aceite incoloro. MS m/z 270 (M^+ + H).

III. Preparación de los intermediarios P1'-P1

12. Preparación de P1P1':

Esquema de reacción 1



Etapa 1:

A una solución de éster etílico del ácido 1(*R*)-terc-Butoxicarbonilamino-2(*S*)-vinil-ciclopropano carboxílico (3.28 g, 13.2 mmol) en THF (7 mL) y metanol (7 mL) se agregó una suspensión de LiOH (1.27 g, 53.0 mmol) en agua (14 mL). La mezcla se agitó durante la noche a temperatura ambiente. A la mezcla se agregó NaOH 1.0M (15 mL), agua (20 mL) y acetato de etilo (20 mL). La mezcla se agitó, las fases se separaron, y la fase orgánica se extrajo

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nuevamente con 20 mL NaOH 0.5M. Las fases acuosas combinadas se acidificaron con HCl 1.0M hasta pH = 4 y se extrajeron con acetato de etilo (3 x 40mL). Los extractos orgánicos combinados se lavaron con salmuera, se secaron ($MgSO_4$), y se filtraron para proporcionar el producto deseado como un sólido blanco (2.62 g, 87%). ^1H RMN: (DMSO-d_6) δ 1.22-1.26 (m, 1H), 1.37 (s, 9H), 1.50-1.52 (m, 1H), 2.05 (c, J = 9 Hz, 1H), 5.04 (d, J = 10 Hz, 1H), 5.22 (d, J = 17 Hz, 1H), 5.64-5.71 (m, 1H), 7.18, 7.53 (s, NH (rotámeros), 12.4 (s a, 1H)); LC-MS MS m/z 228 (M^+ + H).

Etapa 2:

Una solución del producto de la Etapa 1 (2.62 g, 11.5 mmol) y CDI (2.43 g, 15.0 mmol) en THF (40 mL) se calentó a reflujo durante 50 minutos bajo nitrógeno. La solución se enfrió a temperatura ambiente y se transfirió por una cánula a una solución de ciclopropilsulfonamida (1.82 g, 15.0 mmol) en THF (10 mL). A la solución resultante se agregó DBU (2.40 mL, 16.1 mmol) y se agitó continuamente durante 20 horas. La mezcla se apagó con HCl 1.0M hasta pH = 1, y THF se evaporó *in vacuo*. La suspensión se extrajo con acetato de etilo (2 x 50 mL) y los extractos orgánicos se combinaron y se secaron (Na_2SO_4). La filtración, concentración y purificación por recristalización de hexanos-acetato de etilo (1:1) proporcionó el producto

000451

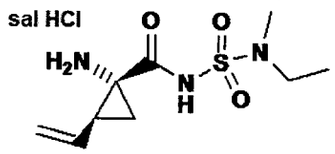
deseado (2.4 g) como un sólido blanco. El licor madre se purificó por una columna Biotage 40S (eluida 9% acetona en diclorometano) para dar un segundo lote del producto deseado (1.1 g). Ambos lotes se combinaron (rendimiento total 92%). ^{1}H RMN: (DMSO-d_6) δ 0.96-1.10 (m, 4H), 1.22 (dd, *J* = 5.5, 9.5 Hz, 1H), 1.39 (s, 9H), 1.70 (t, *J* = 5.5 Hz, 1H), 2.19-2.24 (m, 1H), 2.90 (m, 1H), 5.08 (d, *J* = 10 Hz, 1H), 5.23 (d, *J* = 17 Hz, 1H), 5.45 (m, 1H), 6.85, 7.22 (s, NH (rotámeros)); LC-MS, MS m/z 331 (M^+ + H).

Etapa 3:

Una solución del producto de la Etapa 2 (3.5 g, 10.6 mmol) en diclorometano (35 mL) y TFA (32 mL) se agitó a temperatura ambiente durante 1.5 horas. Los materiales volátiles se removieron *in vacuo* y el residuo se suspendió en HCl 1.0M en éter dietílico (20 mL) y se concentró *in vacuo*. Este procedimiento se repitió una vez más. La mezcla resultante se trituró con pentano y se filtró para dar el compuesto del título como un sólido blanco opaco higroscópico (2.60 g, 92%). ^{1}H RMN (DMSO-d_6) δ 1.01-1.15 (m, 4H), 1.69-1.73 (m, 1H), 1.99-2.02 (m, 1H), 2.38 (c, *J* = 9 Hz, 1H), 2.92-2.97 (m, 1H), 5.20 (d, *J* = 11 Hz, 1H), 5.33 (d, *J* = 17 Hz, 1H), 5.52-5.59 (m, 1H), 9.17 (s a, 3H); LC-MS, MS m/z 231 (M^+ + H).

004452

13. Preparación del derivado de sulfamida P1-P1'



A una solución de ácido (1R, 2S) 1-*terc*-Butoxicarbonilamino-2-vinil-ciclopropano carboxílico (217 mg, 1.194 mmol) en THF (5 mL), se agregó CDI (290 mg, 1.791 mmol) y la mezcla de reacción se calentó a reflujo durante 45 minutos. En otro matraz de fondo redondo, LiHMDS (solución 1.0 M en hexanos, 2.4 mL, 2.4 mmol) se agregó a una solución de *N*-etilmetilsulfamida (330 mg, 2.388 mmol) en THF (5 mL) y la mezcla de reacción se agitó a temperatura ambiente durante 1 hora. Las dos mezclas de reacción se combinaron y se agitaron a temperatura ambiente durante 2 horas. Agua se agregó para apagar la reacción y la solución de reacción se extrajo con acetato de etilo. La capa orgánica se separó y se secó sobre $MgSO_4$. La filtración y concentración dio el producto sin refinar el cual se purificó por HPLC preparativa para proporcionar la N-acilsulfamida protegida N-boc deseada. El grupo protector Boc luego se remueve cuando el compuesto se disuelve en solución HCl 4N en dioxano (2mL) y se agitó a temperatura ambiente durante 4 horas. La concentración proporcionó una aceite café como la sal HCl. (112mg, 33% de rendimiento). ^{1}H RMN (400Mz, CD_3OD) δ 1.16 (t, *J*=7.21 Hz, 3H),

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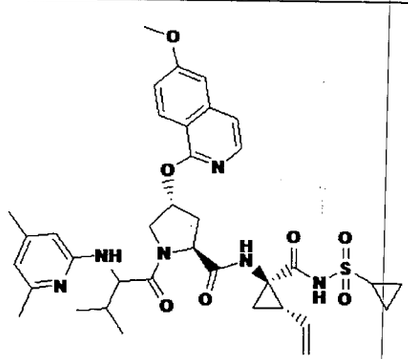
1.68 (dd, *J*=10.03, 7.83 Hz, 1H), 2.15 (m, 1H), 2.37 (m, 1H), 2.89 (s, 3H), 3.30 (m, 2H), 5.31 (d, *J*=10.27 Hz, 1H), 5.42 (d, *J*=17.12 Hz, 3H), 5.68 (m, 1H). LC-MS (tiempo de retención: 0.883 minutos.), MS m/z 270 (M + Na^+).

Isómeros del Compuesto 1:

N-(4,6-dimetil-2-piridinil)-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida y

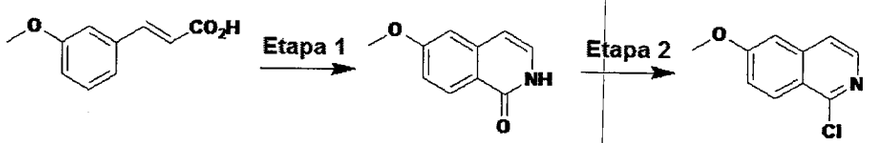
N-(4,6-dimetil-2-piridinil)-D-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida

Ejemplo 1: Preparación de los Compuestos 1A y 1B



Compuestos 1A y 1B

Esquema de reacción 1



Etapa 1:

A una solución de ácido 3-metoxicinámico (11.0 g, 62 mmol) y trietilamina (12.5 g, 124 mmol) en acetona (80 mL) se

00454

agregó cloroformiato de etilo (aproximadamente 1.5 equivalentes) gota a gota a 0°C. Después de agitarse a esta temperatura durante 1 hora, NaN_3 acuoso (6.40 g, 100 mmol en 35 mL H_2O) se agregó gota a gota y la mezcla de reacción se agitó durante 16 horas a temperatura ambiente. Agua (100 mL) se agregó a la mezcla y los materiales volátiles se removieron *in vacuo*. La mezcla resultante se extrajo con tolueno (3 x 50 mL) y las capas orgánicas se combinaron, se secaron sobre $MgSO_4$, y se filtraron. El filtrado se agregó gota a gota a una solución caliente de difenilmetano (50 mL) y triButilamina (30 mL) a 190°C. El tolueno se removió por destilación durante la adición. Después de que se completó la adición, la temperatura de reacción se elevó a 210°C durante 2 horas. Durante el enfriamiento, el producto precipitado se colectó por filtración, se lavó con hexano (2 x 50 mL), y se secó para proporcionar el producto deseado como un sólido blanco (5.53 g, 51%) (Nicolas Briet *et al*, *Tetrahedron*, **2002**, 5761-5766). LC-MS, MS m/z 176 (M^+ + H).

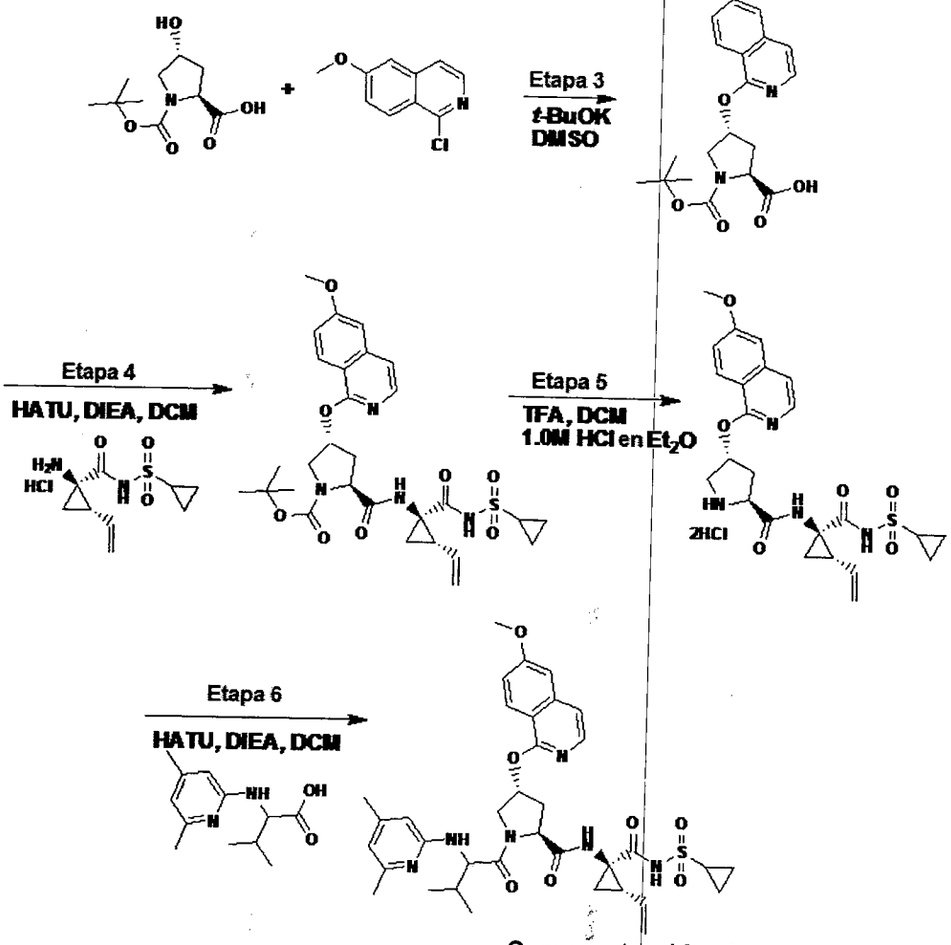
Etapa 2:

La 6-Metoxi-*2H*-isoquinolin-1-ona (5.0 g, 28.4 mmol) en $POCl_3$ (10 mL) se calentó a reflujo suave durante 3 horas y la mezcla luego se concentró *in vacuo* (Nicolas Briet *et al*, *Tetrahedron*, **2002**, 5761-5766). El residuo se vació en agua con hielo (20 mL) y se llevó hasta pH = 10 por la adición de 10.0M NaOH. La mezcla resultante se extrajo con $CHCl_3$. La

100455

capa orgánica se lavó con salmuera, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo se purificó por cromatografía instantánea (1:1 hexano-acetato de etilo) para proporcionar 4.41 g (80%) del producto deseado como un sólido blanco. ^1H RMN (CD_3OD) δ ppm 3.98 (s, 3H), 7.34-7.38 (m, 2H), 7.69 (d, J = 5.5Hz, 1H), 8.10 (d, J = 6.0 Hz, 1H), 8.23 (d, J = 9.5 Hz, 1H); LC-MS, MS m/z 194 (M^+ + H).

Esquema de reacción 2



Compuestos 1A y 1B
Mezcla de dos isómeros

001456

Etapa 3:

A una solución de *N*-Boc-4-(*R*)-hidroxi-L-prolina (0.892 g, 3.89 mmol) en DMSO (40 mL) a temperatura ambiente se agregó terc-butóxido de potasio sólido (1.34 g, 12.0 mmol) en una porción. La suspensión se agitó a temperatura ambiente durante 30 minutos antes de enfriarse a 10°C. 1-Cloro-6-metoxi-isoquinolina (el producto de la Etapa 2, Ejemplo 1) (785 mg, 4.05 mmol) se agregó como un sólido en una porción y la mezcla resultante se agitó a temperatura ambiente durante 12 horas. La mezcla se apagó con ácido cítrico (ac) enfriado con hielo al 5% y luego se extrajo con acetato de etilo (100 mL). La fase acuosa se extrajo con acetato de etilo una vez más. Las capas orgánicas combinadas se lavaron con 5% ácido cítrico (ac) y salmuera respectivamente, se secaron sobre $MgSO_4$ y se filtraron. El filtrado se concentró *in vacuo* hasta secarse para proporcionar el producto deseado como una espuma blanca opaca (1.49 g, 99% de rendimiento). Este material sin refinar se usó en la siguiente etapa sin purificación adicional. ^{1}H RMN (CD_3OD) δ 1.42, 1.44 (rotámeros, 9H), 2.38-2.43 (m, 1H), 2.66-2.72 (m, 1H), 3.80-3.87 (m, 2H), 3.92 (s, 3H), 4.44-4.52 (m, 1H), 5.73 (s a, 1H), 7.16-7.18 (m, 2H), 7.24-7.25 (m, 1H), 7.87-7.88 (m, 1H), 8.07 (d, *J* = 8.5 Hz, 1H); LC-MS, MS m/z 389 (M^+ + H).

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Etapa 4:

A una mezcla del producto de la Etapa 3, Ejemplo 1 (1.49 g, 3.84 mmol), HATU (2.19 g, 5.76 mmol) y sal HCl de la (1-(*R*)-amino-2-(*S*)-vinil-ciclopropanocarbonil)-amida del ácido ciclopropanosulfónico (1.12 g, 4.22 mmol) en CH_2Cl_2 (50 mL) se agregó DIPEA (1.29 g, 11.5 mmol) a 0°C. Después de agitarse a temperatura ambiente durante 12 horas, la solución resultante se diluyó con CH_2Cl_2 (50 mL) y se lavó con ácido cítrico (ac) 5% enfriado con hielo. La capa orgánica se lavó con 5% ácido cítrico (ac) y salmuera respectivamente, se secó sobre $MgSO_4$ y se filtró. El filtrado se concentró *in vacuo* hasta secarse. El residuo se recristalizó a partir de metanol para proporcionar 1.60 g (70%) del producto deseado como un sólido blanco. ^1H RMN (CD_3OD) δ 1.05-1.08 (m, 2H), 1.16-1.20 (m, 1H), 1.24-1.27 (m, 1H), 1.42-1.45 (m, 10H), 1.88 (dd, *J* = 8.09, 5.34 Hz, 1H), 2.24-2.30 (m, 2H), 2.53-2.57 (m, 1H), 2.94-2.98 (m, 1H), 3.80 (d, *J* = 12.5 Hz, 1H), 3.86-3.89 (m, 1H), 3.93 (s, 3H), 4.40-4.42 (m, 1H), 5.13 (d, *J* = 10.5 Hz, 1H), 5.32 (d, *J* = 18.0 Hz, 1H), 5.72-5.81 (m, 2H), 7.17-7.20 (m, 2H), 7.26 (d, *J* = 6.0 Hz, 1H), 7.88 (d, *J* = 6.0 Hz, 1H), 8.07 (d, *J* = 9.0 Hz, 1H); LC-MS, MS m/z 601 (M^+ + H).

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Etapa 5:

A una solución enfriada en hielo del producto de la Etapa 4, Ejemplo 1 (1.50 g, 2.50 mmol) en CH_2Cl_2 (10 mL) se agregó TFA (10 mL). La solución resultante se permitió calentar hasta temperatura ambiente y se agitó durante 2 horas. El solvente se removió *in vacuo*. El residuo se trituró con HCl 1M en éter dietílico, se colectó por filtración, y el sólido se lavó con éter dietílico para proporcionar el producto deseado como un sólido blanco higróscopico (1.43 g, 99.8%). ^{1}H RMN (CD_3OD) δ ppm 1.03-1.21 (m, 4H), 1.26-1.31 (m, 1H), 1.37-1.40 (m, 1H), 1.95-1.97 (m, 1H), 2.32-2.37 (m, 1H), 2.42-2.48 (m, 1H), 2.95-2.99 (m, 1H), 3.88 (d, *J* = 12.5 Hz, 2H), 3.98 (s, 3H), 4.40-4.42 (m. 1H), 5.16 (d, *J* = 10.5 Hz, 1H), 5.33 (d, *J* = 18.0 Hz, 1H), 5.62-5.69 (m, 1H), 5.97 (s a, 1H), 7.30-7.34 (m, 2H), 7.47 (d, *J* = 6.0 Hz, 1H), 7.90 (d, *J* = 6.5 Hz, 1H), 8.34 (d, *J* = 9.0 Hz, 1H), 9.14 (s a, 1H); LC-MS, MS m/z 501 (M^+ + H).

Etapa 6:

A una mezcla del producto de la Etapa 5, Ejemplo 1 (0.350 g, 0.610 mmol), HATU (0.302 g, 0.793 mmol), DIEA (0.277 g, 2.14 mmol) y diclorometano (6 mL) se agregó ácido (+/-)-2-(4,6-dimetilpiridin-2-ilamino)-3-metilbutanoico (0.135 g, 0.610 mmol, adquirido de Specs, catálogo # AP-836/41220382). La reacción se agitó a

001459

temperatura ambiente durante 14 horas. HATU adicional (0.302 g, 0.793 mmol), DIEA (0.079 g, 0.61 mmol) y ácido (+/-)-2-(4,6-dimetilpiridin-2-ilamino)-3-metilbutanoico (0.135 g, 0.610 mmol) se agregaron y la mezcla resultante se agitó durante 6 horas adicionales en un intento por impulsar la reacción a que finalice. La mezcla se concentró *in vacuo*, se disolvió en acetato de etilo (75 mL), y se lavó con HCl acuoso 1.0M (3 x 10mL). Los lavados HCl combinados se extrajeron con acetato de etilo (50 mL). Las fases orgánicas se combinaron y se lavaron con 10% $NaHCO_3$ acuoso (2 x 10 mL) y con salmuera, y luego se secaron sobre $MgSO_4$, se filtraron y se concentraron *in vacuo* hasta un residuo café oscuro. La purificación por HPLC preparativa de fase inversa dio dos productos con m/z idéntica por LCMS. El primer isómero en eluir por HPLC preparativa de fase inversa se etiquetó el Compuesto 1A (47.7 mg, 11.1%) y el segundo isómero en eluir se etiquetó el compuesto 1B (16.9 mg, 3.9%).

Compuesto 1A: ^{1}H RMN (500 MHz, CD_3OD) δ ppm 1.01 (d, J = 6.71 Hz, 3H), 1.10 (d. J = 6.71 Hz, 3H), 1.12-1.17 (m, 2H), 1.26-1.30 (m, 2H), 1.47 (dd, J = 9.46, 5.49 Hz, 1H), 1.85 (dd, J = 8.09, 5.34 Hz, 1H), 2.17 (s, 3H), 2.31 (c, J = 8.85 Hz, 2H), 2.36-2.40 (m, 2H), 2.41 (s, 3H), 2.65 (dd, J = 13.73, 7.02 Hz, 1H), 2.97-3.03 (m, 1H), 3.95 (s, 3H), 4.16 (dd, J =

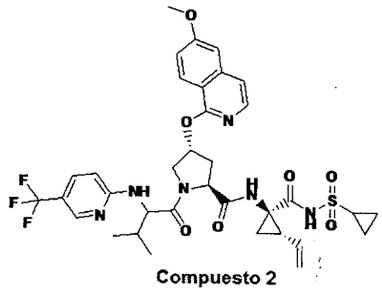
- 000467

12.05, 3.51 Hz, 1H), 4.30 (d, *J* = 11.60 Hz, 1H), 4.49 (d, *J* = 7.02 Hz, 1H), 4.68 (dd, *J* = 10.22, 7.17 Hz, 1H), 5.17 (dd, *J* = 10.38, 1.53 Hz, 1H), 5.35 (dd, *J* = 17.24, 1.07 Hz, 1H), 5.77-5.86 (m, 1H), 5.99 (s, 1H), 6.59 (s, 1H), 6.65 (s, 1H), 7.11 (dd, *J* = 9.16, 2.44 Hz, 1H), 7.23 (d, *J* = 2.44 Hz, 1H), 7.30 (d, *J* = 5.80 Hz, 1H), 7.94 (d, *J* = 5.80 Hz, 1H), 7.98 (d, *J* = 9.16 Hz, 1H); LC-MS, MS m/z 705 (M^+ + H).

Compuesto 1B: ^{1}H RMN (500 MHz, *MeOD*) δ ppm 1.02 (d, *J*=6.7 Hz, 3 H), 1.03-1.06 (m, *J*=2.1 Hz, 2 H), 1.07 (d, *J*=6.7 Hz, 3 H), 1.14-1.19 (m, 1 H), 1.20-1.25 (m, 1 H), 1.32 (dd, *J*=9.5, 5.2 Hz, 1 H), 1.81 (dd, *J*=8.1, 5.3 Hz, 1 H), 2.14 (c, *J*=8.9 Hz, 1 H), 2.25-2.39 (m, 2 H), 2.55 (dd, *J*=13.9, 6.9 Hz, 1 H), 2.88-2.94 (m, 1 H), 3.82 (s, 3 H), 4.12 (dd, *J*=11.7, 4.1 Hz, 1 H), 4.43 (dd, *J*=10.4, 7.0 Hz, 1 H), 4.55 (d, *J*=11.9 Hz, 1 H), 4.62 (d, *J*=9.2 Hz, 1 H), 5.03 (d, *J*=10.4 Hz, 1 H), 5.20 (d, *J*=17.1 Hz, 1 H), 5.65-5.74 (m, 1 H), 5.79 (t, *J*=3.5 Hz, 1 H), 6.99 (dd, *J*=9.2, 2.4 Hz, 1 H), 7.04 (d, *J*=2.1 Hz, 1 H), 7.11 (d, *J*=6.1 Hz, 1 H), 7.68 (t, *J*=7.6 Hz, 1 H), 7.73 (t, *J*=7.3 Hz, 1 H), 7.77 (d, *J*=6.1 Hz, 1 H), 7.79 (d, *J*=7.6 Hz, 1 H), 8.01 (d, *J*=7.6 Hz, 1 H), 8.07 (d, *J*=9.2 Hz, 1 H); LC-MS, MS m/z 705 (M^+ + H).

- 001461

Ejemplo 2: Preparación del Compuesto 2: N-(5-(trifluorometil)-2-piridinil)valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida



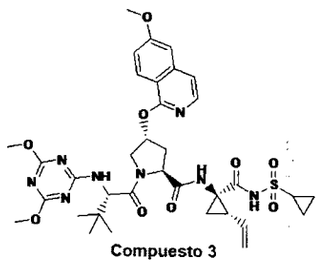
Compuesto 2

A una mezcla del producto de la Etapa 5, Ejemplo 1 (0.350 g, 0.610 mmol), HATU (0.464 g, 1.22 mmol), DIEA (0.316 g, 2.44 mmol) y diclorometano (6 mL) se agregó N-[5-(trifluorometil)-piridin-2-il]valina (0.320 g, 1.22 mmol). La reacción se agitó a temperatura ambiente durante 72 horas. La mezcla se concentró *in vacuo*, se disolvió en acetato de etilo (50 mL), y se lavó con HCl acuoso 1.0M (3 x 5 mL). Los lavados HCl se combinaron y luego se extrajeron con acetato de etilo (25 mL). Las fases orgánicas se combinaron y se lavaron con 10% $NaHCO_3$ acuoso (2 x 5 mL) y con salmuera, y luego se secaron sobre $MgSO_4$, se filtraron y se concentraron *in vacuo* hasta un residuo. El material sin refinar se pasó a través de un tapón de gel de sílice usando 95:5

- 000462

diclorometano:metanol. Además la purificación por HPLC preparativa de fase inversa dio el Compuesto 2 (0.174 g, 38.3%) como un sólido blanco. El compuesto 2 fue el mayor de los dos isómeros que se formaron en la reacción. ^{1}H RMN (500 MHz, *MeOD*) δ ppm 0.68 (d, *J*=5.5 Hz, 1 H), 0.77-0.85 (m, 2 H), 0.93 (d, *J*=6.7 Hz, 3 H), 0.99 (d, *J*=6.4 Hz, 3 H), 1.14 (t, *J*=7.2 Hz, 3 H), 1.31 (dd, *J*=9.3, 5.0 Hz, 1 H), 1.74-1.81 (m, 1 H), 2.02 - 2.12 (m, 1 H), 2.28 - 2.41 (m, 1 H), 2.48-2.61 (m, 1 H), 3.83 (s, 2 H), 3.84 (s, 1 H), 3.99-4.03 (m, 1 H), 4.29 - 4.40 (m, 1 H), 4.50 (c, *J*=8.4 Hz, 1 H), 4.98 (d, *J*=9.2 Hz, 1 H), 5.17 (d, *J*=17.4 Hz, 1 H), 5.60-5.72 (m, 1 H), 5.76 (s, 1 H), 6.35 (d, *J*=8.9 Hz, 1 H), 6.95 (dd, *J*=9.2, 2.4 Hz, 1 H), 7.04-7.12 (m, 2 H), 7.15-7.23 (m, 2 H), 7.79-7.84 (m, 2 H); LC-MS, MS m/z 745 (M^+ + H).

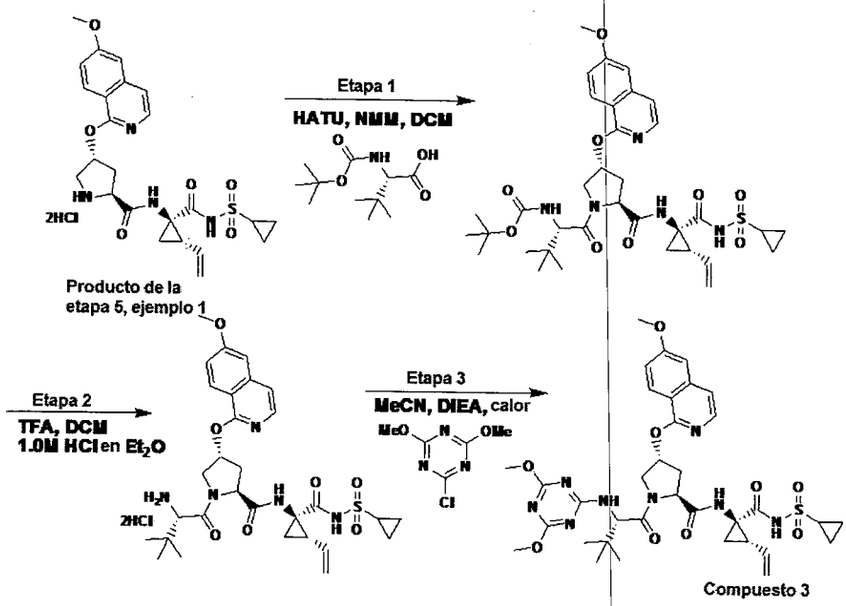
Ejemplo 3: Preparación del Compuesto 3: N-(4,6-dimetoxi-1,3,5-triazin-2-il)-3-metil-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida



Compuesto 3

000463

Esquema de reacción 1



Etapa 1:

Una mezcla del producto de la Etapa 5, Ejemplo 1 (70.2 g, 122 mmol), Boc-*terc*-leucina (31.2 g, 135 mmol), NMM (63.1 g, 624 mmol) y HATU (60.5 g, 159 mmol) en diclorometano (750 mL) se agitó a temperatura ambiente durante la noche. La mezcla se concentró *in vacuo* y al residuo se agregó acetato de etilo (3 L) y pH = 4 solución amortiguadora (1 L). La mezcla se agitó y las fases se separaron. La fase orgánica se lavó nuevamente con pH = 4 solución amortiguadora (2 x 1 L) y con salmuera (300 mL). La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró hasta una espuma anaranjada. El sólido sin refinar se purificó por cromatografía de gel de sílice (etapa de elusión con diclorometano, seguido

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por 10:1 diclorometano:acetona, luego con 7:1 diclorometano:acetona). Las cristalizaciones repetitivas del isopropanol del material concentrado dio el producto puro como hojuelas incoloras grandes (58.3 g, 67% de rendimiento). LC-MS, MS m/z 714 ($M^+ + H$).

Etapa 2:

A una solución agitada del producto de la Etapa 1, Ejemplo 3 (15.0 g, 21.0 mmol) en diclorometano seco (200 mL) se agregó TFA (100 mL). La mezcla se agitó durante 80 minutos y luego se concentró *in vacuo* hasta un residuo. El 1,2-Dicloroetano (200 mL) se agregó, y la mezcla se concentró nuevamente *in vacuo* para dar una espuma blanca. El material se disolvió en diclorometano seco (50 mL) y éter dietílico (50 mL) se agregó. La solución agitada rápidamente luego se trató lentamente con una mezcla de HCl 2.0M en éter (150 mL) y éter dietílico seco (250 mL). La suspensión resultante se agitó bajo nitrógeno durante 30 minutos, y luego se filtró. El sólido filtrado se enjuagó con éter dietílico y se permitió secar al aire. El sólido se secó en un horno al vacío a 40°C durante la noche para proporcionar un producto en polvo de flujo libre blanco como la sal bis-HCl (13.9 g, 96.3% de rendimiento). LC-MS, MS m/z 614 ($M^+ + H$).

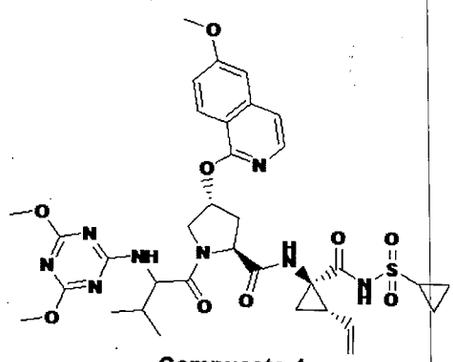
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Etapa 3:

A una solución del producto de la Etapa 2, Ejemplo 3 (0.253 g, 0.369 mmol) y DIEA (0.215 g, 1.66 mmol) en acetonitrilo (4 mL) se agregó 2-cloro-4,6-dimetoxi-1,3,5-triazeno (0.100 g, 0.553 mmol). La mezcla se calentó a 135°C en un recipiente a presión Chemglass durante 2 horas. La mezcla se concentró *in vacuo*, y el residuo se disolvió en acetato de etilo (50 mL) y se lavó con HCl 1.0M acuoso (2 x 5 mL) seguido por 10% carbonato de sodio acuoso y salmuera. El material orgánico se secó sobre $MgSO_4$, se filtró y se concentró. La purificación por cromatografía por desorción súbita en gel de sílice (97:3 diclorometano:metanol) dio el compuesto puro 3 (0.252 g, 91% de rendimiento) como un sólido blanco. ^{1}H RMN (500 MHz, *MeOD*) δ ppm 1.07 (s, 9 H), 1.09-1.14 (m, 2 H), 1.25-1.33 (m, 2 H), 1.48 (dd, *J*=9.5, 5.5 Hz, 1 H), 1.93 (dd, *J*=8.1, 5.3 Hz, 1 H), 2.24-2.39 (m, 2 H), 2.94-3.03 (m, 1 H), 3.55 (s, 3 H), 3.83 (s, 3 H), 3.95 (s, 3 H), 4.04 (dd, *J*=4.9, 3.1 Hz, 1 H), 4.08 (s, 2 H), 4.45 (d, *J*=11.9 Hz, 1 H), 4.67 (dd, *J*=10.4, 7.3 Hz, 1 H), 4.91 (s, 1 H), 5.16 (d, *J*=10.4 Hz, 1 H), 5.34 (d, *J*=17.1 Hz, 1 H), 5.75-5.84 (m, 1 H), 5.90-5.94 (m, 1 H), 7.03 (dd, *J*=9.2, 2.4 Hz, 1 H), 7.16 (d, *J*=2.1 Hz, 1 H), 7.26 (d, *J*=5.8 Hz, 1 H), 7.80 (d, *J*=8.9 Hz, 1 H), 7.89 (d, *J*=5.8 Hz, 1 H); LC-MS, MS m/z 753 (M^+ + H).

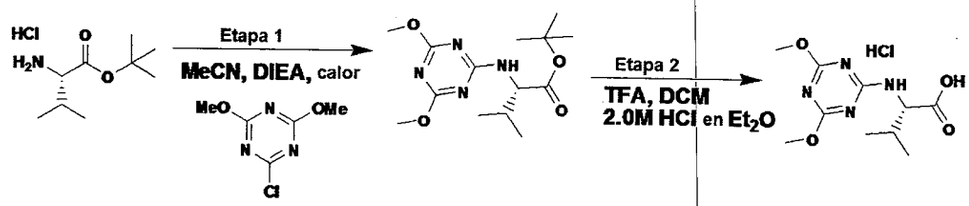
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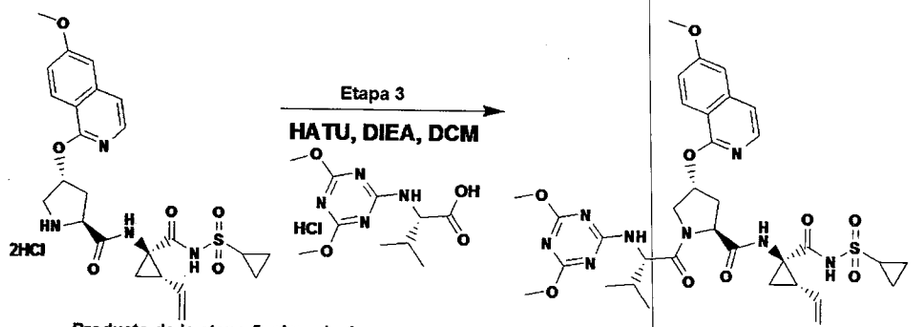
Ejemplo 4: Preparación del Compuesto 4: N-(4,6-dimetoxi-1,3,5-triazin-2-il)valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida



Compuesto 4

Esquema de reacción 1





Producto de la etapa 5, ejemplo 1

Compuesto 4

Etapa 1:

A una mezcla de clorohidrato de éster terc-butílico de valina (0.367 g, 1.75 mmol) y DIEA (0.567 g, 4.38 mmol) en acetonitrilo (5 mL) se agregó 2-cloro-4,6-

000467

dimetoxi-1,3,5-triazeno (0.476 g, 2.63 mmol). La mezcla se calentó a 130°C en un reactor de microondas durante 1 hora. El solvente se removió y el residuo café viscoso se disolvió en acetato de etilo (75 mL) y la solución se lavó con HCl acuoso 1.0M (2 x 10 mL). Los extractos acuosos se combinaron y se volvieron a extraer con acetato de etilo (50 mL), y las fases orgánicas se combinaron y se lavaron con 10% carbonato de sodio acuoso (15 mL) y luego con salmuera. La fase orgánica se secó sobre $MgSO_4$ anhidro, se filtró y se concentró hasta un aceite café el cual se purificó por cromatografía por desorción súbita en gel de sílice (97:3 diclorometano:metanol) para dar el producto como un aceite viscoso café claro (0.521 g, 95% de rendimiento).

Etapa 2:

El producto de la Etapa 1, Ejemplo 4 (0.500 g, 1.60 mmol) se disolvió en diclorometano (5 mL) y se trató con TFA (5 mL). La mezcla se agitó a temperatura ambiente durante 3 horas y luego se concentró *in vacuo*. El residuo luego se disolvió en 1,2-dicloroetano (20 mL) y se concentró nuevamente *in vacuo*. El residuo luego se disolvió en diclorometano (3 mL) y se agregó gota a gota a una solución agitada rápidamente de HCl 2.0M en éter (10 mL). No se presentó precipitación. La solución se concentró *in vacuo*

- 001468

para dar un sólido ligeramente amarillo el cual se secó *in vacuo*. Así se obtuvo un sólido amarillo (0.45 g, 96% de rendimiento) el cual se usó posteriormente sin purificación adicional.

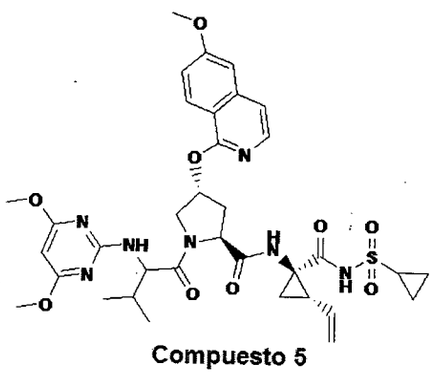
Etapa 3:

A una mezcla del producto de la Etapa 5, Ejemplo 1 (0.421 g, 0.734 mmol) y DIEA (0.428 g, 3.30 mmol) en diclorometano (7 mL) se agregó el producto de la Etapa 2, Ejemplo 4 (0.215 g, 0.734 mmol) y HATU (0.335 g, 0.881 mmol). La mezcla se agitó a temperatura ambiente durante 80 minutos. El solvente se removió y el residuo café viscoso se disolvió en acetato de etilo (50 mL) y la solución se lavó con HCl acuoso 1.0M (2 x 10 mL). Los extractos acuosos se combinaron y se volvieron a extraer con acetato de etilo (50 mL), y las fases orgánicas se combinaron y se lavaron con 10% carbonato de sodio acuoso (15 mL) y luego con salmuera. La fase orgánica se secó sobre $MgSO_4$ anhidro, se filtró y se concentró hasta un sólido café el cual se purificó por cromatografía por desorción súbita en gel de sílice (97:3 diclorometano:metanol) para dar el Compuesto 4 como un sólido blanco (0.243 g, 45% de rendimiento). ^{1}H RMN (500 MHz, *MeOD*) δ ppm 0.71 (d, *J*=6.4 Hz, 3 H), 0.73-

000469

0.78 (m, 1 H), 0.79-0.88 (m, 1 H), 0.90-0.98 (m, 1 H), 1.01-1.07 (m, 1 H), 1.08 (d, *J*=6.7 Hz, 3 H), 1.23 (dd, *J*=9.0, 5.3 Hz, 1 H), 1.90 (c, *J*=8.5 Hz, 1 H), 1.99-2.06 (m, 1 H), 2.09-2.20 (m, 1 H), 2.22-2.33 (m, 1 H), 2.33 - 2.41 (m, 1 H), 2.47 (dd, *J*=13.4, 6.1 Hz, 1 H), 3.25 (s, 3 H), 3.45 (s, 2 H), 3.75 (s, 3 H), 4.11 (dd, *J*=11.7, 3.5 Hz, 1 H), 4.41 (d, *J*=12.2 Hz, 1 H), 4.52 (dd, *J*=11.9, 6.4 Hz, 1 H), 4.63 - 4.70 (m, 1 H), 4.85 (d, *J*=10.7 Hz, 1 H), 4.95 (d, *J*=17.4 Hz, 1 H), 5.81 (t, *J*=3.2 Hz, 1 H), 5.85 - 5.97 (m, 1 H), 6.48 (d, *J*=9.2 Hz, 1 H), 7.04 (s, 1 H), 7.18 (d, *J*=5.8 Hz, 1 H), 7.35 (d, *J*=8.9 Hz, 1 H), 7.80 (d, *J*=6.1 Hz, 1 H); LC-MS, MS m/z 739 (M^+ + H).

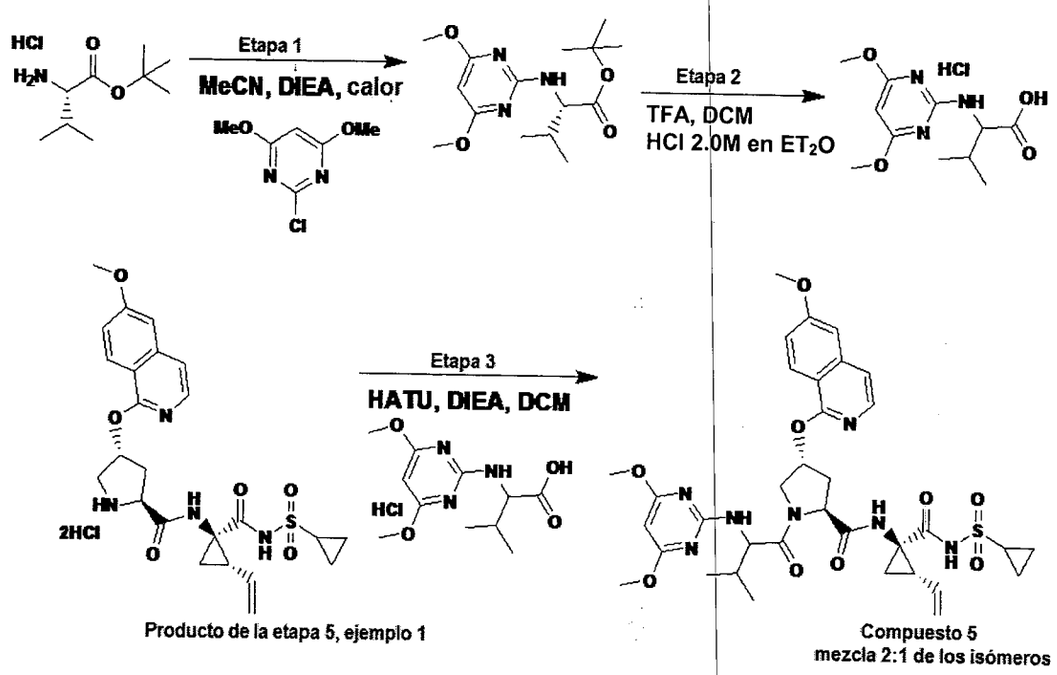
Ejemplo 5: Preparación del Compuesto 5: N-(4,6-dimetoxi-2-pirimidinil)valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida



Compuesto 5

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Esquema de reacción 1



Etapa 1:

A una mezcla de clorohidrato de éster terc-butílico de valina (1.55 g, 7.39 mmol) y DIEA (2.01 g, 15.5 mmol) en acetonitrilo (37 mL) se agregó 2-cloro-4,6-dimetoxipirimidina (1.55 g, 8.87 mmol). La mezcla se calentó a 130°C en un recipiente a presión Chemglass durante 48 horas. El solvente se removió y el residuo café viscoso se disolvió en acetato de etilo (100 mL) y la solución se lavó con HCl acuoso 1.0M (2 x 25 mL). Los extractos acuosos se combinaron y se volvieron a extraer con acetato de etilo (50 mL), y las fases orgánicas se combinaron y se lavaron con 10% carbonato de sodio acuoso y luego con salmuera. La fase orgánica se secó sobre $MgSO_4$ anhidro, se filtró y se

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concentró hasta un aceite café el cual se purificó por cromatografía por desorción súbita en gel de sílice (gradiente de etapa 9:1 hexanos:acetato de etilo luego 1:1 hexanos:acetato de etilo) para dar el producto como un aceite viscoso café (1.02 g, 44% de rendimiento).

Etapa 2:

El producto de la Etapa 1, Ejemplo 5 (0.944 g, 3.03 mmol) se disolvió en diclorometano (10 mL) y se trató con TFA (10 mL). La mezcla se agitó a temperatura ambiente durante 4 horas y luego se concentró *in vacuo*. El residuo luego se disolvió en 1,2-dicloroetano (50 mL) y se concentró nuevamente *in vacuo*. El residuo luego se disolvió en diclorometano (3 mL) y se agregó gota a gota a una solución agitada rápidamente de HCl 1.0M en éter y hexanos (100 mL). No se presentó el precipitado. La solución se concentró *in vacuo* para dar un sólido espumoso café el cual se usó posteriormente sin purificación adicional.

Etapa 3:

A una mezcla del producto de la Etapa 5, Ejemplo 1 (0.425 g, 0.741 mmol) y DIEA (0.432 g, 3.34 mmol) en diclorometano (7 mL) se agregó el producto de la Etapa 2, Ejemplo 5 (0.259 g, 0.889 mmol) y HATU

(0.366 g, 0.963 mmol). La mezcla se agitó a temperatura ambiente durante 16 horas. El solvente se removió y el residuo café viscoso se disolvió en acetato de etilo (50 mL) y la solución se lavó con HCl acuoso 1.0M (2 x 10 mL). Los extractos acuosos se combinaron y luego se extrajeron con acetato de etilo (30 mL), y las fases orgánicas se combinaron y se lavaron con 10% carbonato de sodio acuoso (15 mL) y luego con salmuera. La fase orgánica se secó sobre $MgSO_4$ anhidro, se filtró y se concentró hasta un aceite café viscoso el cual se pasó a través de un tapón de gel de sílice (95:5 diclorometano:metanol). El producto se purificó además por HPLC preparativa de fase inversa para dar el compuesto sólido blanco 5 (0.243 g, 45% de rendimiento) como una mezcla aparente de dos isómeros en una relación 2 hasta 1. Los isómeros no se separaron. LC-MS, MS m/z 738 (M^+ + H).

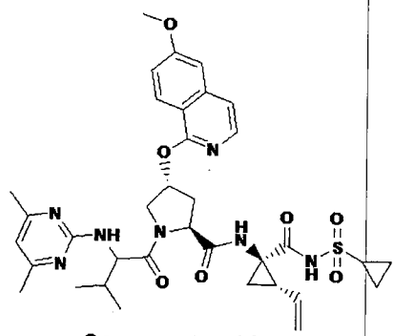
Isómeros del compuesto 6:

N-(4,6-dimetil-2-pirimidinil)-D-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida

N-(4,6-dimetil-2-pirimidinil)-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida

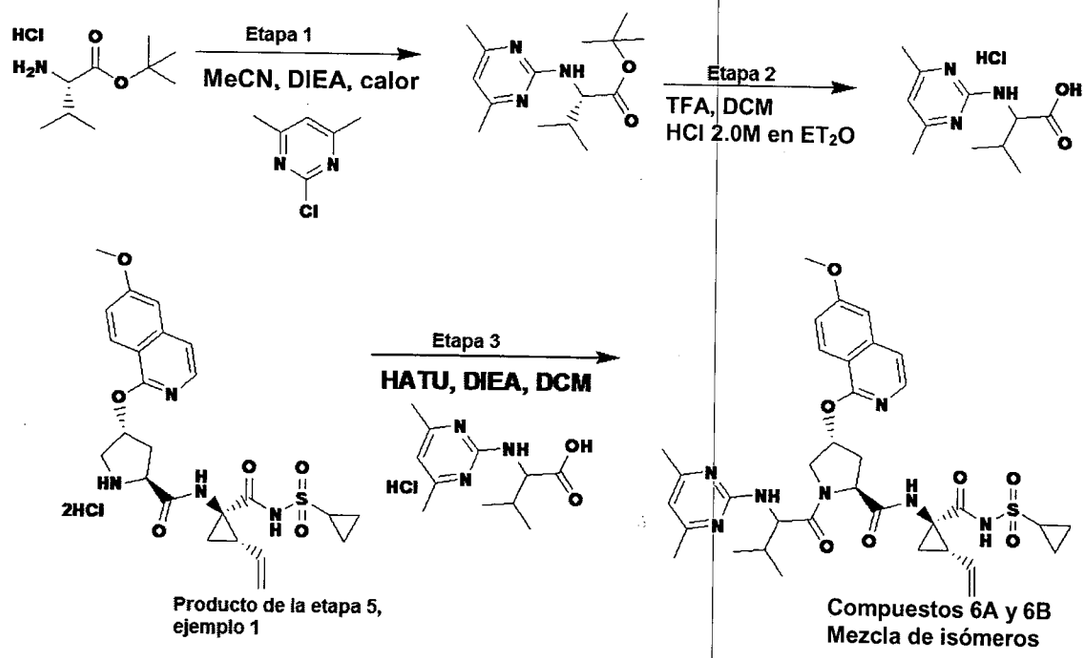
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Ejemplo 6: Preparación de los Compuestos 6A y 6B



Compuestos 6A y 6B

Esquema de reacción 1



Etapa 1:

A una mezcla de clorohidrato de éster terc-butílico de valina (3.09 g, 14.7 mmol) y DIEA (4.01 g, 31.0 mmol) en acetonitrilo (50 mL) se agregó 2-cloro-4,6-dimetilpirimidina (2.31 g, 16.2 mmol). La mezcla se

001474

calentó a 135°C en un recipiente a presión Chemglass durante 72 horas. El solvente se removió y el residuo café viscoso se disolvió en acetato de etilo (150 mL) y la solución se lavó con HCl acuoso 1.0M (2 x 50 mL). Los extractos acuosos se combinaron y se volvieron a extraer con acetato de etilo (2 x 50 mL), y las fases orgánicas se combinaron y se lavaron con 10% carbonato de sodio acuoso y luego con salmuera. La fase orgánica se secó sobre $MgSO_4$ anhidro, se filtró y se concentró hasta un aceite café el cual se purificó por cromatografía por desorción súbita en gel de sílice (4:1 hexanos:acetato de etilo) para dar el producto el cual se usó directamente en la siguiente etapa.

Etapa 2:

El producto de la Etapa 1, Ejemplo 6 (1.80 g, 6.44 mmol) se disolvió en diclorometano (25 mL) y se trató con TFA (25 mL). La mezcla se agitó a temperatura ambiente durante 3 horas y luego se concentró *in vacuo*. El residuo luego se disolvió en 1,2-dicloroetano (50 mL) y se concentró nuevamente *in vacuo*. El residuo luego se disolvió en acetato de etilo (50 mL) y luego se extrajo con acuoso HCl 1N (2 x 50). Los extractos de ácido combinados se concentraron *in vacuo* para dar un sólido amarillo (1.23 g). LC-MS, MS m/z 224 $(M^+ + H)$.

006475

Etapa 3:

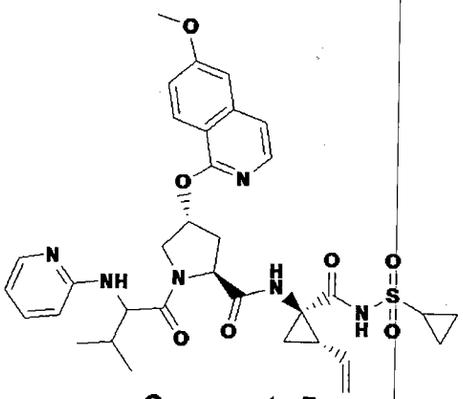
A una mezcla del producto de la Etapa 5, Ejemplo 1 (0.438 g, 0.764 mmol) y DIEA (0.495 g, 3.82 mmol) en diclorometano (10 mL) se agregó el producto de la Etapa 2, Ejemplo 6 (0.218 g, 0.840 mmol) y HATU (0.378 g, 0.993 mmol). La mezcla se agitó a temperatura ambiente durante 15 horas. El solvente se removió y el residuo café viscoso se disolvió en acetato de etilo (75 mL) y la solución se lavó con HCl acuoso 1.0M (2 x 10 mL). Los extractos acuosos se combinaron y luego se extrajeron con acetato de etilo (50 mL), y las fases orgánicas se combinaron y se lavaron con 10% carbonato de sodio acuoso (15 mL) y luego con salmuera. La fase orgánica se secó sobre $MgSO_4$ anhidro, se filtró y se concentró hasta un aceite café viscoso el cual se purificó por cromatografía por desorción súbita en gel de sílice (Gradiente 97:3 diclorometano:metanol luego 95:5 diclorometano:metanol). Dos compuestos distintos con m/z idénticos por LCMS se separaron. El primer producto en eluir fue el compuesto menor y se etiquetó el compuesto 6A (sólido amarillo claro, 0.0408 g, 7.6% de rendimiento). El producto mayor eluido segundo de la columna (sólido amarillo, 0.280 g) y se purificó además por HPLC preparativa de fase inversa para dar el Compuesto 6B (0.040 g, 7.4 % de rendimiento) como una sal bis-HCl sólida amarilla.

- 001475

Compuesto 6A: ^{1}H RMN (500 MHz, *MeOD*) δ ppm 0.85 (d, *J*=7.0 Hz, 3 H), 0.96 (d, *J*=6.7 Hz, 3 H), 1.00 (dd, *J*=12.8, 7.0 Hz, 1 H), 1.05 - 1.14 (m, 2 H), 1.23 - 1.29 (m, 1 H), 1.37 (dd, *J*=9.6, 5.3 Hz, 1 H), 1.87 (dd, *J*=8.1, 5.3 Hz, 1 H), 1.99 - 2.05 (m, 1 H), 2.25 (c, *J*=8.7 Hz, 1 H), 2.30 (d, *J*=6.4 Hz, 1 H), 2.36 - 2.47 (m, 5 H), 2.60 - 2.66 (m, 1 H), 2.83 - 2.85 (m, 1 H), 2.87 - 2.93 (m, 1 H), 3.96 (s, 3 H), 4.28 - 4.32 (m, 1 H), 4.37 - 4.42 (m, 1 H), 4.57 - 4.62 (m, 1 H), 4.72 (d, *J*=8.2 Hz, 1 H), 5.14 (dd, *J*=10.4, 1.5 Hz, 1 H), 5.33 (dd, *J*=17.1, 1.5 Hz, 1 H), 5.71 - 5.80 (m, 1 H), 5.95 (s, 1 H), 7.19 (dd, *J*=9.2, 2.4 Hz, 1 H), 7.24 (d, *J*=2.4 Hz, 1 H), 7.31 (d, *J*=6.1 Hz, 1 H), 7.94 (d, *J*=6.1 Hz, 1 H), 8.05 (d, *J*=9.2 Hz, 1 H); LC-MS, MS m/z 706 (M^+ + H).

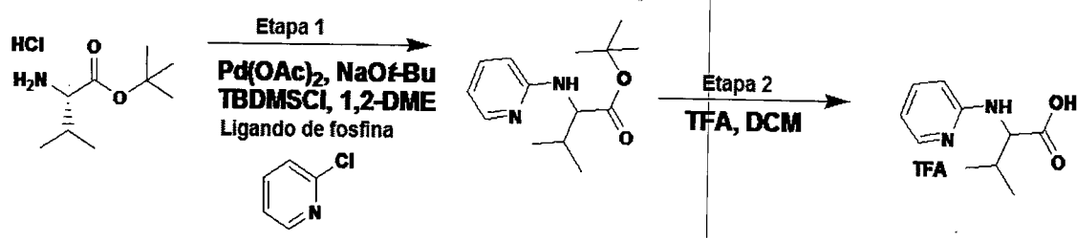
Compuesto 6B: ^{1}H RMN (500 MHz, *MeOD*) δ ppm 1.17 (d, *J*=6.7 Hz, 1 H), 1.28 (d, *J*=6.7 Hz, 1 H), 1.31 (d, *J*=6.7 Hz, 3 H), 1.39 (d, *J*=6.7 Hz, 3 H), 1.43 - 1.56 (m, 2 H), 1.69 (dd, *J*=9.5, 5.2 Hz, 1 H), 2.15 - 2.26 (m, 3 H), 2.50 - 2.56 (m, 1 H), 2.57 - 2.62 (m, 1 H), 2.63 - 2.72 (m, 3 H), 2.89 (dd, *J*=13.9, 6.6 Hz, 1 H), 3.20 - 3.27 (m, 1 H), 4.22 (s, 3 H), 4.48 (dd, *J*=12.2, 3.7 Hz, 1 H), 4.79 (d, *J*=11.9 Hz, 1 H), 4.85 - 4.92 (m, 1 H), 5.02 (d, *J*=7.9 Hz, 1 H), 5.40 (d, *J*=11.6 Hz, 1 H), 5.59 (d, *J*=16.8 Hz, 1 H), 6.00 - 6.09 (m, 1 H), 6.25 (t, *J*=3.2 Hz, 1 H), 6.94 (s, 1 H), 7.42 (dd, *J*=9.0, 2.3 Hz, 1 H), 7.54 (d, *J*=2.1 Hz, 1 H), 7.64 (d, *J*=6.1 Hz, 1 H), 8.19 (d, *J*=6.1 Hz, 1 H), 8.23 (d, *J*=9.2 Hz, 1 H); LC-MS, MS m/z 706 (M^+ + H).

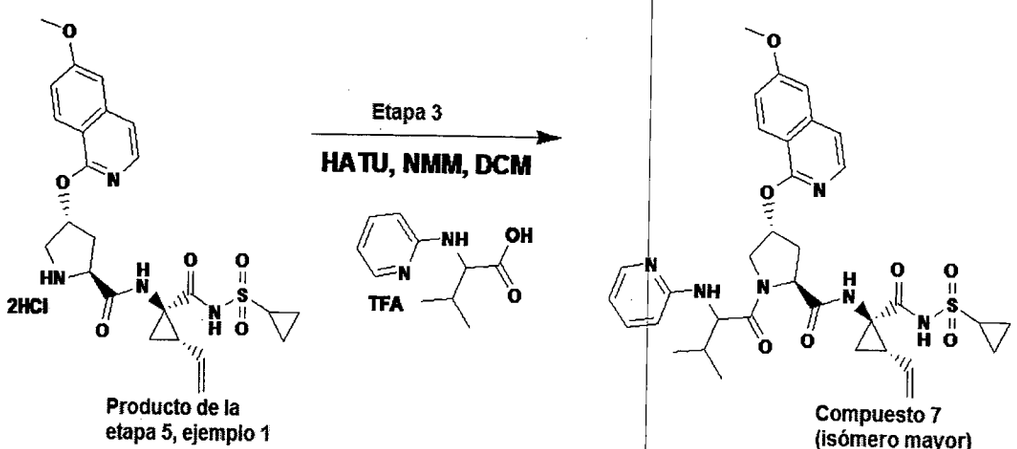
Ejemplo 7: Preparación del Compuesto 7: N-2-piridinilvalil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida



Compuesto 7

Esquema de reacción 1





001478

Etapa 1:

A una mezcla de 2-cloropiridina (0.205 g, 1.80 mmol) y terc-butóxido de sodio (0.590 g, 6.13 mmol) en 1,2-dicloroetano seco (1 mL) se agregó una solución pre-mezclada de $Pd(OAc)_2$ (0.0405 g, 0.180 mmol) y (*R*)-(-)-1-[(*S*)-(diciclohexilfosfino)ferrocenil]etil di-*terc*-Butil fosfina (0.100 g, 0.180 mmol, StrMS Chemicals catálogo # 26-0975, CAS # [158923-11-6]) en 1,2-dimetoxietano seco (1 mL). La mezcla se agitó, y se trató rápidamente con TBDMSCl (0.598 g, 3.97 mmol). La mezcla se agitó brevemente, y se agregó rápidamente clorohidrato de éster terc-butílico de valina (0.454 g, 2.16 mmol) y se agitó nuevamente. Una exotermia moderada resultó inmediatamente. Después de 10 minutos de agitación, la mezcla se agregó para agitar rápidamente a una solución amortiguadora de pH = 7 (50 mL). Se agregó acetato de etilo (50 mL) y se agitaron y se separaron las fases. La fase acuosa se saturó por la adición de NaCl y se extrajo nuevamente con acetato de etilo (2 x 50 mL). Los extractos orgánicos se combinaron y se lavaron con salmuera (20 mL), se secaron sobre $MgSO_4$, se filtraron y se concentraron *in vacuo* hasta un residuo oscuro. El producto sin refinar se purificó por cromatografía por desorción súbita en gel de sílice (8:1 hexanos:acetato de etilo) para dar un líquido incoloro (0.365 g) el cual se determinó que contiene el producto

- 60479

deseado más 0.6 equivalentes de subproducto TBDMS. El material se utilizó como tal en la siguiente etapa sin purificación adicional. El rendimiento aproximado fue 61%. LC-MS, MS m/z 251 ($M^+ + H$).

Etapa 2:

El producto de la Etapa 1, Ejemplo 7 (0.944g, 3.03 mmol) se disolvió en diclorometano (10 mL) y se trató con TFA (10 mL). La mezcla se agitó a temperatura ambiente durante 1.5 horas y luego se concentró *in vacuo*. El residuo luego se purificó por HPLC preparativa de fase inversa, y luego se purificó además por cromatografía por desorción súbita en gel de sílice (Gradiente, 10:1 diclorometano:metanol hasta 5:1 diclorometano:metanol) para dar un sólido ceroso incoloro (0.126 g, 59.0% de rendimiento). LC-MS, MS m/z 195 ($M^+ + H$).

Etapa 3:

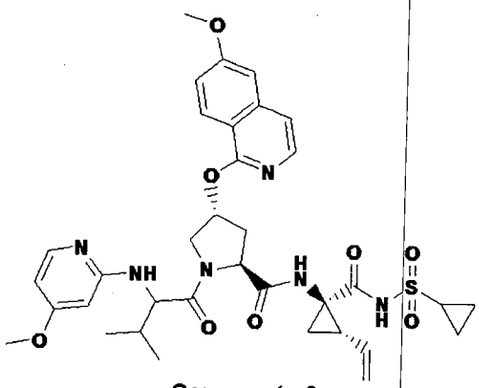
A una mezcla del producto de la Etapa 5, Ejemplo 1 (0.250 g, 0.436 mmol) y NMM (0.176 g, 1.74 mmol) en diclorometano (2 mL) se agregó el producto de la Etapa 2, Ejemplo 7 (0.085 g, 0.44 mmol) y HATU (0.199 g, 0.523 mmol). La mezcla se agitó a temperatura ambiente durante 96 horas. El solvente se removió, el residuo café viscoso se disolvió en acetato de etilo (50 mL), y la solución se lavó con HCl acuoso 1.0M. Los extractos acuosos se combinaron y luego se

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extrajeron con acetato de etilo, y las fases orgánicas se combinaron y se lavaron con 10% carbonato de sodio acuoso y luego con salmuera. La fase orgánica se secó sobre anhidro $MgSO_4$, se filtró y se concentró hasta un residuo el cual se purificó por HPLC preparativa de fase inversa para dar el Compuesto 7 (0.243 g, 45% de rendimiento) como un sólido blanco. El compuesto 7 fue el mayor de los dos isómeros formados en la reacción con MS m/z idéntico por LCMS. El isómero menor (más retenido en la Columna HPLC preparativa de fase inversa que el isómero mayor) no se aisló. ^{1}H RMN (500 MHz, MeOD) δ ppm 0.99 (d, *J*=6.71 Hz, 3 H) 1.12 (d, *J*=6.41 Hz, 3 H) 1.14 - 1.19 (m, 2 H) 1.24 - 1.31 (m, 1 H) 1.31 - 1.37 (m, 1 H) 1.48 (dd, *J*=9.46, 5.49 Hz, 1 H) 1.95 (dd, *J*=8.09, 5.34 Hz, 1 H) 2.32 (c, *J*=8.85 Hz, 1 H) 2.42 (ddd, *J*=13.96, 10.15, 4.27 Hz, 1 H) 2.47 - 2.55 (m, 1 H) 2.68 (dd, *J*=13.73, 7.02 Hz, 1 H) 3.02 (ddd, *J*=12.59, 8.16, 4.88 Hz, 1 H) 3.37 (s, 1 H) 3.95 (s, 3 H) 4.22 (dd, 1 H) 4.31 (d, *J*=11.90 Hz, 1 H) 4.34 (d, *J*=8.54 Hz, 1 H) 4.70 (dd, *J*=10.22, 7.17 Hz, 1 H) 5.17 (d, *J*=10.38 Hz, 1 H) 5.36 (d, *J*=17.09 Hz, 1 H) 5.82 (ddd, *J*=17.24, 9.61, 9.46 Hz, 1 H) 5.97 (t, *J*=3.20 Hz, 1 H) 6.93 (t, *J*=6.71 Hz, 1 H) 7.02 (d, *J*=9.16 Hz, 1 H) 7.14 (dd, *J*=9.00, 2.29 Hz, 1 H) 7.23 (d, *J*=2.14 Hz, 1 H) 7.31 (d, *J*=6.10 Hz, 1 H) 7.83 (t, *J*=7.93 Hz, 1 H) 7.88 (d, *J*=6.41 Hz, 1 H) 7.93 (d, *J*=6.10 Hz, 1 H) 8.03 (d, *J*=9.16 Hz, 1 H); LC-MS, MS m/z 677 (M^+ + H).

001481

Ejemplo 8: Preparación del Compuesto 8: N-(4-metoxi-2-piridinil)valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida



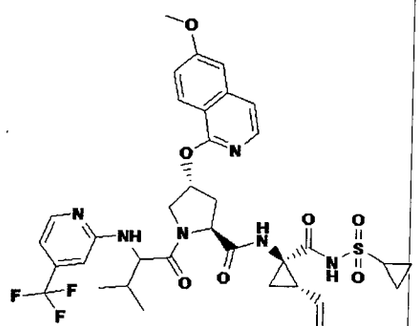
Compuesto 8

El compuesto 8 se preparó por el mismo procedimiento como se describe por la preparación del Compuesto 7, excepto que 2-cloro-4-metoxipiridina (259 mg, 1.80 mmol) se usó en la Etapa 1 en lugar de 2-cloropiridina, y HCl 2.0M en éter se agregó al producto de la etapa 1 concentrado en diclorometano para dar la sal de clorohidrato en la etapa 2. La escala de las etapas 2 y 3 se ajustó también con base en los rendimientos de las etapas previas. El compuesto 8 (0.0290 g, 11.6% de rendimiento) se obtuvo como una sal bis-TFA de polvo blanco opaco a partir de la HPLC preparativa de fase inversa. Este compuesto fue un isómero sencillo. ^{1}H RMN (500 MHz, MeOD) δ ppm 1.00 (d, *J*=6.71 Hz, 3 H) 1.11 (d, *J*=6.71 Hz, 3 H) 1.16 (dd, *J*=7.63, 2.75 Hz, 2 H) 1.22 - 1.42 (m, 4 H) 1.48 (dd, *J*=9.61, 5.34 Hz, 1 H) 1.93 - 1.97 (m, 1 H) 2.32 (c,

000482

J=8.85 Hz, 1 H) 2.36 - 2.50 (m, 2 H) 2.67 (dd, *J*=13.43, 7.02 Hz, 1 H) 2.89 (s, 1 H) 3.01 (ddd, *J*=12.82, 8.09, 4.73 Hz, 1 H) 3.17 - 3.27 (m, 1 H) 3.84 (s, 3 H) 3.95 (s, 3 H) 3.98 - 4.08 (m, 1 H) 4.20 (dd, 1 H) 4.26 - 4.33 (m, 2 H) 4.70 (dd, *J*=10.38, 7.02 Hz, 1 H) 5.17 (dd, *J*=10.53, 1.37 Hz, 1 H) 5.36 (dd, *J*=17.09, 1.22 Hz, 1 H) 5.77 - 5.87 (m, *J*=17.17, 9.58, 9.58 Hz, 1 H) 5.97 (t, *J*=3.36 Hz, 1 H) 6.32 (d, *J*=2.44 Hz, 1 H) 6.55 (dd, *J*=7.32, 2.14 Hz, 1 H) 7.14 (dd, *J*=9.16, 2.44 Hz, 1 H) 7.22 (d, *J*=2.44 Hz, 1 H) 7.30 (d, *J*=5.80 Hz, 1 H) 7.72 (d, *J*=7.32 Hz, 1 H) 7.93 (d, *J*=5.80 Hz, 1 H) 8.01 (d, *J*=9.16 Hz, 1 H); LC-MS, MS m/z 707 (M^+ + H).

Ejemplo 9: Preparación de Compuesto 9: N-(4-(trifluorometil)-2-piridinil)valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida



Compuesto 9

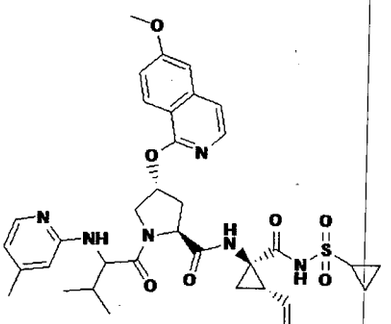
El compuesto 9 se preparó por el mismo procedimiento como se describe por la preparación del

080483

Compuesto 7, excepto que 2-cloro-4-trifluorometil piridina (0.328 g, 1.80 mmol) se usó en la etapa 1 en lugar de 2-cloropiridina, y HCl 2.0M en éter se agregó al producto de la etapa 1 concentrado en diclorometano para dar la sal de clorohidrato en la etapa 2. La escala de las etapas 2 y 3 se ajustó también con base en los rendimientos de las etapas previas. El compuesto 9 (0.0630 g, 12.6% de rendimiento) se obtuvo como una sal bis-TFA sólida azul turquesa oscuro a partir de la HPLC preparativa de fase inversa. Este compuesto fue un isómero sencillo. ^{1}H RMN (500 MHz, MeOD) δ ppm 1.04 (d, *J*=6.41 Hz, 3 H) 1.08 (d, *J*=6.41 Hz, 3 H) 1.10 - 1.16 (m, 2 H) 1.18 - 1.38 (m, 3 H) 1.45 (dd, *J*=9.46, 5.19 Hz, 1 H) 1.93 (dd, *J*=7.93, 5.49 Hz, 1 H) 2.18 - 2.24 (m, 1 H) 2.29 (c, *J*=8.95 Hz, 1 H) 2.33 - 2.42 (m, 1 H) 2.58 (dd, *J*=12.97, 6.56 Hz, 1 H) 2.89 (s, 1 H) 2.96 - 3.05 (m, 1 H) 3.85 - 3.93 (m, 1 H) 3.96 (s, 3 H) 4.10 (dd, *J*=11.60, 2.75 Hz, 1 H) 4.49 (d, *J*=9.77 Hz, 1 H) 4.57 (dd, *J*=10.68, 6.71 Hz, 1 H) 4.92 (d, *J*=11.90 Hz, 1 H) 5.16 (d, *J*=10.38 Hz, 1 H) 5.34 (d, *J*=17.40 Hz, 1 H) 5.75 - 5.86 (m, 1 H) 5.94 (s, 1 H) 6.20 (d, *J*=4.58 Hz, 1 H) 6.69 (s, 1 H) 7.05 (dd, *J*=9.00, 2.29 Hz, 2 H) 7.25 (d, *J*=2.14 Hz, 1 H) 7.86 (d, *J*=9.16 Hz, 1 H) 7.96 (d, *J*=5.80 Hz, 1 H); LC-MS, MS m/z 745 (M^+ + H).

- 000484

Ejemplo 10: Preparación del Compuesto 10: N-(4-metil-2-piridinil)valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida



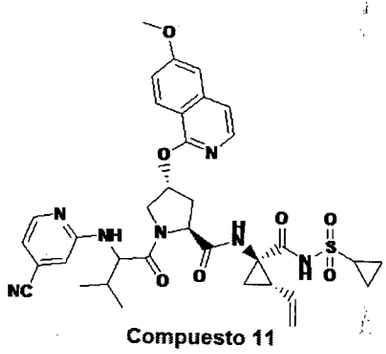
Compuesto 10

El compuesto 10 se preparó por el mismo procedimiento como se describe por la preparación del Compuesto 7, excepto que 2-bromo-4-metil piridina (0.310 g, 1.80 mmol) se usó en la etapa 1 en lugar de 2-cloropiridina, y HCl 2.0M en éter se agregó al producto de la etapa 1 concentrado en diclorometano para dar la sal de clorohidrato en la etapa 2. La escala de las etapas 2 y 3 se ajustó también con base en los rendimientos de las etapas previas. El compuesto 10 (0.0110 g, 8.9% de rendimiento) se obtuvo como una sal bis-TFA de polvo blanco opaco a partir de la HPLC preparativa de fase inversa. Este compuesto fue un isómero sencillo. ^{1}H RMN (500 MHz, MeOD) δ ppm 0.98 (d, *J*=6.41 Hz, 3 H) 1.11 (d, *J*=6.71 Hz, 3 H) 1.14 - 1.19 (m, 2 H) 1.23 - 1.38 (m, 4 H) 1.48 (dd, *J*=9.46, 5.49 Hz, 1 H) 1.95 (dd, *J*=7.93, 5.49 Hz, 1 H) 2.30 (s, 3 H) 2.31 - 2.36 (m, 1 H) 2.37 - 2.52 (m, 2 H) 2.67 (dd,

001485

J=14.04, 7.02 Hz, 1 H) 2.89 (s, 1 H) 2.98 - 3.05 (m, 1 H) 3.95 (s, 3 H) 3.96 (d, *J*=1.83 Hz, 1 H) 4.21 (dd, 1 H) 4.26 - 4.33 (m, 2 H) 4.69 (dd, *J*=10.22, 7.17 Hz, 1 H) 5.18 (d, *J*=10.38 Hz, 1 H) 5.36 (d, *J*=17.09 Hz, 1 H) 5.77 - 5.87 (m, *J*=17.17, 9.58, 9.58 Hz, 1 H) 5.97 (s, 1 H) 6.78 (d, *J*=6.41 Hz, 1 H) 6.81 (s, 1 H) 7.13 (dd, *J*=9.00, 2.29 Hz, 1 H) 7.22 (d, *J*=2.14 Hz, 1 H) 7.30 (d, *J*=6.10 Hz, 1 H) 7.72 (d, *J*=6.41 Hz, 1 H) 7.93 (d, *J*=6.10 Hz, 1 H) 8.01 (d, *J*=9.16 Hz, 1 H); LC-MS, MS m/z 691 (M^+ + H).

Ejemplo 11: Preparación del Compuesto 11: N-(4-ciano-2-piridinil)valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida



Compuesto 11

El compuesto 11 se preparó por el mismo procedimiento como se describe por la preparación del Compuesto 7, excepto que 2-cloro-4-ciano piridina (0.328 mg, 1.80 mmol) se usó en la etapa 1 en lugar de 2-cloropiridina, y HCl 2.0M en éter se agregó al producto de la etapa 1 concentrado en diclorometano

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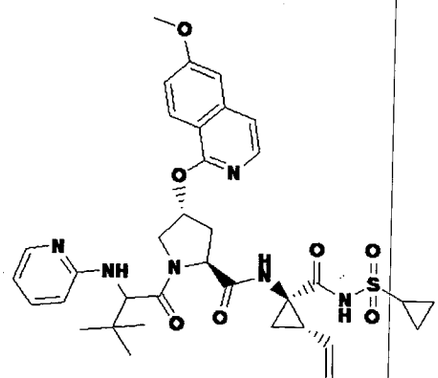
para dar la sal de clorohidrato en la etapa 2. La escala de las etapas 2 y 3 se ajustó también con base en los rendimientos de las etapas previas. El compuesto 11 (0.0210 g, 6.0% de rendimiento) se obtuvo como una sal bis-TFA sólida morada a partir de la HPLC preparativa de fase inversa. Este material fue una mezcla inseparable de dos isómeros en una relación de aproximadamente 2 hasta 1. LC-MS, MS m/z 702 (M^+ + H).

Isómeros del Compuesto 12:

3-metil-N-2-piridinil-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida

3-metil-N-2-piridinil-D-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida

Ejemplo 12: Preparación de los Compuestos 12A y 12B



Compuestos 12A y 12B

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Los compuestos 12A y 12B se preparan por el mismo procedimiento como se describe por la preparación del Compuesto 7, excepto que clorohidrato de éster terc-butílico de leucina (0.486 g, 2.16 mmol) se usó en la etapa 1 en lugar de clorohidrato de éster terc-butílico de valina, y HCl 2.0M en éter se agregó al producto de la etapa 1 concentrado en diclorometano para dar la sal de clorohidrato en la etapa 2. La escala de las etapas 2 y 3 se ajustó también con base en los rendimientos de las etapas previas. La purificación del producto sin refinar de la etapa 3 por HPLC preparativa de fase inversa dio dos compuestos en pureza buena con MS m/z idéntico. El compuesto 12A (0.0772 g, 20.9% de rendimiento) fue el primero de dos isómeros formados en la reacción en eluir a partir de la HPLC preparativa de fase inversa y se obtuvo como una sal bis-TFA sólida cristalina beige. El compuesto 12B (0.0204 g, 5.5% de rendimiento) fue el segundo de dos isómeros formados en la reacción en eluir a partir de la HPLC preparativa de fase inversa y se obtuvo como una sal bis-TFa sólida beige.

Compuesto 12A: ^{1}H RMN (500 MHz, MeOD) δ ppm 1.09 - 1.14 (m, 2 H) 1.15 (s, 9 H) 1.28 (d, *J*=3.05 Hz, 2 H) 1.47 (dd, *J*=9.00, 5.04 Hz, 1 H) 1.91 - 1.97 (m, 1 H) 2.25 - 2.38 (m, 2 H) 2.66 (dd, *J*=13.28, 6.56 Hz, 1 H) 2.95 - 3.03 (m, 1 H) 3.95 (s, 3 H) 4.14 (d, *J*=11.60 Hz, 1 H) 4.39 (d, *J*=12.51 Hz, 1 H) 4.54 (s, 1 H) 4.65 - 4.71 (m, 1 H) 5.17 (d, *J*=10.68 Hz, 1 H) 5.34

(d, *J*=17.09 Hz, 1 H) 5.74 - 5.84 (m, 1 H) 5.94 (s, 1 H) 6.78 (t, *J*=6.71 Hz, 1 H) 6.96 (d, *J*=9.16 Hz, 1 H) 7.07 (d, *J*=9.16 Hz, 1 H) 7.22 (s, 1 H) 7.30 (d, *J*=6.10 Hz, 1 H) 7.57 (t, *J*=8.09 Hz, 1 H) 7.75 (d, *J*=6.10 Hz, 1 H) 7.92 (d, *J*=9.46 Hz, 1 H) 7.94 (d, *J*=6.10 Hz, 1 H); LC-MS, MS m/z 691 (M^+ + H).

Compuesto 12B: ^{1}H RMN (500 MHz, MeOD) δ ppm 0.91 (s, 9 H) 1.02 - 1.17 (m, 3 H) 1.20 - 1.31 (m, 2 H) 1.32 - 1.38 (m, 1 H) 1.40 - 1.46 (m, 1 H) 1.90 - 1.96 (m, 1 H) 2.30 - 2.37 (m, 1 H) 2.39 - 2.47 (m, 1 H) 2.69 (dd, *J*=15.11, 8.09 Hz, 1 H) 2.89 (s, 1 H) 2.91 - 2.99 (m, 1 H) 3.97 (s, 3 H) 4.21 (dd, *J*=12.05, 2.90 Hz, 1 H) 4.44 (d, *J*=12.21 Hz, 1 H) 4.66 (s, 1 H) 4.68 - 4.73 (m, 1 H) 5.18 (d, *J*=10.38 Hz, 1 H) 5.38 (d, *J*=17.09 Hz, 1 H) 5.77 - 5.86 (m, 1 H) 5.95 (s, 1 H) 6.99 (t, *J*=6.56 Hz, 1 H) 7.21 (d, *J*=9.16 Hz, 1 H) 7.24 - 7.29 (m, 2 H) 7.32 (d, *J*=6.41 Hz, 1 H) 7.95 (d, *J*=6.10 Hz, 1 H) 7.97 - 8.02 (m, 1 H) 8.05 (d, *J*=8.85 Hz, 1 H); LC-MS, MS m/z 691 (M^+ + H).

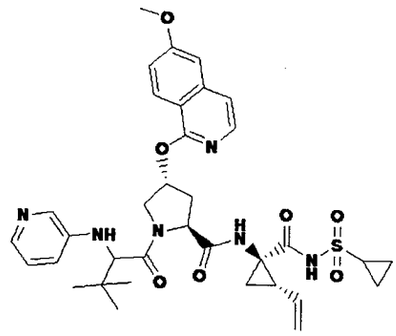
Isómeros del Compuesto 13:

3-metil-N-3-piridinil-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida y

3-metil-N-3-piridinil-D-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida

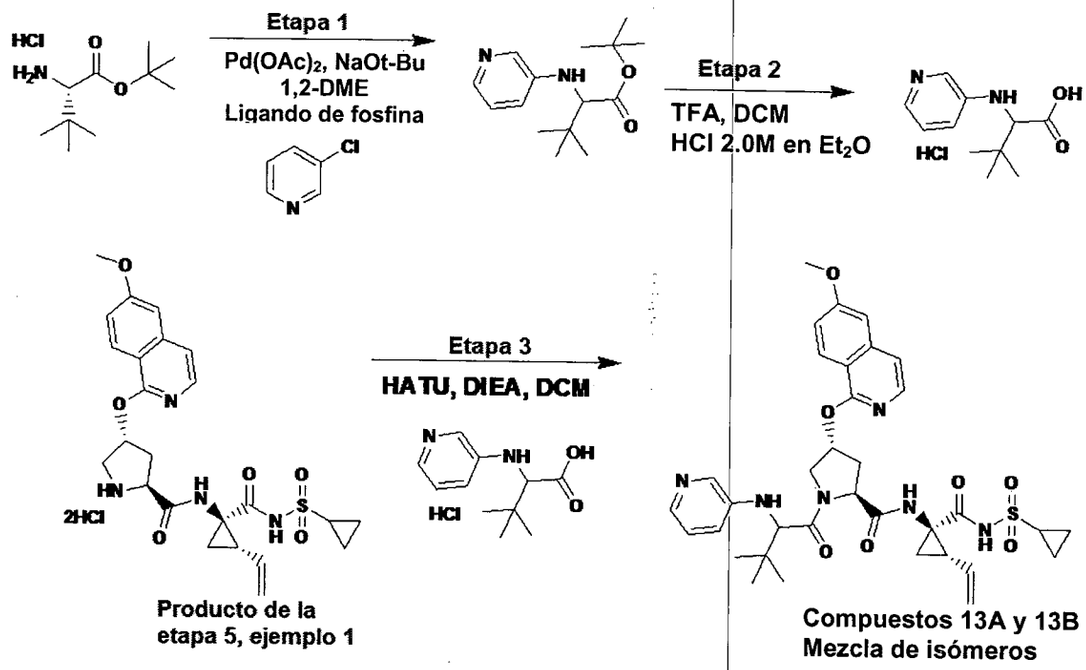
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Ejemplo 13: Preparación de los Compuestos 13A y 13B



Compuestos 13A y 13B

Esquema de reacción 1



Etapa 1:

A una mezcla de 3-cloropiridina (0.410 g, 3.61 mmol) y terc-butóxido de sodio (1.18 g, 12.3 mmol) en 1,2-dicloroetano seco (5 mL) se agregó una solución pre-mezclada de $Pd(OAc)_2$ (0.0405 g, 0.180 mmol) y (*R*)-(-)-1-[(*S*)-

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(diciclohexilfosfino)ferrocenil]etil di-*terc*-Butil fosfina (0.100 g, 0.180 mmol, StrMS Chemicals catálogo # 26-0975, CAS # [158923-11-6]) en 1,2-dimetoxietano seco (2 mL). La mezcla se agitó brevemente, se trató rápidamente con clorohidrato de éster terc-butílico de leucina (0.970 g, 4.33 mmol) y se agitó nuevamente. La mezcla se calentó a 100°C durante 20 horas, se agregó a una mezcla agitada rápidamente de pH = 7 solución amortiguadora (100 mL) y HCl acuoso 1.0M (12 mL), se trató con acetato de etilo, y se agitó. Las fases se dejaron separar y el extracto orgánico se lavó con salmuera, se secó sobre $MgSO_4$, se filtró y se concentró *in vacuo* hasta un residuo anaranjado oscuro. El producto sin refinar se purificó por cromatografía por desorción súbita en gel de sílice (gradiente lineal 100% hexanos hasta 1:1 hexanos:acetato de etilo) para dar un sólido color carne (0.583 g, 61.1% de rendimiento). LC-MS, MS m/z 265 ($M^+ + H$).

Etapa 2:

El producto de la Etapa 1, Ejemplo 13 (0.200g, 0.756 mmol) se disolvió en diclorometano (5 mL) y se trató con TFA (5 mL). La mezcla se agitó a temperatura ambiente durante 5 horas y luego se concentró *in vacuo*. El residuo luego se disolvió en 1,2-dicloroetano (15 mL) y se concentró nuevamente *in vacuo*. El residuo luego se disolvió en diclorometano (3 mL) y se agregó gota a gota a una agitación

rápida HCl 2.0M en éter (40 mL). El precipitado beige resultante se aisló por filtración y se permitió secar al aire. Polvo beige (0.160 g, 86.4% de rendimiento). LC-MS, MS m/z 209 (M^+ + H).

Etapa 3:

A una mezcla del producto de la Etapa 5, Ejemplo 1 (0.242 g, 0.422 mmol) y NMM (0.203 g, 2.01 mmol) en diclorometano (2 mL) se agregó el producto de la Etapa 2, Ejemplo 13 (0.098 g, 0.40 mmol) y HATU (0.242 g, 0.422 mmol). La mezcla se agitó a temperatura ambiente durante 18 horas. El solvente se removió *in vacuo* y el residuo café viscoso se purificó directamente por HPLC preparativa de fase inversa para dar dos compuestos en pureza buena con MS m/z idéntico. El compuesto 13A (0.154 g, 41.6% de rendimiento) fue el primero de dos isómeros en eluir de la columna HPLC preparativa de fase inversa y se obtuvo como una sal bis-TFA sólida blanca opaca. El Compuesto 13B (0.118 g, 31.9% de rendimiento) fue el segundo de los dos isómeros en eluir de la columna HPLC preparativa de fase inversa y se obtuvo como una sal bis-TFA en polvo beige.

Compuesto 13A: ^{1}H RMN (500 MHz, MeOD) δ ppm 1.06 - 1.18 (m, 12 H) 1.24 - 1.36 (m, 2 H) 1.42 - 1.48 (m, 1 H) 1.93 (t, *J*=6.71 Hz, 1 H) 2.23 - 2.33 (m, 2 H) 2.61 (dd, *J*=13.73, 7.02 Hz, 1 H) 2.96 - 3.05 (m, 1 H) 3.96 (s, 3 H) 3.98 -

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4.04 (m, 1 H) 4.23 (s, 1 H) 4.38 (d, *J*=12.21 Hz, 1 H) 4.66 (t, *J*=8.70 Hz, 1 H) 5.17 (dd, *J*=10.53, 0.76 Hz, 1 H) 5.34 (d, *J*=17.09 Hz, 1 H) 5.74 - 5.83 (m, 1 H) 5.89 (s, 1 H) 7.08 (dd, *J*=9.16, 0.92 Hz, 1 H) 7.22 (s, 1 H) 7.23 - 7.28 (m, 1 H) 7.30 (d, *J*=6.10 Hz, 1 H) 7.57 (d, *J*=8.85 Hz, 1 H) 7.80 (d, *J*=5.49 Hz, 1 H) 7.86 (d, *J*=9.16 Hz, 1 H) 7.94 (d, *J*=6.10 Hz, 1 H) 8.09 (s, 1 H) 9.26 (s, 1 H); LC-MS, MS m/z 691 (M^+ + H).

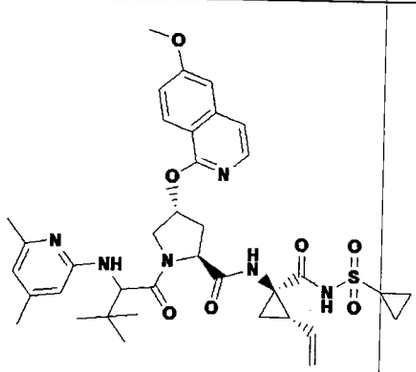
Compuesto 13B: ^{1}H RMN (500 MHz, MeOD) δ ppm 0.94 (s, 9 H) 1.10 (d, *J*=7.32 Hz, 2 H) 1.17 - 1.35 (m, 2 H) 1.41 (dd, *J*=9.46, 5.19 Hz, 1 H) 1.87 - 1.94 (m, 1 H) 2.31 (c, *J*=8.65 Hz, 1 H) 2.35 - 2.43 (m, 1 H) 2.59 - 2.69 (m, 1 H) 2.92 - 3.01 (m, 1 H) 3.97 (s, 3 H) 4.12 (d, *J*=11.90 Hz, 1 H) 4.38 (s, 1 H) 4.49 (d, *J*=11.90 Hz, 1 H) 4.67 (t, *J*=8.85 Hz, 1 H) 5.17 (d, *J*=10.38 Hz, 1 H) 5.36 (d, *J*=17.09 Hz, 1 H) 5.75 - 5.87 (m, 1 H) 5.94 (s, 1 H) 7.20 (d, *J*=8.85 Hz, 1 H) 7.25 (s, 1 H) 7.31 (d, *J*=5.80 Hz, 1 H) 7.71 - 7.78 (m, 1 H) 7.89 - 7.99 (m, 3 H) 8.04 (d, *J*=8.85 Hz, 1 H) 8.22 (s, 1 H) 9.57 (s, 1 H); LC-MS, MS m/z 691 (M^+ + H).

Isómeros del compuesto 14:

N-(4,6-dimetil-2-piridinil)-3-metil-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida y

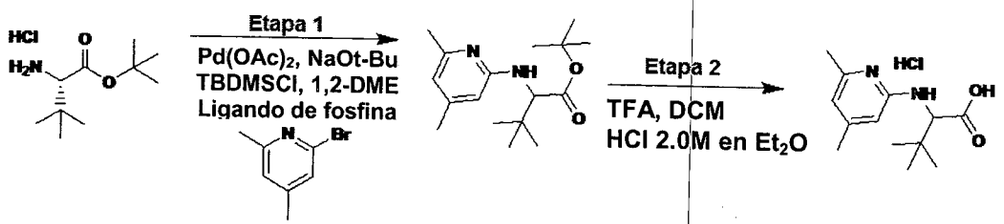
N-(4,6-dimetil-2-piridinil)-3-metil-D-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida

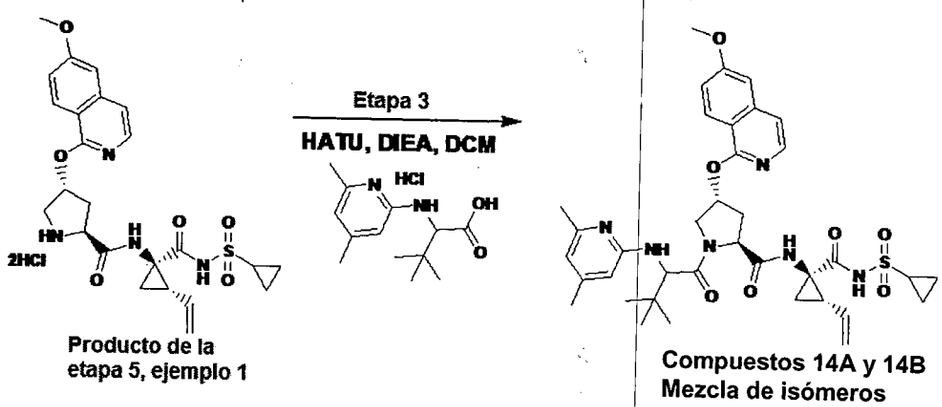
Ejemplo 14: Preparación de los compuestos 14A y 14B



Compuestos 14A y 14B

Esquema de reacción 1





Producto de la etapa 5, ejemplo 1

Compuestos 14A y 14B
Mezcla de isómeros

Etapa 1:

La 2-Bromo-4,6-dimetilpiridina (0.839 g, 4.51 mmol), terc-butóxido de sodio (1.47 g, 15.3 mmol), clorohidrato de

éster terc-butílico de leucina (1.21 g, 5.41 mmol) y TBDMSCl (1.5 g, 9.9 mmol) se combinaron y se trataron con 1,2-dimetoxietano (6 mL). La mezcla se agitó y una solución pre-mezclada de $Pd(OAc)_2$ (0.202 g, 0.902 mmol) y (*R*)-(-)-1-[(*S*)-(diciclohexilfosfino) ferrocenil] etil di-*terc*-Butil fosfina (0.500 g, 0.902 mmol, StrMS Chemicals catálogo # 26-0975, CAS # [158923-11-6]) en 1,2-dimetoxietano seco (2 mL) se agregó inmediatamente. Una exotermia moderada resulta y la mezcla se volvió café oscura en color. Después de 10 minutos, la mezcla fue anaranjada en color. La mezcla se agitó a temperatura ambiente durante 72 horas. La mezcla luego se agregó a una mezcla agitada rápidamente de pH = 7 solución amortiguadora (75 mL) y HCl acuoso 1.0M (15 mL). Acetato de etilo (40 mL) se agregó y la mezcla se agitó y se separaron las fases. La fase acuosa se extrajo con acetato de etilo (2 x 50 mL). Los extractos orgánicos se combinaron y se lavaron con salmuera (40 mL), se secaron sobre $MgSO_4$, se filtraron y se concentraron *in vacuo* hasta un residuo café. El producto sin refinar se purificó por cromatografía por desorción súbita en gel de sílice (gradiente lineal 100% hexanos hasta 10:1 hexanos:acetato de etilo) para dar un aceite amarillo (0.786 g) el cual se determinó que contiene el producto deseado más 1.9 equivalentes del subproducto TBDMS. El material se utilizó como tal en la siguiente etapa sin purificación adicional. LC-MS, MS m/z 293 ($M^+ + H$).

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Etapa 2:

El producto de la Etapa 1, Ejemplo 14 (0.750 g) se disolvió en diclorometano (10 mL) y se trató con TFA (10 mL). La mezcla se agitó a temperatura ambiente durante 7 horas y luego se concentró *in vacuo*. El residuo luego se disolvió en 1,2-dicloroetano (15 mL) y se concentró nuevamente *in vacuo*. El residuo luego se disolvió en diclorometano (3 mL) y se agregó gota a gota a HCl 2M agitado rápidamente en éter dietílico (40 mL). No se presentó precipitación. Las preparaciones reiteradas del material sin refinar a partir de diclorometano usando hexanos y acetato de etilo como los contrasolventes eventualmente produjeron un polvo amarillo (0.286 g, 23% de rendimiento durante 2 etapas). LC-MS, MS m/z 237 ($M^+ + H$).

Etapa 3:

A una mezcla del producto de la Etapa 5, Ejemplo 1 (0.189 g, 0.330 mmol) y NMM (0.167 g, 1.65 mmol) en diclorometano (2 mL) se agregó el producto de la Etapa 2, Ejemplo 14 (0.090 g, 0.33 mmol) y HATU (0.151 g, 0.396 mmol). La mezcla se agitó a temperatura ambiente durante 18 horas. El producto adicional de la etapa 2, Ejemplo 14 (0.049 g, 0.18 mmol), HATU (0.082 g, 0.216 mmol) y NMM (0.0381 g, 0.377 mmol) se agregaron a la mezcla, y la solución se agitó a 40°C durante la noche. El solvente se removió *in vacuo* y el

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residuo se purificó directamente por HPLC preparativa de fase inversa para dar dos compuestos separados con MS m/z idéntico. El compuesto 14A (0.118 g, 37.8% de rendimiento) fue el primero de dos isómeros en eluir a partir de la Columna HPLC preparativa de fase inversa y se obtuvo como una sal bis-TFA de polvo blanco opaco. El Compuesto 14B (0.044 g, 14.1% de rendimiento) fue el segundo de los dos isómeros en eluir a partir de la columna HPLC preparativa de fase inversa y se obtuvo como una sal bis-TFA en polvo beige.

Compuesto 14A: ^{1}H RMN (500 MHz, MeOD) δ ppm 1.07 - 1.11 (m, 2 H) 1.13 (s, 9 H) 1.25 - 1.30 (m, 2 H) 1.46 (dd, *J*=9.46, 5.49 Hz, 1 H) 2.25 - 2.37 (m, 2 H) 2.38 (s, 3 H) 2.65 (dd, *J*=13.58, 7.78 Hz, 1 H) 2.94 - 3.03 (m, 1 H) 3.95 (s, 3 H) 4.09 (dd, *J*=12.21, 2.75 Hz, 1 H) 4.36 (d, *J*=12.21 Hz, 1 H) 4.48 (s, 1 H) 4.69 - 4.75 (m, 1 H) 5.17 (d, *J*=10.38 Hz, 1 H) 5.35 (d, *J*=17.40 Hz, 1 H) 5.72 - 5.83 (m, 1 H) 5.96 (s, 1 H) 6.53 (s, 1 H) 6.60 (s, 1 H) 7.02 - 7.07 (m, 1 H) 7.19 - 7.22 (m, 1 H) 7.30 (d, *J*=6.10 Hz, 1 H) 7.87 (d, *J*=9.16 Hz, 1 H) 7.94 - 7.97 (m, 1 H); LC-MS, MS m/z 719 (M^+ +H).

Compuesto 14B: ^{1}H RMN (500 MHz, MeOD) δ ppm 0.92 (s, 9 H) 1.05 - 1.10 (m, 2 H) 1.13 - 1.19 (m, 1 H) 1.21 - 1.26 (m, 1 H) 1.41 (dd, *J*=9.46, 5.19 Hz, 1 H) 1.89 - 1.94 (m, 1 H) 2.32 (c, *J*=8.75 Hz, 1 H) 2.40 - 2.44 (m, 1 H) 2.45 (s, 3 H) 2.48 (s, 3 H) 2.65 - 2.71 (m, 1 H) 2.90 - 2.96 (m, 1 H) 3.96 (d, *J*=1.83 Hz, 1 H) 3.97 (d, *J*=1.53 Hz, 3 H) 4.20 (dd,

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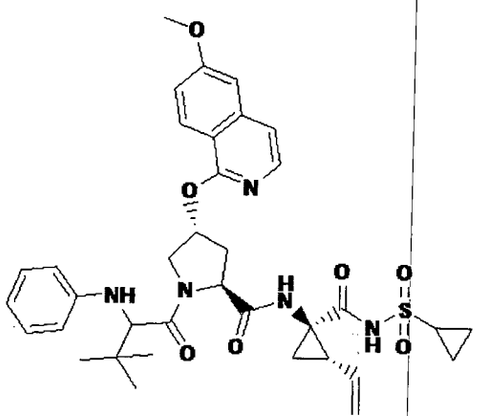
J=12.36, 2.90 Hz, 1 H) 4.51 (d, *J*=12.51 Hz, 1 H) 4.62 (s, 1 H) 4.69 (t, *J*=8.39 Hz, 1 H) 5.17 (d, *J*=10.07 Hz, 1 H) 5.36 (d, *J*=17.40 Hz, 1 H) 5.75 - 5.83 (m, 1 H) 5.97 (s, 1 H) 6.71 (s, 1 H) 6.88 (s, 1 H) 7.19 - 7.23 (m, 1 H) 7.25 (d, *J*=2.14 Hz, 1 H) 7.32 (d, *J*=5.80 Hz, 1 H) 7.95 (dd, *J*=5.95, 1.68 Hz, 1 H) 8.05 (d, *J*=9.16 Hz, 1 H); LC-MS, MS m/z 719 (M^+ + H).

Isómeros del compuesto 15:

3-metil-N-fenil-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida y

3-metil-N-fenil-D-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida

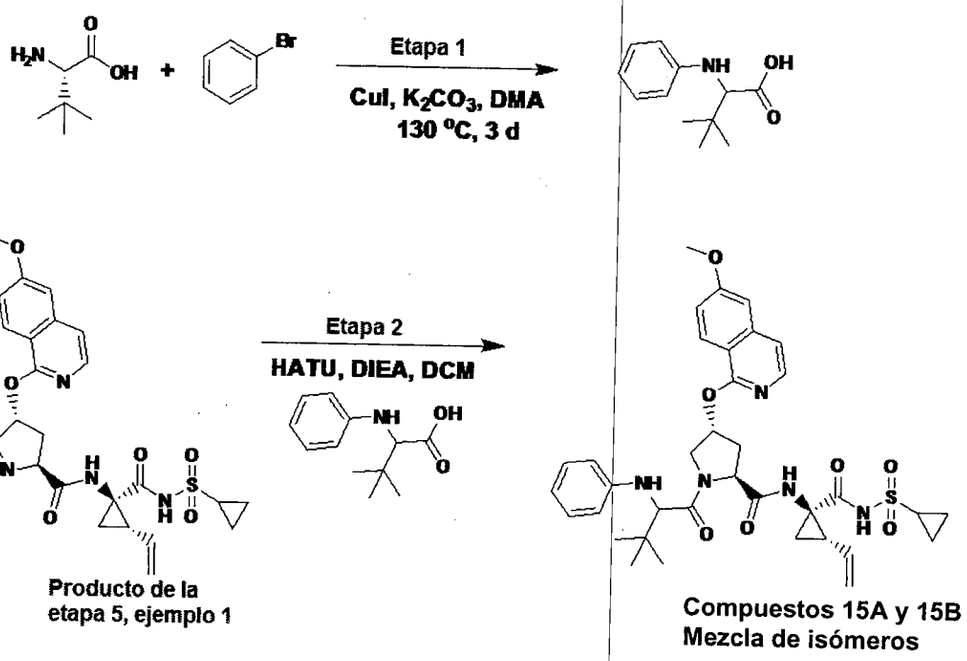
Ejemplo 15: Preparación de los compuestos 15A y 15B



Compuestos 15A y 15B

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Esquema de reacción 1



Etapa 1:

La L-*terc*-Leucina (0.840 g, 6.40 mmol), K_2CO_3 (1.33 g, 9.60 mmol) y CuI (0.122 g, 0.64 mmol) se combinaron en un recipiente a presión Chemglass de 35 ml. El Bromobenceno (1.01 g, 6.4 mmol) y DMA (8 mL) se agregaron, el espacio de domo del recipiente fue nitrógeno, el recipiente se selló, y la mezcla se calentó a 90°C durante la noche. DMA adicional (8 mL) se agregó para facilitar la agitación y la mezcla se calentó a 130°C durante la noche. Con solamente una cantidad pequeña de la formación del producto como se determinó por LCMS, la mezcla se cargó con un exceso de CuI (aproximadamente 1 g), la reacción se volvió a sellar y se calentó a 130°C durante 2 días. La mezcla se enfrió a

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temperatura ambiente y se trató con HCl acuoso 1.0M hasta que se logró pH = 5, luego pH = 7 solución amortiguadora (50 mL) y acetato de etilo (50 mL) se agregaron y la mezcla se agitó y las fases se separaron. La fase acuosa se extrajo con acetato de etilo (2 x 50 mL), y los orgánicos se combinaron y se lavaron con salmuera, se secaron sobre $MgSO_4$, se filtraron y se concentraron *in vacuo* hasta un residuo sólido. La purificación por cromatografía por desorción súbita en gel de sílice (20:1 diclorometano:metanol) dio un sólido de color carne ceroso (0.286 g) el cual contiene aproximadamente 1.2 equivalentes del DMA arrastrado por ^1H RMN. LC-MS, MS m/z 208 $(M^+ + H)$.

Etapa 2:

A una mezcla del producto de la Etapa 5, Ejemplo 1 (0.200 g, 0.349 mmol) y NMM (0.141 g, 1.40 mmol) en diclorometano (2 mL) se agregó el producto de la Etapa 1, Ejemplo 15 (0.108 g, 0.35 mmol, 67% puro) y HATU (0.160 g, 0.418 mmol). La mezcla se agitó a temperatura ambiente durante 18 horas. El solvente se removió *in vacuo* y al residuo se agregó acetato de etilo (30 mL) y agua (30 mL). No todos los sólidos se disolvieron. La mezcla se transfirió a un matraz de fondo redondo de 250 ml con Solvente 1:1 diclorometano:metanol, y la mezcla se concentró *in vacuo* hasta que los solventes orgánicos se removieron, dando la

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fase acuosa y los sólidos sin disolver. Se determinó por HPLC que la purificación en bruto ha ocurrido en donde la fase acuosa mantiene mayormente los subproductos solubles en agua con poco producto, y el sólido consiste mayormente del producto. El sólido se filtró del líquido para dar un polvo blanco (0.225 g). La purificación adicional del polvo blanco por HPLC preparativa de fase inversa dio dos compuestos separados con MS m/z idéntico. El compuesto 15A (0.124 g, 38.8% de rendimiento) fue el primero de dos isómeros en eluir a partir de la columna HPLC preparativa de fase inversa y se obtuvo como una sal bis-TFA en polvo café. El compuesto 15B (0.0633 g, 19.8% de rendimiento) fue el segundo de los dos isómeros en eluir a partir de la columna HPLC preparativa de fase inversa y se obtuvo como una sal bis-TFA en polvo café.

Compuesto 15A: ^{1}H RMN (500 MHz, MeOD) δ ppm 1.09 - 1.15 (m, 2 H) 1.19 (s, 9 H) 1.27 - 1.33 (m, *J*=2.44 Hz, 2 H) 1.43 - 1.48 (m, 1 H) 1.89 - 1.94 (m, 1 H) 2.21 - 2.30 (m, 1 H) 2.57 (dd, *J*=13.58, 7.17 Hz, 1 H) 2.96 - 3.03 (m, 1 H) 3.99 (d, *J*=1.83 Hz, 3 H) 4.02 - 4.08 (m, 1 H) 4.14 (s, 1 H) 4.28 (d, *J*=12.21 Hz, 1 H) 4.44 - 4.51 (m, 1 H) 5.16 (d, *J*=10.38 Hz, 1 H) 5.32 (d, *J*=17.09 Hz, 1 H) 5.73 - 5.83 (m, 2 H) 6.41 (t, *J*=7.17 Hz, 1 H) 6.69 - 6.73 (m, 2 H) 6.76 (t, *J*=7.02 Hz, 2 H) 7.10 (d, *J*=9.16 Hz, 1 H) 7.26 (s, 1 H) 7.30 - 7.34 (m, 1 H) 7.73 (dd, *J*=9.00, 1.37 Hz, 1 H) 7.92 (dd, *J*=5.80, 1.83 Hz, 1 H); LC-MS, MS m/z 690 (M^+ +H).

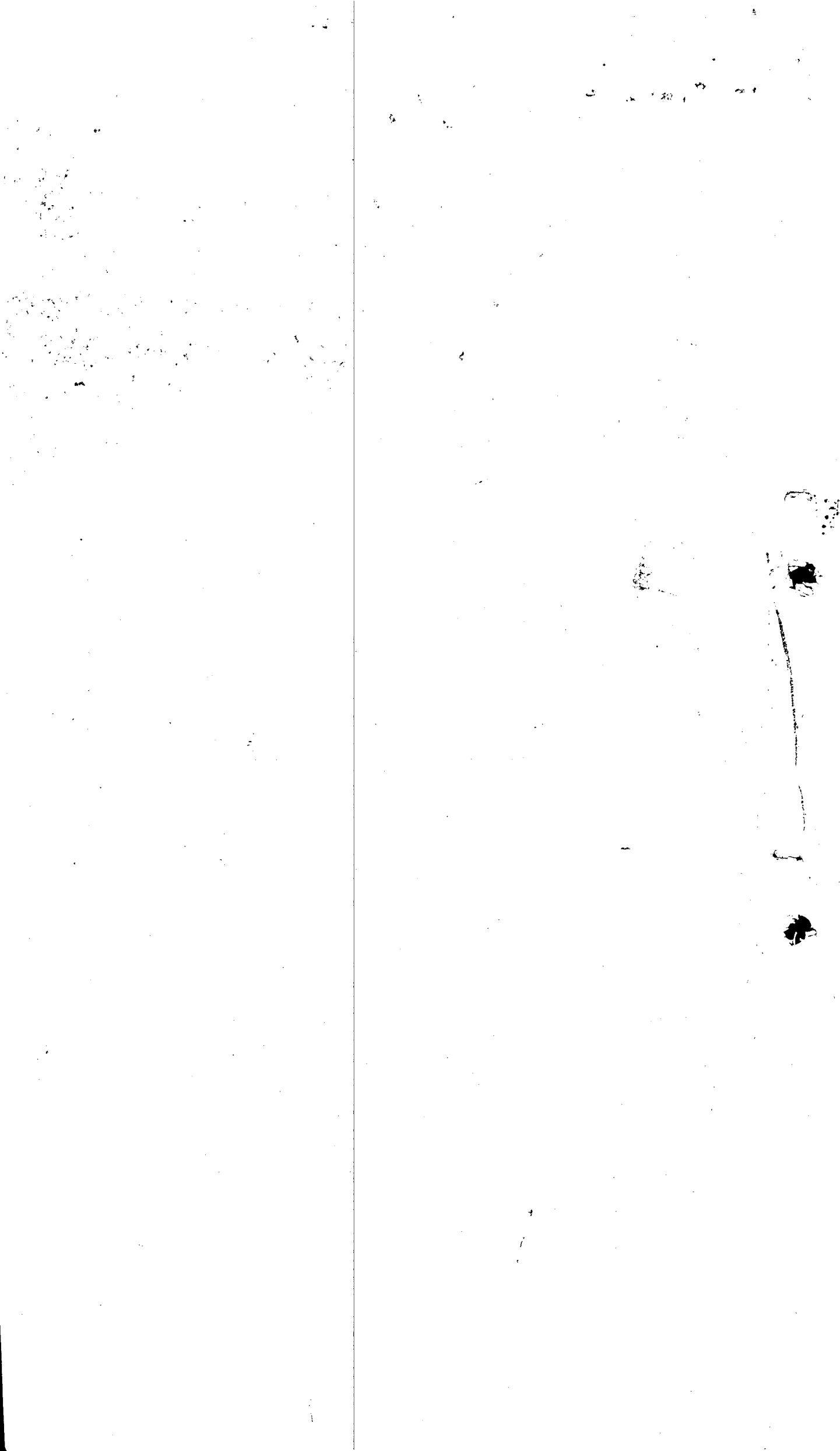
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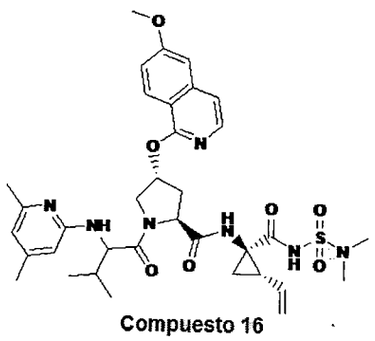
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Compuesto 15B: ^{1}H RMN (500 MHz, DMSO-D6) δ ppm 0.87 (s, 9 H) 0.94 - 1.00 (m, 1 H) 1.00 - 1.05 (m, *J*=6.41 Hz, 2 H) 1.10 - 1.19 (m, 1 H) 1.28 (dd, *J*=9.31, 5.04 Hz, 1 H) 1.72 (dd, *J*=7.63, 5.19 Hz, 1 H) 2.05 - 2.13 (m, 1 H) 2.21 - 2.28 (m, 1 H) 2.40 - 2.48 (m, 1 H) 2.81 - 2.88 (m, 1 H) 3.91 (d, *J*=1.83 Hz, 3 H) 3.94 - 4.00 (m, 1 H) 4.19 (s, 1 H) 4.41 (d, *J*=11.90 Hz, 1 H) 4.43 - 4.49 (m, 1 H) 5.12 (d, *J*=10.07 Hz, 1 H) 5.27 (d, *J*=17.09 Hz, 1 H) 5.58 - 5.71 (m, 1 H) 5.87 (s, 1 H) 6.55 (t, *J*=7.17 Hz, 1 H) 6.74 (d, *J*=7.63 Hz, 2 H) 7.03 - 7.10 (m, 2 H) 7.22 - 7.27 (m, 1 H) 7.31 - 7.37 (m, 2 H) 7.88 (d, *J*=9.16 Hz, 1 H) 7.97 (dd, *J*=5.80, 2.14 Hz, 1 H) 9.18 (s, 1 H) 10.74 (s, 1 H); LC-MS, MS m/z 690 (M^+ + H).

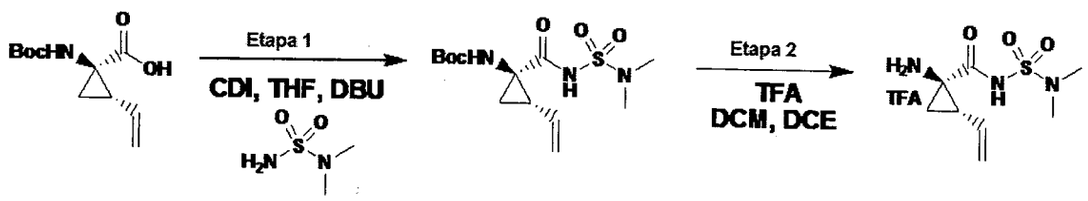
Ejemplo 16: Preparación del Compuesto 16: N-(4,6-dimetil-2-piridinil)valil-(4R)-N-((1R,2S)-1-((dimetilsulfamoil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida



Compuesto 16

0015 2

Esquema de reacción 1



Etapa 1:

A una solución de ácido *N*-Boc-vinilciclopropano carboxílico (1.83 g, 8.05 mmol) y THF (32 mL) se agregó 1,1'-carbonildiimidazol (1.44 g, 8.86 mmol). Después de agitarse a temperatura ambiente durante 3 horas, la mezcla de reacción se trató con *N,N*-dimetilsulfamida (1.0 g, 8.05 mmol) seguido por DBU (2.45 g, 16.1 mmol) y se agitó a temperatura ambiente durante 15 horas adicionales. La reacción luego se diluyó con acetato de etilo (50 mL) y se lavó con HCl acuoso 1.0M (2 x 25 mL). La capa acuosa se extrajo con acetato de etilo (2 x 50 mL). La porción orgánica combinada se lavó con H_2O (25 mL) y salmuera, se secó sobre $MgSO_4$, se filtró y se concentró hasta un sólido amarillo claro (2.6 g, 97% de rendimiento) el cual se usó sin purificación adicional. LC-MS, MS m/z 356 (M^+ + Na).

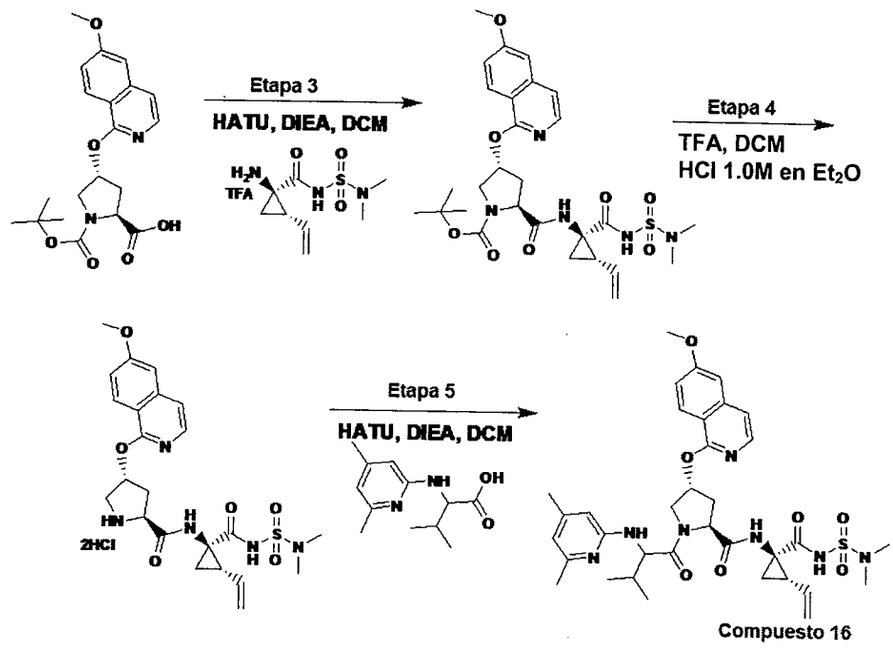
Etapa 2:

A una solución del producto de la Etapa 2, Ejemplo 16, (1.42 g, 4.26 mmol) en 1:1 diclorometano:1,2-dicloroetano (20 mL) se agregó TFA (10 mL). Después de agitarse a temperatura ambiente durante 0.5 horas, El solvente y exceso de TFA se

0065.3

removieron y el residuo se volvió a disolver en 1,2-dicloroetano (20 mL) y se concentró nuevamente para dar un sólido amarillo (1.46g, 99% de rendimiento). LC-MS, MS m/z 234 (M^++ H).

Esquema de reacción 2



Etapa 3:

El producto de la Etapa 3, Ejemplo 16, se preparó con 91% de rendimiento de producto de la Etapa 2, Ejemplo 16, por el mismo procedimiento como se describe por la preparación del producto de la Etapa 4, Ejemplo 1.

Etapa 4:

El producto de la Etapa 4, Ejemplo 16, se preparó con 95% de rendimiento de producto de la Etapa 3, Ejemplo 16, por el mismo procedimiento como se describe por la preparación del producto de la Etapa 5, Ejemplo 1. LC-MS, MS m/z 504 (M^++

0085 4

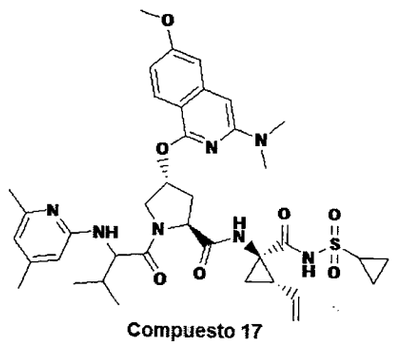
H).

Etapa 5:

A una mezcla del producto de la Etapa 4, Ejemplo 16 (0.200 g, 0.347 mmol) y DIEA (0.180 g, 1.39 mmol) en diclorometano (4 mL) se agregó ácido 2-(4,6-dimetilpiridina-2-ilamino)-3-metilbutanoico (0.092 g, 0.416 mmol) y HATU (0.198 g, 0.520 mmol). La mezcla se agitó a temperatura ambiente durante 8 horas. La reacción fue incompleta por LCMS. El ácido 2-(4,6-dimetilpiridina-2-ilamino)-3-metilbutanoico adicional (0.039 g, 0.174 mmol) y HATU (0.066 g, 0.174 mmol) se agregaron y la mezcla se agitó a temperatura ambiente durante otras 16 horas. La reacción fue todavía incompleta por LCMS. Nuevamente, el ácido 2-(4,6-dimetilpiridina-2-ilamino)-3-metilbutanoico adicional (0.039 g, 0.174 mmol) y HATU (0.066 g, 0.174 mmol) se agregaron y la mezcla se agitó a temperatura ambiente durante otras 16 horas. El solvente se removió y el residuo se disolvió en acetato de etilo (50 mL) y la solución se lavó con HCl acuoso 1.0M (2 x 5 mL). Los extractos acuosos se combinaron y se volvieron a extraer con acetato de etilo (50 mL), y las fases orgánicas se combinaron y se lavaron con 10% carbonato de sodio acuoso y luego con salmuera. La fase orgánica se secó sobre anhidro $MgSO_4$, se filtró y se concentró hasta un residuo el cual se purificó por HPLC preparativa de fase inversa para dar el Compuesto 16 (el mayor de los dos

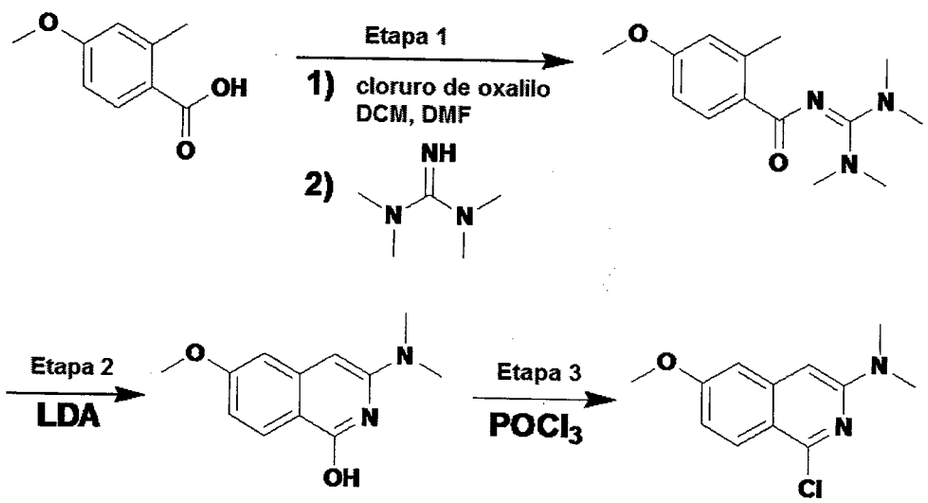
isómeros formado) como una sal bis-HCl sólida amarilla (0.060 g, 22.1% de rendimiento). ^{1}H RMN (500 MHz, *MeOD*) δ ppm 1.01 (d, *J*=6.7 Hz, 3 H), 1.10 (d, *J*=6.7 Hz, 3 H), 1.43 (dd, *J*=9.5, 5.2 Hz, 1 H), 1.88 - 1.95 (m, 1 H), 2.20 (s, 3 H), 2.23 - 2.32 (m, 1 H), 2.39 (s, 1 H), 2.43 (s, 3 H), 2.69 (dd, *J*=13.7, 7.0 Hz, 1 H), 2.77 - 2.80 (m, 1 H), 2.87 - 2.90 (m, 1 H), 2.93 (s, 6 H), 3.97 (s, 3 H), 4.18 (dd, *J*=12.2, 3.4 Hz, 1 H), 4.38 (d, *J*=12.2 Hz, 1 H), 4.57 (d, *J*=6.7 Hz, 1 H), 4.70 (dd, *J*=10.1, 7.0 Hz, 1 H), 5.18 (dd, *J*=10.4, 1.8 Hz, 1 H), 5.35 (d, *J*=17.1 Hz, 1 H), 5.72 - 5.83 (m, 1 H), 5.98 (d, *J*=2.7 Hz, 1 H), 6.60 (s, 1 H), 6.69 (s, 1 H), 7.17 (dd, *J*=9.2, 2.4 Hz, 1 H), 7.28 (d, *J*=2.4 Hz, 1 H), 7.39 (d, *J*=6.1 Hz, 1 H), 7.94 (d, *J*=6.1 Hz, 1 H), 8.05 (d, *J*=9.2 Hz, 1 H); LC-MS, MS m/z 708 (M^+ + H).

Ejemplo 17: Preparación del Compuesto 17: N-(4,6-dimetil-2-piridinil)valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((3-(dimetilamino)-6-metoxi-1-isoquinolinil)oxi)-L-prolinamida



Compuesto 17

Esquema de reacción 1



Etapa 1:

Una solución de ácido 4-metoxi-2-metilbenzoico (10.2 g, 61.4 mmol) en diclorometano (200 mL) se trató lentamente con cloruro de oxalilo. Una gota de DMF se agregó y la reacción se agitó a temperatura ambiente durante 12 horas. La mezcla luego se trató con 1,1,3,3-tetrametilguanidina (14.9 g, 128.9 mmol) y se agitó a temperatura ambiente durante 4 horas. La mezcla se lavó con 5% ácido cítrico acuoso (2 x 100 mL). La fase acuosa se volvió a extraer con diclorometano (2 x 100 mL), y las fases orgánicas se combinaron, se secaron sobre $MgSO_4$ anhidro, se filtraron y se concentraron para proporcionar una cantidad mínima del producto deseado. La fase acuosa se hizo básica por la adición de NaOH acuoso 10.0M hasta que se logró pH = 13 y luego se extrajo con diclorometano

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(4 x 200 mL). Las fases orgánicas se combinaron, se secaron sobre anhidro $MgSO_4$, se filtraron y se concentraron. El aceite resultante se combinó con el producto obtenido fácilmente y la mezcla se trató con éter dietílico para dar un precipitado blanco el cual se removió por filtración. El filtrado se concentró para dar el producto deseado (11.3 g, 70% de rendimiento) como un aceite amarillo viscoso. ^1H RMN (CD_3OD) δ 2.54 (s, 3H), 3.97 (s, 6H), 3.79 (s, 3H), 6.60 (d, J = 9.2 Hz, 1H), 6.75 (s, 1H), 7.65 (d, J = 8.9 Hz, 1H). LC-MS, MS m/z 264 ($M^+ + H$).

Etapa 2:

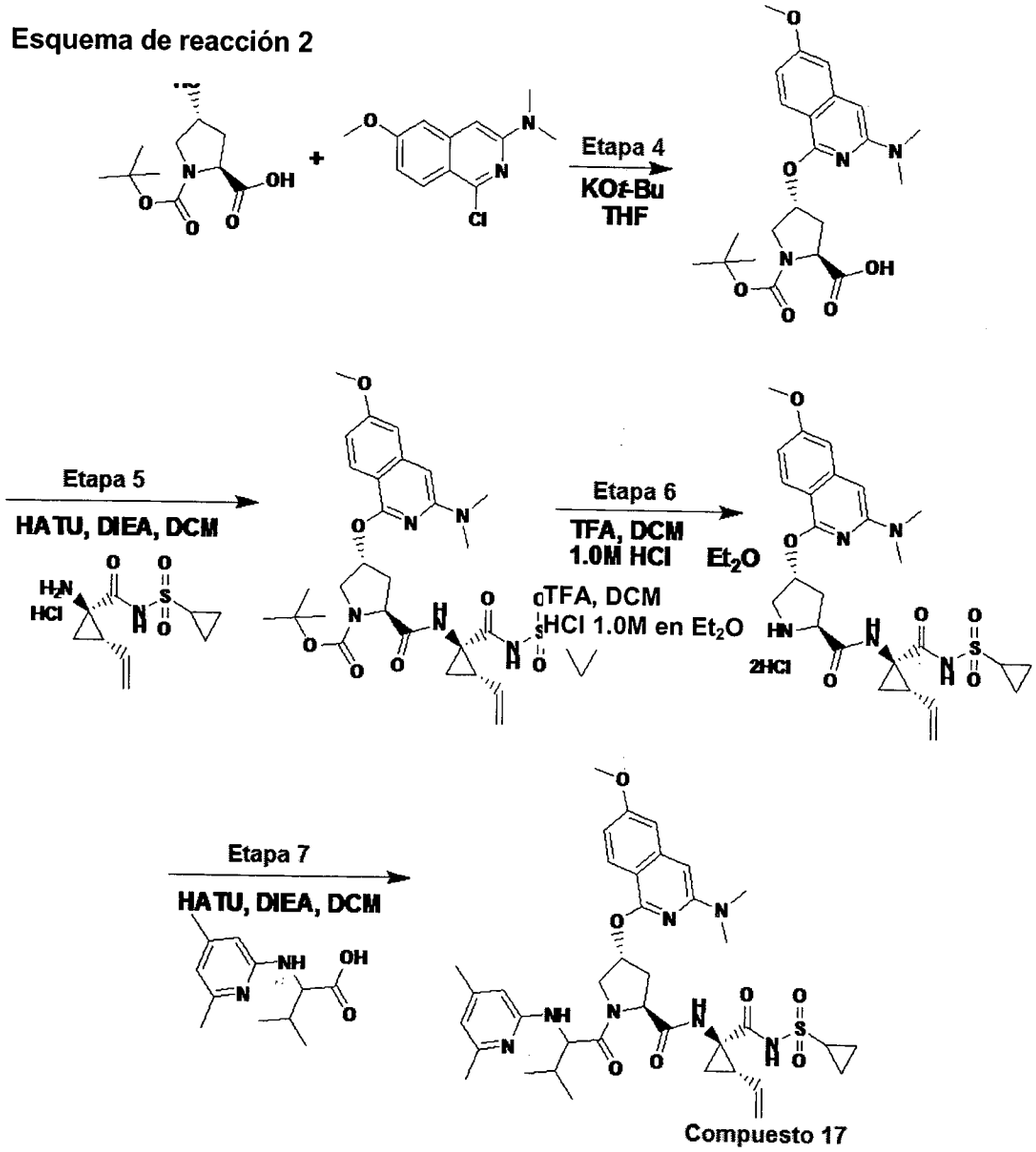
Una solución del producto de la Etapa 1, Ejemplo 17 (0.461 g, 1.78 mmol) en THF (5 mL) a 0°C se trató con Solución LDA (1.8M en THF/hexanos, 1.2 mL, 2.14 mmol). La reacción se agitó a temperatura ambiente durante 5 horas y luego se trató con LDA adicional (1 mL) y se agitó a temperatura ambiente durante 14 horas. La mezcla se apagó con cloruro de amonio saturado (10 mL) y luego se extrajo con acetato de etilo (3 x 25 mL). Las fases orgánicas se combinaron, se secaron sobre $MgSO_4$ anhidro, se filtraron y se concentraron. El concentrado se disolvió en diclorometano mínimo y éter dietílico se agregó. El precipitado resultante se

colectó por filtración para proporcionar el producto deseado (0.312 g, 80% de rendimiento) como un sólido café. ^{1}H RMN (CD_3OD) δ 2.94 (s, 6H), 3.86 (s, 3H), 5.71 (s, 1H), 6.75 (dd, J = 8.9, 2.4 Hz, 1H), 6.83 (d, J = 2.4 Hz, 1H). 7.97 (d, J = 9.2 Hz, 1H). LC-MS, MS m/z 219 (M^+ + H).

Etapa 3:

El producto de la Etapa 2, Ejemplo 17 (10.0 g, 45.8 mmol) se trató con $POCl_3$ (43 mL) y la mezcla se calentó a 110°C durante 5 horas en un recipiente a presión Chemglass. Durante el enfriamiento a temperatura ambiente, la torta resultante se disolvió en diclorometano (200 mL) y la solución se apagó por la adición lenta de bicarbonato de sodio acuoso saturado. Resulta la evolución de gas vigorosa. Cuando resulta la evolución de gas, la mezcla se agitó en un embudo de separación y las fases se separaron. La fase acuosa se extrajo con diclorometano (3 x 200 mL). La fase orgánica combinada se lavó con salmuera, se secó sobre anhidro $MgSO_4$, se filtró y se concentró. Éter dietílico se agregó al residuo para afectar la precipitación de un sólido negro el cual se colectó por filtración y se lavó con éter. Así se obtuvo el producto deseado (5.72 g, 53.0% de rendimiento). LC-MS, MS m/z 237 (M^+ + H).

Esquema de reacción 2



Etapa 4:

A una solución de Boc-Hyp-OH (5.60 g, 24.2 mmol) en THF (100 mL) se agregó terc-butóxido de potasio (1.0M en THF, 53.2 mL, 53.2 mmol). La mezcla se volvió café y se volvió un gel que se rompe con agitación vigorosa. Después de 15 minutos, el producto de la Etapa 3, Ejemplo 17 (5.72 g, 24.2

006510

mmol) se agregó en porciones. La mezcla se calentó a 70°C durante 48 horas. La mezcla se apagó por la adición de HCl 1.0M y luego se extrajo con acetato de etilo. La fase acuosa se extrajo con acetato de etilo una vez más. Las fases orgánicas se combinaron y se lavaron con salmuera, se secaron sobre $MgSO_4$, y se filtraron. El filtrado se evaporó *in vacuo* hasta secarse para dar el producto deseado. LC-MS, MS m/z 430 (M-H).

Etapa 5:

Una mezcla del producto de la Etapa 4, Ejemplo 17 (8.90 g, 20.6 mmol), DIEA (8.01 g, 61.9 mmol), y sal HCl de (1-(R)-amino-2-(S)-vinil-ciclopropanocarbonil)-amida del ácido ciclopropanosulfónico (6.60 g, 24.8 mmol) en diclorometano (150 mL) se trató con HATU (10.2 g, 26.8 mmol), y la solución café resultante se agitó a temperatura ambiente durante 18 horas. El solvente se removió in vacuo, y el residuo se tomó en acetato de etilo (200 mL) y se lavó con agua (100 mL). Las fases se separaron y la fase acuosa se volvió a extraer con acetato de etilo (3 x 100 mL). La fase orgánica combinada se lavó con HCl acuoso 0.10 M (100 mL), luego con 10% carbonato de sodio acuoso (50 mL) y finalmente con salmuera. La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró para dar un sólido espumoso café oscuro. El producto se purificó por cromatografía por desorción súbita en gel de sílice (95:5

- 000511

diclorometano:metanol) para dar un sólido café (12.9 g, 97% de rendimiento). LC-MS, MS m/z 642 (M-H).

Etapa 6:

A una solución del producto de la Etapa 5, Ejemplo 17 (12.7 g, 19.6 mmol) en 1:1 diclorometano:1,2-dicloroetano (100 mL) se agregó TFA (50 mL). La mezcla se agitó a temperatura ambiente durante 30 minutos y luego se concentró *in vacuo*. El residuo se volvió a disolver en 1,2-dicloroetano (100 mL) y se concentró nuevamente *in vacuo*. El residuo luego se disolvió en diclorometano (50 mL) y se agregó gota a gota hasta agitación vigorosa HCl 1.0M en éter dietílico (500 mL). El precipitado sólido café claro resultante se aisló por filtración y se lavó con HCl 1.0M en éter dietílico para dar un polvo café (10.2 g, 85.0% de rendimiento). LC-MS, MS m/z 544 ($M^+ + H$).

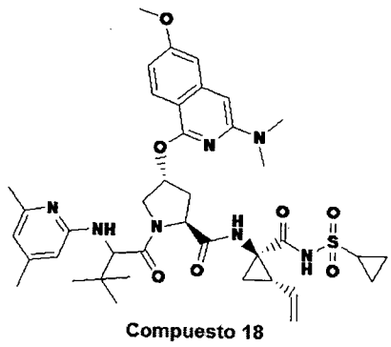
Etapa 7:

El producto de la Etapa 6, Ejemplo 17 (0.258 g, 0.419 mmol), ácido 2-(4,6-dimetilpiridin-2-ilamino)-3-metil butanoico (0.111 g, 0.503 mmol), DIEA (0.217 g, 1.68 mmol) y HATU (0.239 g, 0.629 mmol) se combinaron en diclorometano (4 mL) y la mezcla se agitó durante 8 horas a temperatura ambiente. El ácido 2-(4,6-dimetilpiridin-2-ilamino)-3-metilbutanoico adicional (0.0465 g, 0.210 mmol) y HATU

(0.080 g, 0.21 mmol) se agregaron y la mezcla se agitó a temperatura ambiente durante 14 horas adicionales. El solvente se removió y el residuo se volvió a disolver en acetato de etilo (50 mL) y se lavó con HCl acuoso 1.0M (2 x 5 mL). Los extractos acuosos se combinaron y se volvieron a extraer con acetato de etilo (50 mL), y las fases orgánicas se combinaron y se lavaron con 10% carbonato de sodio acuoso y luego con salmuera. La fase orgánica se secó sobre anhidro $MgSO_4$, se filtró y se concentró hasta un residuo el cual se purificó por HPLC preparativa de fase inversa para dar el Compuesto 17 (0.037 g, 10.8% de rendimiento) como una sal bis-HCl de polvo café. ^{1}H RMN (500 MHz, *MeOD*) δ ppm 1.02 (d, *J*=6.7 Hz, 3 H), 1.10 (d, *J*=6.4 Hz, 3 H), 1.12 - 1.18 (m, 3 H), 1.22 - 1.30 (m, 2 H), 1.35 (t, *J*=7.3 Hz, 1 H), 1.46 (dd, *J*=9.6, 5.3 Hz, 1 H), 1.95 (dd, *J*=7.9, 5.5 Hz, 1 H), 2.22 (s, 3 H), 2.28 - 2.36 (m, 2 H), 2.41 (s, 3 H), 2.52 (d, *J*=14.6 Hz, 1 H), 2.66 (dd, *J*=13.7, 7.3 Hz, 1 H), 2.96 - 3.03 (m, 2 H), 3.21 (s, 6 H), 3.91 (s, 3 H), 4.01 - 4.06 (m, 1 H), 4.18 (dd, *J*=11.9, 3.4 Hz, 1 H), 4.31 (d, *J*=11.9 Hz, 1 H), 4.56 (d, *J*=7.0 Hz, 1 H), 4.68 (dd, *J*=9.9, 7.2 Hz, 1 H), 5.14 - 5.19 (m, 1 H), 5.35 (d, *J*=17.1 Hz, 1 H), 5.75 - 5.85 (m, 1 H), 6.01 (s, 1 H), 6.60 (s, 1 H), 6.69 (s, 1 H), 6.83 (d, *J*=8.9 Hz, 1 H), 7.05 (s, 1 H), 7.81 (d, *J*=9.2 Hz, 1 H); LC-MS, MS m/z 748 (M^+ + H).

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Ejemplo 18: Preparación del Compuesto 18: N-(4,6-dimetil-2-piridinil)-3-metilvalil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((3-(dimetilamino)-6-metoxi-1-isoquinolinil)oxi)-L-prolinamida



Compuesto 18

El compuesto 18 se preparó por el mismo método como se describe en la etapa 3, Ejemplo 14, excepto que el producto de la Etapa 6, Ejemplo 17 (0.203 g, 0.330 mmol) se usó en lugar del producto de la Etapa 5, Ejemplo 1. Dos productos con LCMS m/z idéntico se formaron en la reacción, pero solamente el compuesto de isómero sencillo 18 se aisló en pureza razonable. El Compuesto 18 fue el primero de dos isómeros en eluir por HPLC preparativa de fase inversa y se obtuvo como una sal bis-TFA en polvo café (0.102 g, 40.6% de rendimiento). ^{1}H RMN (500 MHz, MeOD) δ ppm 1.08 - 1.11 (m, *J*=3.05 Hz, 2 H) 1.13 (s, 9 H) 1.15 - 1.19 (m, *J*=1.83 Hz, 2 H) 1.25 - 1.30 (m, 2 H) 1.43 - 1.48 (m, 1 H) 1.92 - 1.97 (m, 1 H) 2.06 (s, 3 H) 2.26 - 2.35 (m, 2 H) 2.37 (s, 3 H) 2.61 - 2.67 (m, 1 H) 2.96 - 3.03 (m, 2 H) 3.13 (d, *J*=1.83 Hz, 6 H) 3.88 (d, *J*=1.83 Hz, 3 H) 4.06 (dd, *J*=12.21,

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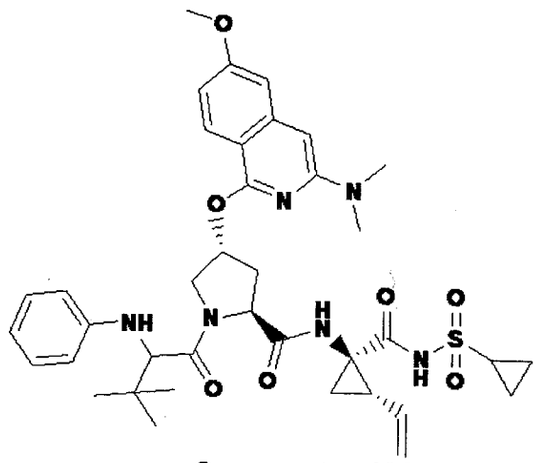
2.75 Hz, 1 H) 4.28 (d, *J*=12.51 Hz, 1 H) 4.47 (s, 1 H) 4.71 (t, *J*=8.70 Hz, 1 H) 5.17 (d, *J*=10.38 Hz, 1 H) 5.35 (d, *J*=17.09 Hz, 1 H) 5.73 - 5.82 (m, 1 H) 5.99 (s, 1 H) 6.52 (s, 1 H) 6.54 - 6.58 (m, 1 H) 6.61 (s, 1 H) 6.87 (t, *J*=1.98 Hz, 1 H) 7.56 (dd, *J*=9.00, 1.98 Hz, 1 H); LC-MS, MS m/z 762 (M^+ + H).

Isómeros del Compuesto 19:

3-metil-N-fenil-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((3-(dimetilamino)-6-metoxi-1-isoquinolinil)oxi)-L-prolinamida y

3-metil-N-fenil-D-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((3-(dimetilamino)-6-metoxi-1-isoquinolinil)oxi)-L-prolinamida

Ejemplo 19: Preparación de los compuestos 19A y 19B



Compuestos 19A y 19B

000515

El producto de la Etapa 6, Ejemplo 17 (0.203 g, 0.330 mmol), NMM (0.134 g, 1.32 mmol), HATU (0.151 g, 0.396 mmol) y el producto de la Etapa 1, Ejemplo 15 (0.102 g, 0.330 mmol) se combinaron en diclorometano (2 mL) y se agitaron durante 72 horas. Dos productos con LCMS m/z idéntico se formaron en la reacción. La mezcla se concentró y se purificó por HPLC preparativa de fase inversa. El Compuesto 19A fue el primero de dos isómeros en eluir por HPLC preparativa de fase inversa y se obtuvo como una sal bis-TFA en polvo café (0.0806 g, 33.3% de rendimiento). El Compuesto 19B fue el segundo de los dos isómeros en eluir por HPLC preparativa de fase inversa y se obtuvo como una sal bis-TFA en polvo café (0.0573 g, 23.7% de rendimiento).

Compuesto 19A: LC-MS, MS m/z 733 (M^+ +H).

Compuesto 19B: LC-MS, MS m/z 733 (M^+ + H).

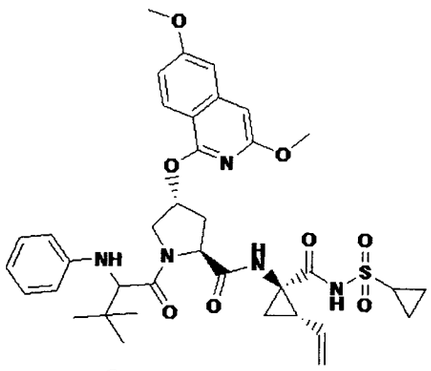
Isómeros del Compuesto 20:

3-metil-N-fenil-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((3,6-dimetoxi-1-isoquinolinil)oxi)-L-prolinamida y

3-metil-N-fenil-D-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((3,6-dimetoxi-1-isoquinolinil)oxi)-L-prolinamida

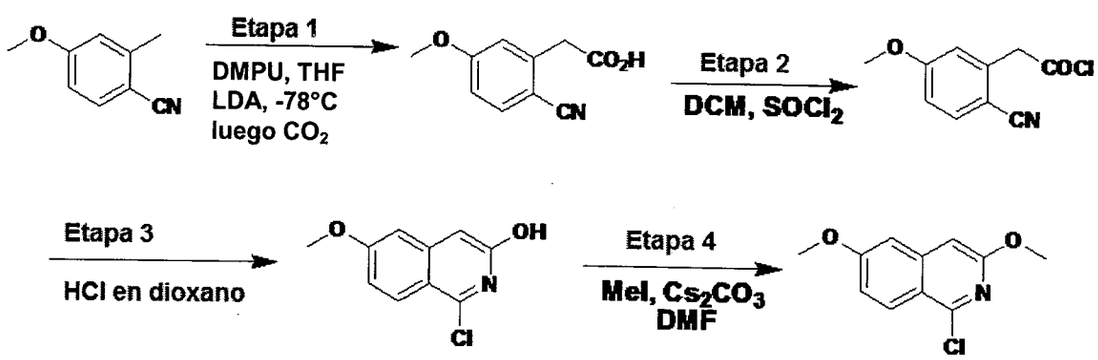
000516

Ejemplo 20: Preparación de los compuestos 20A y 20B



Compuestos 20A y 20B

Esquema de reacción 1



Etapa 1:

A una solución de 1,3-dimetil-3,4,5,6-tetrahidro-2(*1H*)-pirimidinona (DMPU, 7.02 g, 55 mmol) en THF (100 mL) se agregó LDA (2.0M en THF, 27.5 mL, 55 mmol) gota a gota a -78°C. La solución anaranjada resultante se mantuvo a esta temperatura durante 10 minutos con agitación y luego 4-metoxi-2-metilbenzonitrilo (7.36 g, 50 mmol en 5 mL THF) se agregó gota a gota. La solución anaranjada oscura resultante se mantuvo a esta temperatura durante 30 minutos con agitación. El gas CO_2

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luego se burbujeó en esta solución a -78°C hasta que se volvió incolora. La solución final se mantuvo a esta temperatura durante 30 minutos adicionales con agitación antes de ser purgada con N_2 durante 5 minutos. La mezcla se apagó con H_2O (80 mL) a -78°C, luego se permitió calentar hasta temperatura ambiente. 10.0M NaOH (ac, 20 mL, 200 mmol) se agregó, conduciendo a una solución homogénea la cual se extrajo con éter dietílico (100 mL). La capa acuosa se acidificó por HCl concentrado hasta pH = 2, y el precipitado resultante se colectó por filtración. La torta se lavó con H_2O a fondo y se secó *in vacuo* durante la noche para proporcionar el producto deseado (7.90 g 83.0% de rendimiento) como una hojuela blanca. ^{1}H RMN (300 MHz, CD_3OD) δ ppm 3.83 (s, 2H), 3.86 (s, 3H), 6.99 (m, 2H), 7.64 (d, J = 8.42 Hz, 1H).

Etapa 2:

Una mezcla espesa de ácido 2-(2-ciano-5-metoxifenil)acético en diclorometano (40 mL) y cloruro de tionilo (40 mL) se agitó a temperatura ambiente durante la noche. Los materiales volátiles se removieron, y el residuo se trituró con diclorometano (50 mL) y se filtró. El filtrado se concentró *in vacuo* para proporcionar el producto deseado como un aceite viscoso café (6.80 g, 97% de rendimiento). ^{1}H RMN (300 MHz, $CDCl_3$) δ ppm 3.86 (m, 3H), 4.35 (s, 2H), 6.92

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(m, 2H), 7.63 (d, J = 8.78 Hz, 1H).

Etapa 3:

Una solución de cloruro de 2-(2-ciano-5-metoxifenil)acetilo (6.40 g, 30.6 mmol) en 4.0M HCl en 1,4-dioxano (100 mL) se calentó en un recipiente sellado a 60°C con agitación durante la noche. Después de enfriarse a temperatura ambiente, la mezcla se filtró y la torta se lavó con acetato de etilo a fondo y se secó *in vacuo* para proporcionar el producto deseado como un polvo amarillo pálido fino (6.14 g, 96% de rendimiento). ^{1}H RMN (500 MHz, CD_3OD) δ ppm 3.98 (s, 3H), 6.94 (s, 1H), 7.14 (m, 2H), 8.10 (d, J = 9.16 Hz, 1H); LC-MS MS m/z 210 (M^++ H).

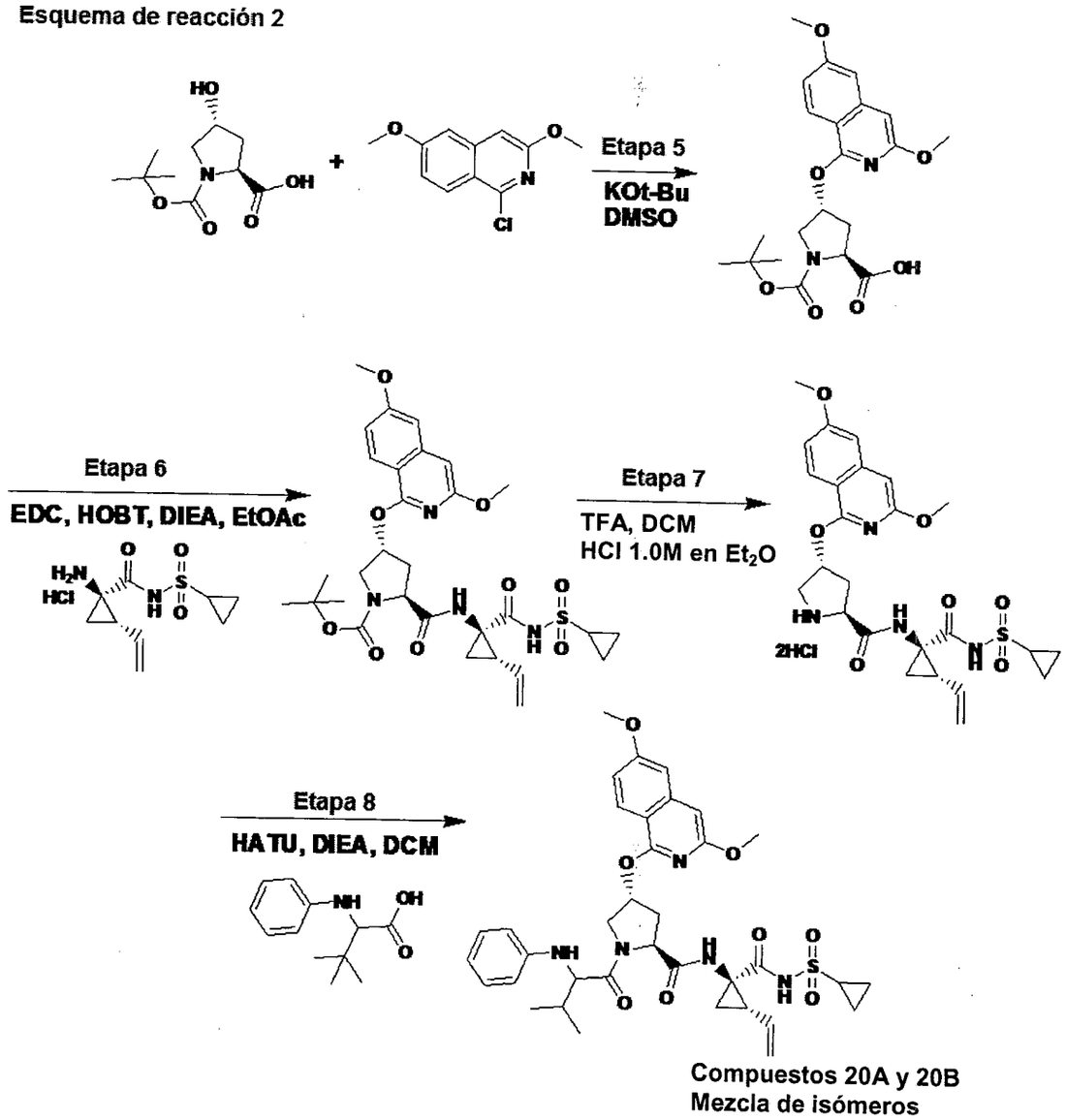
Etapa 4:

Una mezcla espesa de 1-cloro-6-metoxiisoquinolin-3-ol (0.209 g, 1.0 mmol), Cs_2CO_3 (0.715 g, 2.2 mmmol), y CH_3I (0.284 g, 2.0 mmol) en DMF (2.5 mL) se calentó a 85°C en un tubo sellado durante 3 horas. Durante el enfriamiento a temperatura ambiente, la capa superior de la solución café se decantó en 5% de ácido cítrico congelado. La mezcla se extrajo con acetato de etilo (20 mL). La capa orgánica se lavó con 5% ácido cítrico, NaOH 1.0M (ac), y salmuera secuencialmente, se secó sobre $MgSO_4$, y se filtró. El filtrado se concentró y el residuo se purificó por una columna de cromatografía por desorción súbita en gel de

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sílice. La elución con diclorometano proporcionó el producto deseado como un sólido blanco opaco (0.152 g, 68.0% de rendimiento). LC-MS MS m/z 224 (M^++ H).

Esquema de reacción 2



Etapa 5:

El producto de la Etapa 5, Ejemplo 20 se obtuvo por el mismo procedimiento como se describe por la preparación del

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producto de la Etapa 3, Ejemplo 1, excepto que el producto de la Etapa 4, Ejemplo 20 (1.25 g, 5.60 mmol) se usó como material de partida en lugar del producto de la Etapa 2 Ejemplo 1. El producto sin refinar se purificó por cromatografía por desorción súbita en gel de sílice (gradiente de etapa 3:1 hexanos:acetona, seguido por 2:1 y luego 1:1 del mismo) para dar una espuma blanca opaca (2.34 g, 91.6% de rendimiento). LC-MS MS m/z 419 (M^++ H).

Etapa 6:

A una solución a 0°C del producto de la Etapa 5, Ejemplo 20 (1.94 g, 5.68 mmol) en acetato de etilo (150 mL) se agregó sal HCl de (1-(R)-amino-2-(S)-vinil-ciclopropancarbonil)-amida del ácido ciclopropansulfónico (2.29 g, 5.68 mmol) en una porción. La mezcla se agitó durante 15 minutos, y luego DIPEA (1.91 g, 17.0 mmol) se agregó gota a gota y la suspensión se agitó durante 5 minutos. La mezcla luego se trató con EDC (1.41 g, 7.38 mmol) y HOBT (0.767 g, 5.68 mmol) y se agitó durante la noche. La mezcla se vació en 5% de ácido cítrico acuoso enfriado en hielo y la mezcla resultante se agitó y las fases se separaron. La fase orgánica se lavó con 5% ácido cítrico acuoso, 5 % citrato de sodio acuoso, y finalmente con salmuera. El material orgánico se secó sobre $MgSO_4$, se filtró y se concentró. La purificación por columna de cromatografía por desorción súbita en gel de sílice (1:1

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hexanos:acetona) dio el producto como una espuma blanca (2.50 g, 79% de rendimiento). LC-MS MS m/z 631 (M^++ H).

Etapa 7:

El producto de la Etapa 6, Ejemplo 20 (3.20 g, 5.08 mmol) se disolvió en diclorometano (20 mL) y la solución se trató con TFA (20 mL) a temperatura ambiente durante 1 hora. El solvente se removió *in vacuo*, y el residuo se combinó con HCl 1.0M en éter y se agitó durante la noche. El sólido resultante se aisló por filtración, se enjuagó con éter y se secó *in vacuo* para dar un sólido blanco opaco (2.97 g, 95.0% de rendimiento). LC-MS MS m/z 531 (M^++ H).

Etapa 8:

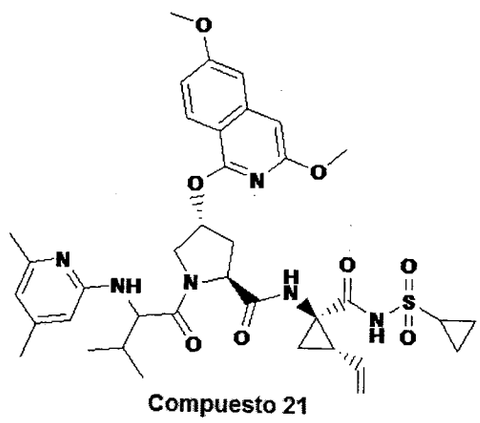
Los Compuestos 20A y 20B se preparan por el mismo procedimiento como se describe para la Preparación de los compuestos 19A y 19B, excepto que el producto de la Etapa 7, Ejemplo 20 (0.100 g, 0.166 mmol) se usó en lugar del producto de la Etapa 6, Ejemplo 17. El Compuesto 20A fue el primero de dos isómeros en eluir por HPLC preparativa de fase inversa y se obtuvo como una sal bis-TFA en polvo beige (0.0564 g, 35.9% de rendimiento). El Compuesto 20B fue el segundo de los dos isómeros en eluir por HPLC preparativa de fase inversa y se obtuvo como una sal bis-TFA en polvo beige (0.0367 g, 23.4% de rendimiento).

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Compuesto 20A: LC-MS, MS m/z 720 (M^+ +H).

Compuesto 20B: ^{1}H RMN (500 MHz, MeOD) δ ppm 0.98 (s, 9 H) 1.00 - 1.09 (m, 2 H) 1.14 - 1.21 (m, 1 H) 1.28 - 1.41 (m, 3 H) 1.88 (dd, *J*=8.09, 5.34 Hz, 1 H) 2.25 (c, *J*=9.05 Hz, 1 H) 2.31 - 2.39 (m, 1 H) 2.60 (dd, *J*=13.73, 7.02 Hz, 1 H) 2.79 - 2.87 (m, 1 H) 3.92 (s, 3 H) 3.98 (d, *J*=1.53 Hz, 3 H) 4.08 (dd, *J*=12.21, 3.36 Hz, 1 H) 4.20 (s, 1 H) 4.45 (d, *J*=11.90 Hz, 1 H) 4.54 - 4.60 (m, 1 H) 5.15 (d, *J*=10.38 Hz, 1 H) 5.34 (d, *J*=17.09 Hz, 1 H) 5.76 - 5.86 (m, 1 H) 5.91 (s, 1 H) 6.57 - 6.63 (m, 2 H) 6.77 (d, *J*=8.54 Hz, 2 H) 6.93 (dd, *J*=9.16, 2.44 Hz, 1 H) 7.05 - 7.13 (m, 3 H) 7.87 (d, *J*=9.16 Hz, 1 H) 9.33 (s, 1 H); LC-MS, MS m/z 720 (M^+ + H).

Ejemplo 21: Preparación del Compuesto 21: N-(4,6-dimetil-2-piridinil)valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((3,6-dimetoxi-1-isoquinolinil)oxi)-L-prolinamida



Compuesto 21

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El compuesto 21 se preparó por el mismo procedimiento como se describe en la etapa 7, Ejemplo 17, excepto que el producto de la Etapa 7, Ejemplo 20 (0.253 g, 0.419 mmol) se usó en lugar del producto de la Etapa 6, Ejemplo 17. El Compuesto 21 (0.052 g, 15.3 % de rendimiento) se obtuvo como una sal bis-HCl de polvo café. ^{1}H RMN (500 MHz, *MeOD*) δ ppm 1.01 (d, *J*=6.7 Hz, 1 H), 1.10 (d, *J*=6.7 Hz, 3 H), 1.12 - 1.16 (m, 2 H), 1.23 - 1.29 (m, 2 H), 1.30 - 1.37 (m, 1 H), 1.43 - 1.49 (m, 1 H), 1.91 - 1.97 (m, 1 H), 2.19 (s, 3 H), 2.26 - 2.34 (m, 1 H), 2.40 (s, 3 H), 2.62 - 2.70 (m, 1 H), 2.89 (s, 1 H), 2.95 - 3.03 (m, 1 H), 3.16 - 3.22 (m, 1 H), 3.92 (s, 3 H), 3.99 (s, 3 H), 4.17 (dd, *J*=12.1, 3.5 Hz, 1 H), 4.23 - 4.29 (m, 1 H), 4.50 (d, *J*=7.0 Hz, 1 H), 4.64 - 4.70 (m, 1 H), 5.17 (d, *J*=10.4 Hz, 1 H), 5.35 (d, *J*=17.1 Hz, 1 H), 5.75 - 5.86 (m, 1 H), 5.98 (d, *J*=2.1 Hz, 1 H), 6.60 (d, *J*=8.2 Hz, 1 H), 6.66 (s, 1 H), 6.87 (dd, *J*=9.2, 2.4 Hz, 1 H), 7.06 (t, *J*=2.1 Hz, 1 H), 7.83 (d, *J*=9.2 Hz, 1 H); LC-MS, MS m/z 748 (M^+ + H).

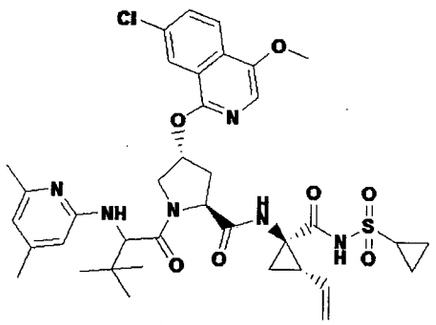
Isómeros del Compuesto 22:

N-(4,6-dimetil-2-piridinil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

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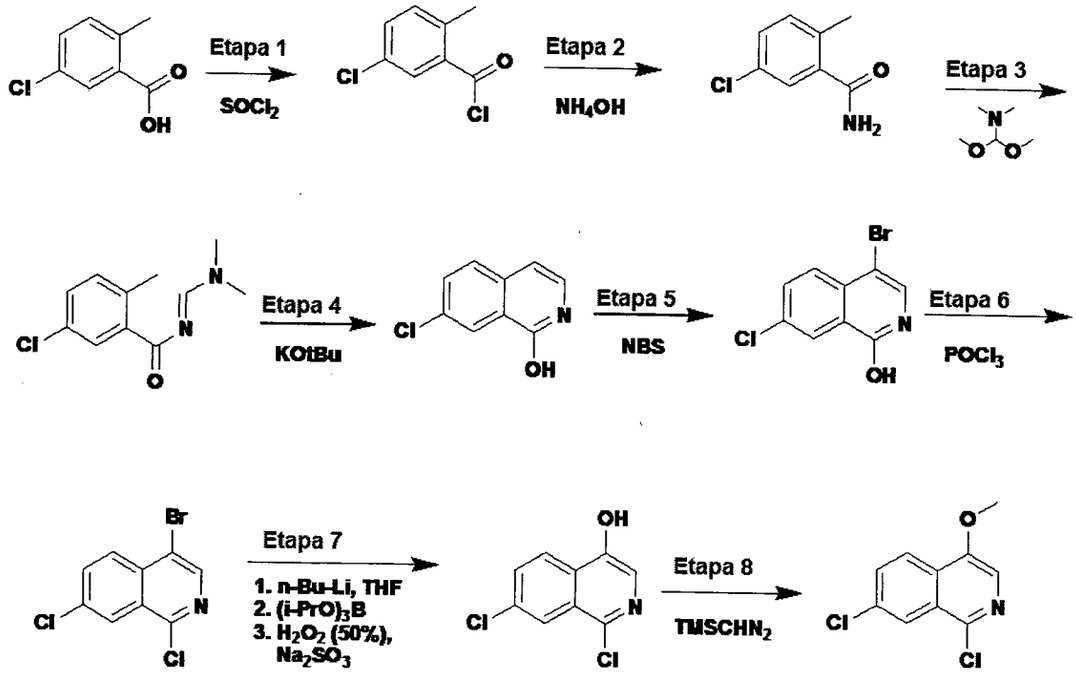
N-(4,6-dimetil-2-piridinil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

Ejemplo 22: Preparación de los compuestos 22A y 22B:



Compuestos 22A y 22B

Esquema de reacción 1 del ejemplo 22



Etapa 1:

Una mezcla espesa de ácido 3-cloro-6-metilbenzoico (17.0 g, 0.10 mol) en cloruro de tionilo (23.5 ml, 0.30 mol) se calentó lentamente a un reflujo suave y se mantuvo a esta temperatura durante 2h. La mezcla de reacción luego se enfrió a t.a. y el exceso de cloruro de tionilo se removió *in vacuo*. El residuo se tomó en DCM (50 ml), y el solvente luego se removió *in vacuo*. (Se deberá notar que este proceso se repitió varias veces para asegurar el retiro del residuo de cloruro de tionilo y HCl). El producto resultante luego se disolvió en THF (80 ml) el cual se usó directamente en la siguiente reacción como se describe a continuación.

Etapa 2:

A una solución de 30% amonio (58 ml) en agua (240 ml), se enfrió por baño de sal-hielo (-10°C), se agregó gota a gota una solución THF del producto de la Etapa 1 de arriba. Después de que la adición se completó, la mezcla de reacción resultante (mezcla espesa) se agitó a -10°C durante 1 hr. La mezcla de reacción luego se calentó a temperatura ambiente y se decantó. El sólido restante en el recipiente de reacción luego se trituró con agua (50 ml). Este Proceso de trituración y de decantado luego se repitió. El sólido resultante luego

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se filtró y la torta del filtro se lavó con agua. El sólido luego se secó *in vacuo* durante la noche para proporcionar 13.8 g (82%) del producto deseado como un material cristalino blanco. ^{1}H RMN (DMSO-D_6) δ ppm 2.33 (s, 3H), 7.24-7.27 (m, 1H), 7.35-7.38 (m , 2H), 7.44 (a, 1H), 7.80 (a, 1H); ^{13}C RMN (100 MHz, DMSO-D_6) δ ppm 18.87, 126.64, 128.86, 129.81, 132.31, 134.19, 138.65, 169.41; LC-MS, MS m/z 170.

Etapa 3:

Una mezcla del producto de la Etapa 2 (11.5 g, 68 mmol), DMF-acetal (10.9 ml, 82 mmol), y THF (150 ml) se calentó a reflujo y se mantuvo a esta temperatura durante 2 hr. La mezcla de reacción luego se enfrió a temperatura ambiente y los materiales volátiles se removieron in vacuo. El residuo resultante se recristalizó a partir de hexano (150 ml) para proporcionar 14.7 g (96%) del producto deseado como agujas blancas.

^{1}H RMN (DMSO-D_6) δ 2.49-2.51 (m, 3H), 3.09 (s, 3H), 3.20 (s, 3H), 7.24, 7.27 (d, J=13.5 Hz, 1H), 7.37-7.41 (dd, J1=14 Hz, J2=4.5 Hz, 1H), 7.91, 7.92 (d, J=4.0 Hz, 1H), 8.55 (s, 1H); ^{13}C RMN (100 MHz, DMSO-D_6) δ ppm 20.69, 35.09, 40.91, 129.50, 129.72, 132.98, 136.86,138.87, 160.60, 177.04; LC-MS, MS m/z 225.

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Etapa 4:

Una mezcla del producto de la Etapa 3 y KOtBu (14.7 g, 131 mmol) en THF (300 ml) se calentó a reflujo y se mantuvo a esta temperatura durante 2 hr (la mezcla de reacción se volvió una solución oscura durante el calentamiento). El volumen de la mezcla de reacción luego se redujo por destilación completa de aproximadamente 100 ml del Solvente. La solución resultante luego se vació cuidadosamente en agua (1 L) y la mezcla resultante se acidificó con HCl 1M hasta un pH resultante de 4. La mezcla luego se filtró, y el sólido colectado se lavó a fondo con agua, luego se secó *in vacuo* durante la noche para proporcionar 7.0 g (60%) del producto deseado como un polvo blanco opaco.

^{1}H RMN (400 Hz, CD_3OD) δ ppm 6.66 (d, J=7.05 Hz, 1 H), 7.18 (d, J=7.05 Hz, 1 H), 7.66 (s, 1 H) 7.67 (d, J=2.01 Hz, 1 H), 8.24 (d, J=2.27 Hz, 1 H); ^{13}C RMN (100 MHz, DMSO-D_6) δ ppm 104.05, 125.62, 127.21, 128.54, 129.52, 130.77, 132.43, 136.55, 160.72; LC-MS, MS m/z 180.

Etapa 5:

Una mezcla espesa del producto de la Etapa 4 y NBS (39.747 g, 223.3 mmol) en MeCN (500 mL, anhidro) se calentó lentamente a un reflujo suave durante un periodo de aproximadamente 2 h y se mantuvo a un reflujo suave durante

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1.5 h (Esta reacción puede monitorearse por CL/EM). La mezcla de reacción luego se enfrió lentamente a temperatura ambiente durante un periodo de 3 h y el sólido observado se removió por filtración sencilla. El sólido colectado se lavó con MeCN (100 mL x 3) para proporcionar 47 g del producto deseado. Este material se usó en la siguiente etapa sin purificación adicional.

^{1}H RMN (400 MHz, CD_3OD) δ ppm 7.46 (s, 1H), 7.81 (dd, J=8.40, 2.00 Hz, 1 H), 7.88 (d, J=8.8 Hz, 1 H), 8.27 (d, J=2.00 Hz, 1 H); ^{13}C RMN (100 MHz, DMSO-D_6) δ ppm 96.68, 126.34, 127.58, 127.71, 130.73, 132.20, 133.47, 134.46, 159.88; LC-MS, MS m/z 258.

Etapa 6:

Una solución heterogénea del producto de la Etapa 5 (47 g, 182 mmol) en $POCl_3$ (200 mL, 2.15 mol) se calentó lentamente a reflujo durante un periodo de 1 h. La mezcla de reacción se mantuvo a reflujo durante 4 h. La mezcla de reacción luego se enfrió a temperatura ambiente y se concentró *in vacuo* para remover el exceso de $POCl_3$. El residuo resultante luego se tomó en 600 mL de CH_2Cl_2, se enfrió a -35°C, luego se neutralizó cuidadosamente con 1 N NaOH (400 mL) hasta que la mezcla se hizo ligeramente básica (pH = 8). La capa orgánica resultante se separó, se lavó con agua, se secó sobre $MgSO_4$ y se concentró *in vacuo*.

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El residuo resultante se cristalizó a partir de EtOAc (aproximadamente 50 mL) para dar 32 g del producto deseado. El sólido colectado se lavó con 10% EtOAc/Hexanos (3 x 50 ml).

El líquido madre se concentró y se purificó por Biotage (elución con 16% EtOAc en hexanos) para dar 4 g del producto deseado como un sólido.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 7.80 (dd, J=8.81, 2.01 Hz, 1 H), 8.14 (d, J=9.06 Hz, 1 H), 8.34 (d, J=1.76 Hz, 1 H), 8.48 (s, 1 H); ^{13}C RMN (100 MHz, DMSO-D_6) δ ppm 118.39, 125.06, 127.59, 128.71, 133.89, 134.14, 134.93, 143.18, 148.98; LC-MS, MS m/z 275.

Etapa 7:

A una mezcla espesa del producto de la Etapa 6 (22.16 g, 80 mmol) en THF (500 ml) a -78°C se agregó 100 ml de 1.6 M n-BuLi (en hexanos, 160 mmol) gota a gota por medio de una cánula durante 15 min (manteniendo la temperatura interna < -65°C). La solución resultante se agitó durante 0.5 h, después de este tiempo, $(i\text{-PrO})_3B$ (37 ml, 160 mmol) se agregó gota a gota por medio de una jeringa durante 10 min (manteniendo la temperatura interna <-65°C). La mezcla de reacción resultante se agitó durante 0.5 h. Después de verificar que la reacción por CL/MS se completó, 80 ml de 30% H_2O_2 (776 mmol) se agregaron gota a gota por medio de un embudo de adición

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durante 10 min (la temperatura interna alcanzó hasta -60°C durante la adición), seguido por la adición de 80 ml de 1 N NaOH (80 mmol). El baño de enfriamiento se removió, y la mezcla de reacción se permitió calentar a temperatura ambiente y se agitó a temperatura ambiente durante 1 hora adicional. Después de confirmar que la reacción se completó por CL/EM, la mezcla de reacción luego se enfrió a -40°C, y una solución de 100 g de Na_2SO_3 (0.793 moles) en 400 ml de agua se agregó gota a gota por medio de un embudo de adición como un medio para apagar el exceso de H_2O_2 durante 30 min (manteniendo la temperatura interna de 5-10°C). La mezcla resultante luego se neutralizó con HCl 6 N (aproximadamente 50 ml) a 0°C hasta pH ~ 6, luego se diluyó con 500 ml de EtOAc y se decantó hasta un embudo de separación de 2L. Al sólido restante en el recipiente de reacción se agregó 500 mL de agua y 300 ml de EtOAc, luego se neutralizó con HCl 6 N (aproximadamente 20 ml). Las capas orgánicas combinadas se lavaron con salmuera (300 ml x 3), luego agua (200 ml x 3), se secaron sobre $MgSO_4$ y se concentraron para dar el producto sin refinar el cual se trituró con 50 ml de EtOAc. El sólido se colectó por filtración, se enjuagó con EtOAc (3 x 25 ml) y se secó para dar el producto deseado (2 corridas: 12.0 g, 70% y 13.8 g, 81%). Los filtrados se combinaron, se concentraron y se purificaron por Biotage eluido con 35% EtOAc en hexanos para dar 2.1 g del producto. En general, 44.4 g de bromuro

000551

dio 27.9 g (81%) del producto 4-OH.

^{1}H RMN (400 MHz, CD_3OD) δ ppm 4.05 (s, 3 H), 7.4 (s, 1 H), 7.76 (dd, J=8.8, 2, Hz, 1 H), 8.16 (d, J=2 Hz, 1 H), 8.23 (d, J=8.8 Hz, 1 H); ^{13}C RMN (100 MHz, DMSO-D_6) δ ppm 123.78, 124.66, 125.62, 127.03, 127.71, 130.72, 133.80, 137.63; 148.88; LC-MS, MS m/z 213.

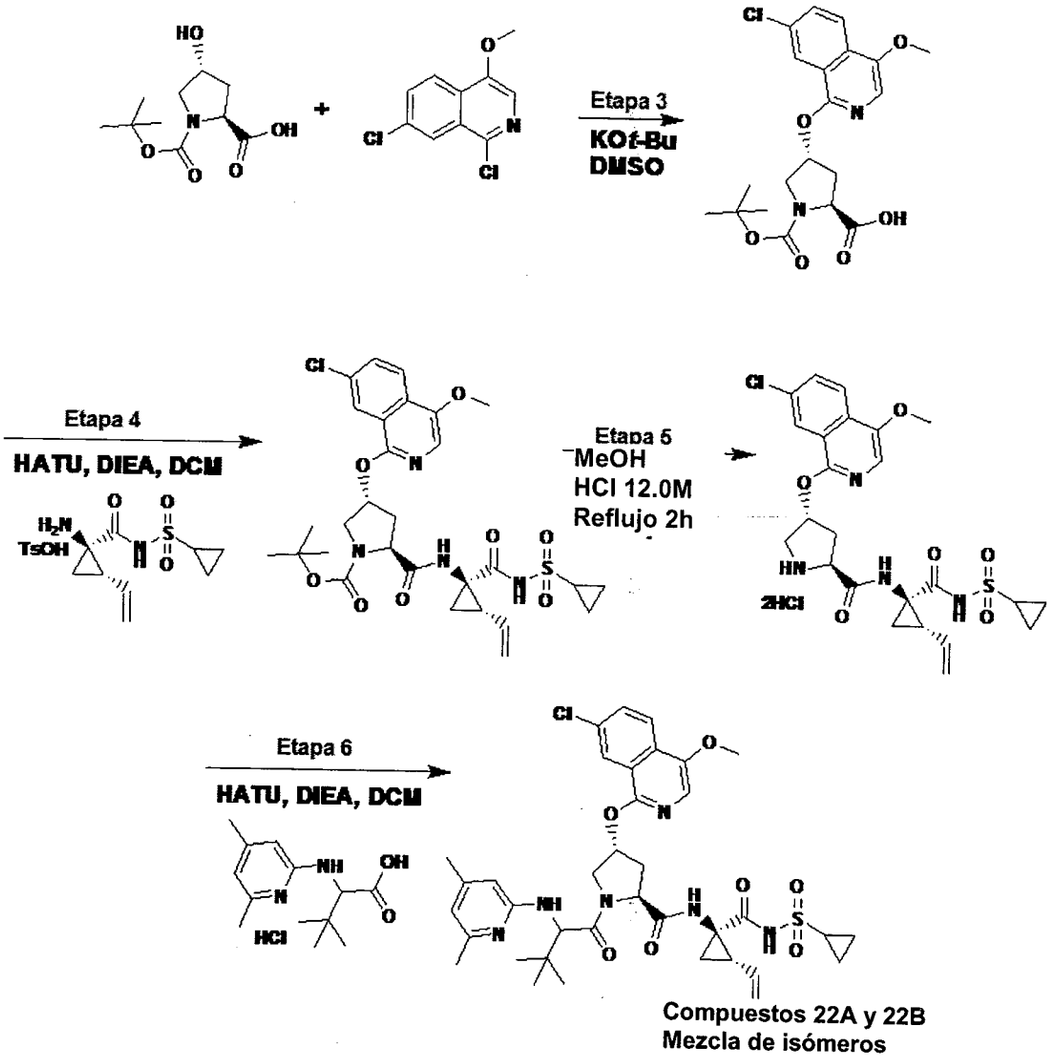
Etapa 8:

A una mezcla espesa del producto de la Etapa 7 (16 g, 75.5 mmol) en MeOH-MeCN (30 mL/300 mL) a 0°C se agregó gota a gota 60 ml de solución 2M de $TMSCHN_2$ en hexanos (120 mmol). La mezcla de reacción se permitió calentar a temperatura ambiente, luego se agitó durante 14 h. La solución luego se concentró y el sólido resultante se recristalizó a partir de EtOAc (alrededor de 50 mL) para dar 8.1 g del producto deseado el cual se lavó con 25% EtOAc en hexanos; 20 x3 veces. El líquido madre se concentró y se purificó por Biotage (elución con 16% EtOAc en hexanos) para proporcionar 3.2 g del producto deseado como un sólido.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 4.05 (s, 3 H), 7.67 (dd, J=9.06, 2.01 Hz, 1 H), 7.80 (s, 1 H), 8.16 (d, J=8.81 Hz, 1 H), 8.23 (d, J=2.01 Hz, 1 H); ^{13}C RMN (100 MHz, DMSO-D_6) δ ppm 56.68, 122.70, 123.99, 124.14, 126.67, 127.83, 131.43, 134.10, 139.75, 149.94; LC-MS, MS m/z 229.

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Esquema de reacción 2 del ejemplo 22



Etapa 3:

El producto de la Etapa 2, Ejemplo 22 (0.452 g, 1.98 mmol), Boc-HYP-OH (0.508 g, 2.20 mmol), y terc-butóxido de potasio (0.672 g, 6.0 mmol) en DMSO (20 mL) se agitó a temperatura ambiente durante 4 horas. La mezcla se apagó con agua y se neutralizó con HCl acuoso 1.0M. La mezcla se extrajo con acetato de etilo y el material orgánico se lavó

000533

con salmuera, se secó sobre $MgSO_4$ anhidro, se filtró y se concentró para dar un sólido sin refinar (0.844 g, cuantitativo) el cual se usó en la siguiente etapa sin purificación adicional.

Etapa 4:

El producto de la Etapa 3, Ejemplo 22 (0.422 g, 1.00 mmol) se disolvió en diclorometano (10 mL) y DIEA (2 mL). A la solución se agregaron sal del ácido p-toluensulfónico de la (1-(*R*)-amino-2-(*S*)-vinil-ciclopropanocarbonil)-amida del ácido ciclopropansulfónico (0.402 g, 1.00 mmol) y HATU (0.600 g, 1.58 mmol) y la mezcla se agitó durante 6 horas y se concentró. La purificación por columna de cromatografía por desorción súbita en gel de sílice (1:1 hexano:acetona) dio el producto sólido deseado (0.600 g, 94.5% de rendimiento). LC-MS, MS m/z 636 (M^+ + H).

Etapa 5:

El producto de la Etapa 4, Ejemplo 22 (6.34 g, 9.98 mmol) se disolvió en metanol (50 mL) se trató con 1HCl 2M (3 mL) y la mezcla se calentó a reflujo durante 2 horas y se concentró. El material sin refinar se usó directamente en la siguiente etapa.

Etapa 6:

Una solución del producto de la Etapa 5, Ejemplo 22

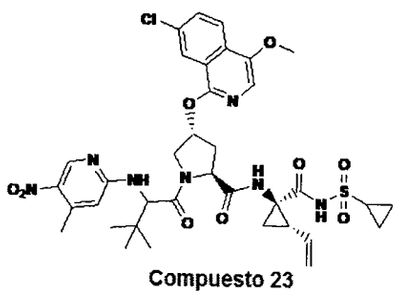
000534

(0.480 g, 0.790 mmol), DIEA (1 mL) y el producto de la Etapa 2, Ejemplo 14 (0.240 g, 0.880 mmol) en DMF (5 mL) se roció con nitrógeno. La mezcla se enfrió a 0°C, se trató con HATU (0.456 g, 1.12 mmol) y se agitó a temperatura ambiente durante 5 horas. La reacción luego se calentó a 46°C durante 25 horas. La mezcla se concentró, y el residuo se purificó por HPLC preparativa de fase inversa para dar dos productos separados con MS m/z idéntico como se observó por LCMS. El Compuesto 22A (0.045 g, 7.6% de rendimiento) fue el primero de dos isómeros en eluir por HPLC preparativa de fase inversa. El Compuesto 22B (0.050 g, 8.4% de rendimiento) fue el segundo de los dos isómeros en eluir por HPLC preparativa de fase inversa.

Compuesto 22A: LC-MS, MS m/z 754 ($M^+ + H$).

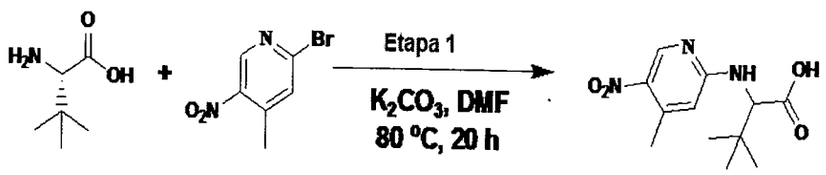
Compuesto 22B: LC-MS, MS m/z 754 ($M^+ + H$).

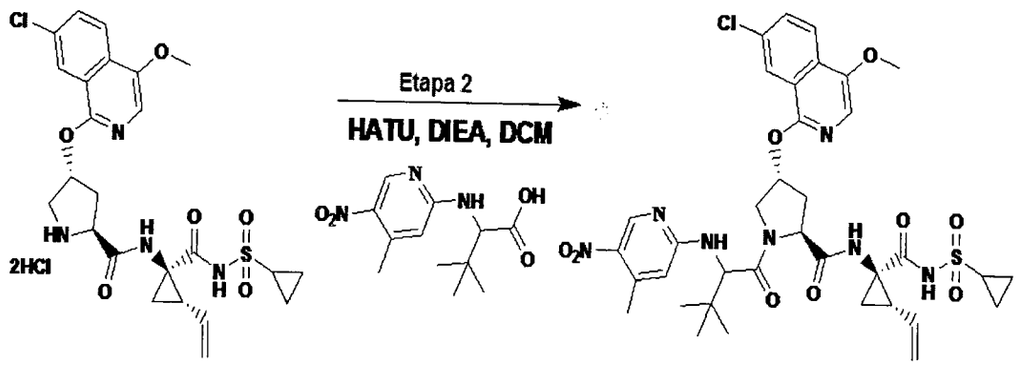
Ejemplo 23: Preparación del Compuesto 23: 3-metil-N-(4-metil-5-nitro-2-piridinil)valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida



Compuesto 23

Esquema de reacción 1





Producto de la etapa 5, ejemplo 22

Compuesto 23

Etapa 1:

Una mezcla de 2-bromo-5-nitro-4-picolina (2.00 g, 9.22 mmol), L-terc-leucina (1.27 g, 9.68 mmol) y carbonato de potasio (3.18 g, 23.0 mmol) en DMF anhidro (50 mL) se calentó a 80°C durante 20 h. La mezcla se concentró *in vacuo* hasta un residuo (aproximadamente 25 mL), luego DCM (200 mL) y agua (100 mL) se agregaron y la mezcla resultante se agitó y las dos fases se separaron. La fase acuosa se extrajo con DCM (3 x 100 mL), y los extractos orgánicos se combinaron y se secaron sobre sulfato de magnesio anhidro, se filtraron y se concentraron *in vacuo* hasta un sólido rojo oscuro. La

000536

purificación por HPLC preparativa de fase inversa proporcionó un sólido amarillo (0.66 g, 27% de rendimiento). LC-MS, MS m/z 268 ($M^+ + H$).

Etapa 2:

El producto de la Etapa 1, Ejemplo 23, (0.145 g, 0.543 mmol) se combinó con el producto de la Etapa 5, Ejemplo 22, (0.300 g, 0.493 mmol) y HATU (0.281 g, 0.740 mmol) en DCM (4 mL). A la mezcla se agregó N-metilmorfolina (0.250 g, 2.47 mmol), y la mezcla resultante se agitó a temperatura ambiente durante la noche, luego a 60°C durante 3 d. El producto adicional de la etapa 1, Ejemplo 23 (0.145 g, 0.543 mmol) y HATU (0.281 g, 0.740 mmol) se agregaron, y la mezcla se agitó a t.a. durante la noche. La purificación por HPLC preparativa de fase inversa dio el compuesto 23 como una sal bis-TFA sólida anaranjada/café (0.097 g, 19.4% de rendimiento). ^{1}H RMN (500 MHz, CD_3OD) δ ppm 1.10 (s, 9 H) 1.11 - 1.15 (m, 2 H) 1.23 - 1.32 (m, 2 H) 1.43 - 1.50 (m, 1 H) 1.93 (dd, *J*=8.24, 5.49 Hz, 1 H) 2.24 - 2.32 (m, 2 H) 2.33 (s, 3 H) 2.60 (dd, *J*=13.58, 6.87 Hz, 1 H) 2.96 - 3.03 (m, 1 H) 3.99 - 4.03 (m, 1 H) 4.05 (s, 3 H) 4.65 (dd, *J*=10.68, 7.02 Hz, 1 H) 4.78 - 4.83 (m, 1 H) 4.90 (s, 1 H) 5.16 (dd, *J*=10.38, 1.53 Hz, 1 H) 5.31 - 5.37 (m, 1 H) 5.78 (ddd, *J*=17.17, 10.15, 9.00 Hz, 1

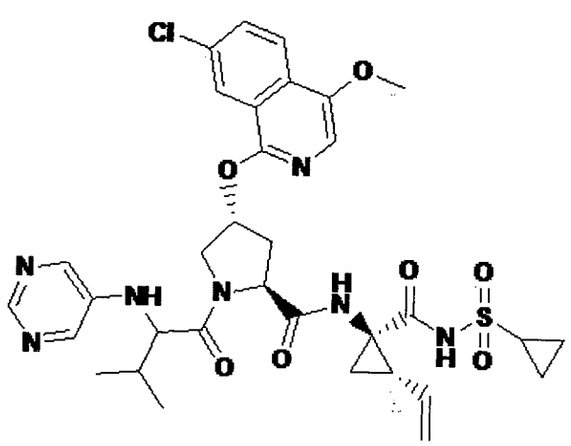
H) 5.87 (t, *J*=3.05 Hz, 1 H) 6.29 (s, 1 H) 7.57 - 7.64 (m, 2 H) 7.71 (s, 1 H) 7.76 (d, *J*=2.14 Hz, 1 H) 8.03 (d, *J*=8.85 Hz, 1 H) 9.22 (s, 1 H); LC-MS, MS m/z 785 (M^+ + H).

Isómeros del Compuesto 24:

N-5-pirimidinil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

N-5-pirimidinil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

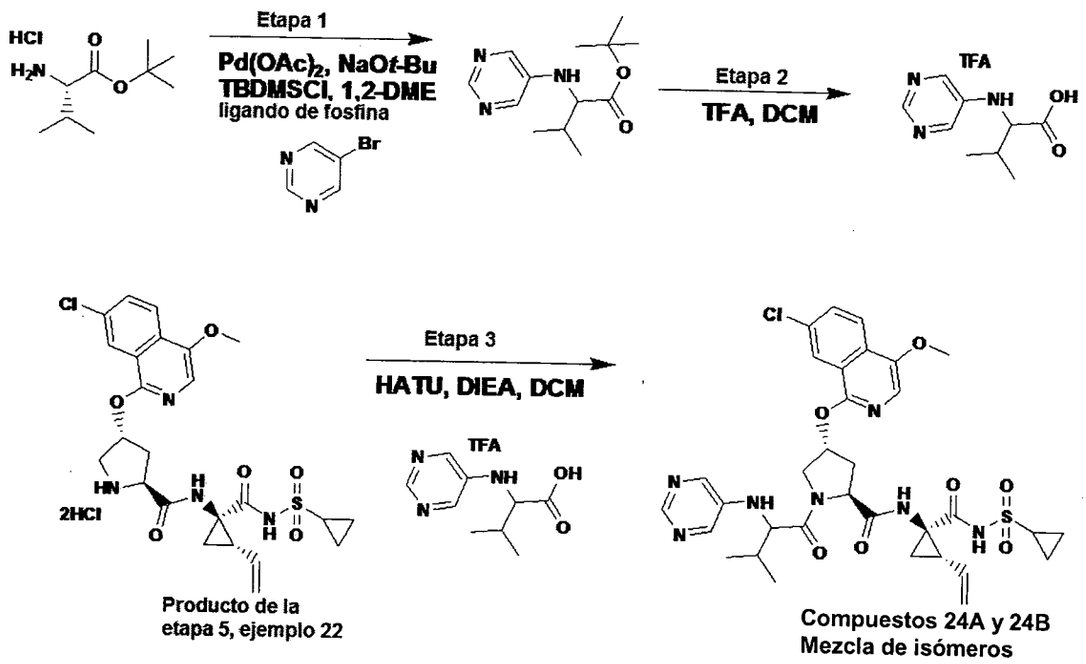
Ejemplo 24: Preparación de los compuestos 24A y 24B



Compuestos 24A y 24B

000538

Esquema de reacción 1



Etapa 1:

La 5-Bromopirimidina (1.15 g, 7.21 mmol) y terc-butóxido de sodio (2.36 g, 24.5 mmol), se combinaron con 1,2-dimetoxietano anhidro (15 mL) en un recipiente a presión Chemglass de 75 ml. La mezcla se agitó, y una solución pre-mezclada de $Pd(OAc)_2$ (0.0405 g, 0.180 mmol) y (*R*)-(-)-1-[(*S*)-(diciclohexilfosfino) ferrocenil] etil di-*terc*-Butil fosfina (0.100 g, 0.180 mmol, StrMS Chemicals catálogo # 26-0975, CAS # [158923-11-6]) en 1,2-dimetoxietano seco (2 mL) se agregó inmediatamente. El clorohidrato de éster terc-butílico de *L*-valina (1.18 g, 5.62 mmol) luego se agregó rápidamente a la mezcla resultante. El recipiente a presión se selló y la mezcla se agitó a 110°C durante 20 horas. El producto sin

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refinar se pasó a través de un tapón de gel de sílice (elución 100% DCM luego 100% EtOAc) para remover los contaminantes de la línea base. El solvente se removió *in vacuo*, y 300 mg del material sin refinar recuperado se purificó por cromatografía por desorción súbita en gel de sílice (Gradiente 4:1 hexanos:EtOAc hasta 1:1 hexanos:EtOAc) para dar un sólido amarillo (0.200 g, 14.2% de rendimiento). ^{1}H RMN (500 MHz, CLOROFORMO-D) δ ppm 1.03 (t, *J*=6.87 Hz, 6 H) 1.45 (s, 9 H) 2.11 - 2.19 (m, 1 H) 3.75 (dd, *J*=9.16, 5.19 Hz, 1 H) 4.24 (d, *J*=9.16 Hz, 1 H) 8.13 (s, 2 H) 8.60 (s, 1 H); LC-MS, MS m/z 252 (M^+ + H).

Etapa 2:

El producto de la Etapa 1, Ejemplo 24, (0.200 g) se disolvió en diclorometano (10 mL) y se trató con TFA (10 mL). La mezcla se agitó a temperatura ambiente durante 3 h y luego se concentró *in vacuo*. El residuo luego se disolvió en 1,2-dicloroetano (15 mL) y se concentró nuevamente *in vacuo*. El residuo verde oscuro luego se purificó por HPLC preparativa de fase inversa para proporcionar un sólido cristalino verde oscuro como la sal HCl (0.091 g, 49% de rendimiento). ^{1}H RMN (500 MHz, DMSO-D_6) δ ppm 0.99 (dd, *J*=9.16, 7.02 Hz, 6 H) 2.14 (td, *J*=13.28, 6.71 Hz, 1 H) 3.90 (d, *J*=5.80 Hz, 1 H) 6.32 (s, 1 H) 8.22 (s, 2 H) 8.44 (s, 1 H); LC-MS, MS m/z 196 (M^+ + H).

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Etapa 3:

Una mezcla del producto de la Etapa 2, Ejemplo 24, (0.084 g, 0.362 mmol), el producto de la Etapa 5, Ejemplo 22, (0.200 g, 0.329 mmol) y HATU (0.188 g, 0.493 mmol) se suspendió en DCM (4 mL) se trató con NMM (0.167 g, 1.65 mmol). La mezcla se agitó a temperatura ambiente durante 3 horas. El solvente se removió bajo una corriente de nitrógeno y la mezcla sin refinar se purificó por HPLC preparativa de fase inversa para dar dos compuestos separados con MS m/z idéntico. El Compuesto 24A (0.0902 g, 29.2% de rendimiento) fue el primero de dos isómeros en eluir a partir de la columna HPLC preparativa de fase inversa y se obtuvo como una sal bis-TFA en polvo beige. El Compuesto 24B (0.0957 g, 30.9% de rendimiento) fue el segundo de los dos isómeros en eluir a partir de la columna HPLC preparativa de fase inversa y se obtuvo como una sal bis-TFA en polvo beige.

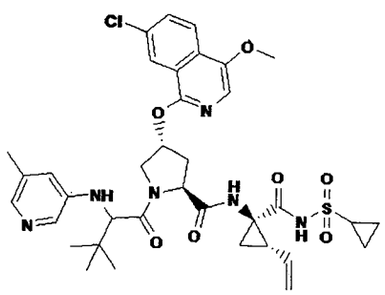
Compuesto 24A: ^{1}H RMN (300 MHz, CD_3OD) δ ppm 0.91 (dd, *J*=6.95, 3.29 Hz, 2 H) 1.04 (d, *J*=6.59 Hz, 3 H) 1.09 (d, *J*=6.59 Hz, 3 H) 1.19 - 1.38 (m, 8 H) 1.43 (dd, *J*=9.51, 5.12 Hz, 1 H) 1.91 (dd, *J*=8.23, 5.31 Hz, 1 H) 2.03 (s, 1 H) 2.19 - 2.38 (m, 3 H) 2.57 (dd, *J*=13.54, 7.32 Hz, 1 H) 2.94 - 3.06 (m, 1 H) 4.03 (s, 3 H) 4.06 - 4.21 (m, 2 H) 4.34 (d, *J*=12.08 Hz, 1 H) 4.57 (dd, *J*=10.25, 6.95 Hz, 1 H) 5.14 (dd, *J*=10.61, 1.10 Hz, 1 H) 5.32 (dd, *J*=17.20, 1.46 Hz, 1 H) 5.72 - 5.87 (m, 1 H) 5.89 (s, 1 H) 7.56 (s, 1 H) 7.70 (dd, *J*=8.78, 2.20

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Hz, 1 H) 7.99 (d, *J*=2.20 Hz, 1 H) 8.07 - 8.16 (m, 3 H) 8.29 (s, 1 H); LC-MS, MS m/z 713 (M^+ + H).

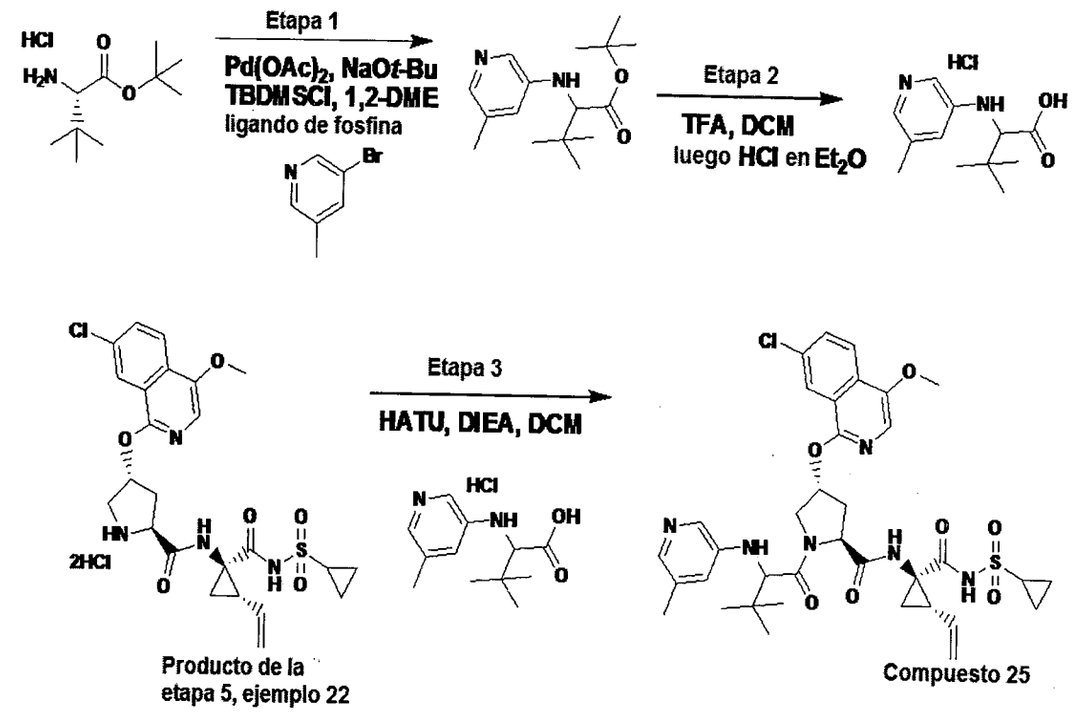
Compuesto 24B: ^{1}H RMN (300 MHz, CD_3OD) δ ppm 0.91 (d, *J*=6.95 Hz, 3 H) 0.95 (d, *J*=6.59 Hz, 3 H) 0.98 - 1.13 (m, 3 H) 1.20 - 1.31 (m, 2 H) 1.40 (dd, *J*=9.51, 5.12 Hz, 1 H) 1.90 (dd, *J*=8.23, 5.31 Hz, 1 H) 1.98 - 2.07 (m, 1 H) 2.22 - 2.41 (m, 2 H) 2.57 - 2.66 (m, 1 H) 2.82 - 2.93 (m, *J*=7.82, 7.82, 5.12, 4.85 Hz, 1 H) 4.04 (s, 3 H) 4.05 - 4.16 (m, 1 H) 4.23 (d, *J*=6.95 Hz, 1 H) 4.41 (d, *J*=12.08 Hz, 1 H) 4.62 (dd, *J*=9.70, 7.14 Hz, 1 H) 5.15 (dd, *J*=10.43, 1.65 Hz, 1 H) 5.34 (dd, *J*=17.20, 1.46 Hz, 1 H) 5.78 (ddd, *J*=17.20, 10.25, 8.78 Hz, 1 H) 5.87 (s, 1 H) 7.61 (s, 1 H) 7.73 (dd, *J*=8.97, 2.01 Hz, 1 H) 7.96 (d, *J*=1.83 Hz, 1 H) 8.13 (d, *J*=9.15 Hz, 1 H) 8.21 (s, 2 H) 8.33 (s, 1 H); LC-MS, MS m/z 713 (M^+ + H).

Ejemplo 25: Preparación del Compuesto 25: 3-metil-N-(5-metil-3-piridinil)valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida



Compuesto 25

Esquema de reacción 1



Etapa 1:

La 5-Bromo-3-picolina (1.00 g, 5.81 mmol), terc-butóxido de sodio (1.90 g, 19.8 mmol) y clorohidrato de éster terc-butílico de terc-leucina (1.665 g, 6.98 mmol) se combinaron en 1,2-dimetoxietano anhidro (20 mL) en un recipiente a presión Chemglass de 75 ml. La mezcla se agitó brevemente, y una solución pre-mezclada de $Pd(OAc)_2$ (0.0652 g, 0.291 mmol) y (*R*)-(-)-1-[(*S*)-(diciclohexilfosfino)ferrocenil] etil di-*terc*-Butil fosfina (0.161 g, 0.291 mmol, StrMS Chemicals catálogo # 26-0975, CAS # [158923-11-6]) en 1,2-dimetoxietano seco (2 mL) se agregó inmediatamente. El recipiente a presión se selló y la mezcla se agitó a 100°C durante 20 horas. La

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mezcla se vació en una mezcla agitada rápidamente de pH = 7 solución amortiguadora (200 mL), HCl acuoso 1.0M (25 mL) y acetato de etilo (100 mL). Las fases se separaron y la fase acuosa se extrajo con acetato de etilo (2 x 50 mL). Las fases orgánicas se combinaron, se secaron sobre sulfato de magnesio anhidro, se filtraron y se concentraron *in vacuo* hasta un residuo. El material sin refinar se purificó por cromatografía por desorción súbita en gel de sílice (Gradiente hexanos hasta 1:1 hexanos:EtOAc) para dar un aceite rojo (0.852 g, 52.6 % de rendimiento). 1H RMN (500 MHz, CLOROFORMO-D) δ ppm 1.06 (s, 9 H) 1.40 (s, 9 H) 2.23 (s, 3 H) 3.63 (d, *J*=10.38 Hz, 1 H) 4.11 (dd, *J*=8.55, 1.22 Hz, 1 H) 6.74 (s, 1 H) 7.81 (s, 1 H) 7.89 (d, *J*=2.75 Hz, 1 H); LC-MS, MS m/z 279 (M^+ + H).

Etapa 2:

El producto de la Etapa 1, Ejemplo 25, (0.809 g, 2.91 mmol) se disolvió en diclorometano (20 mL) y se trató con TFA (20 mL). La mezcla se agitó a temperatura ambiente durante 20 h y luego se concentró *in vacuo*. El residuo luego se disolvió en 1,2-dicloroetano (15 mL) y se concentró nuevamente *in vacuo* para dar un aceite café. El residuo luego se disolvió en DCM mínimo y se agregó gota a gota a una mezcla agitada rápidamente de HCl 2.0M en éter (30 mL), éter dietílico (30 mL) y 1,2-DCE (50 mL). La mezcla se agitó durante 10 min y

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luego se concentró *in vacuo*. El sólido espumoso café resultante luego se tomó en HCl acuoso 1.0M y la solución se concentró *in vacuo* para dar un sólido amarillo cristalino (0.600 g, 80 % de rendimiento). 1H RMN (500 MHz, DMSO-D_6) δ ppm 1.05 (s, 9 H) 2.35 (s, 3 H) 4.02 (d, *J*=9.77 Hz, 1 H) 7.03 (d, *J*=9.77 Hz, 1 H) 7.68 (s, 1 H) 7.95 (s, 1 H) 8.13 (s, 1 H) LC-MS, MS m/z 223 (M^+ + H).

Etapa 3:

Una mezcla del producto de la Etapa 2, Ejemplo 25 (0.094 g, 0.362 mmol), el producto de la Etapa 5, Ejemplo 22, (0.200 g, 0.329 mmol) y HATU (0.188 g, 0.493 mmol) se suspendió en DCM (2 mL) se trató con NMM (0.167 g, 1.65 mmol). La mezcla se agitó a temperatura ambiente durante 20 horas. El solvente se removió *in vacuo* y la mezcla sin refinar se purificó por HPLC preparativa de fase inversa para dar el compuesto 25 (0.1421 g, 44.7% de rendimiento) como un sal bis-TFA de polvo blanco. ^{1}H RMN (500 MHz, CD_3OD) δ ppm 1.07 - 1.21 (m, 11 H) 1.23 - 1.34 (m, 2 H) 1.45 (dd, *J*=9.46, 5.19 Hz, 1 H) 1.93 (dd, *J*=8.09, 5.65 Hz, 1 H) 2.14 (s, 3 H) 2.22 - 2.32 (m, 2 H) 2.59 (dd, *J*=13.73, 7.32 Hz, 1 H) 2.96 - 3.05 (m, 1 H) 4.01 (dd, *J*=12.21, 3.05 Hz, 1 H) 4.04 (s, 3 H) 4.26 (s, 1 H) 4.33 (d, *J*=12.21 Hz, 1 H) 4.66 (dd, *J*=10.22, 7.48 Hz, 1 H) 5.16 (d, *J*=10.38 Hz, 1 H) 5.34 (d, *J*=17.40 Hz, 1 H) 5.72 - 5.83 (m, 1 H) 5.89 (s, 1 H) 7.48 (s, 1 H) 7.59 (s, 1 H) 7.67 -

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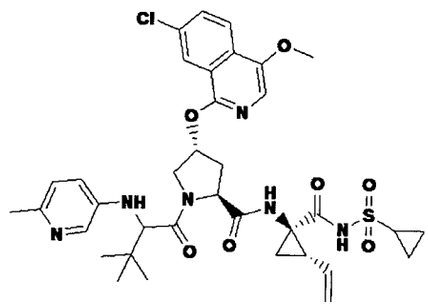
7.72 (m, 2 H) 7.81 (d, *J*=2.14 Hz, 1 H) 7.96 (d, *J*=1.83 Hz, 1 H) 8.11 (d, *J*=8.85 Hz, 1 H) 9.27 (s, 1 H); LC-MS, MS m/z 740 (M^+ + H).

Isómeros del Compuesto 26:

3-metil-N-(6-metil-3-piridinil)-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

3-metil-N-(6-metil-3-piridinil)-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

Ejemplo 26: Preparación de los compuestos 26A y 26B



Compuestos 26A y 26B

Los compuestos 26A y 26B se preparan por un procedimiento similar como aquel descrito para la preparación del Compuesto 25, excepto que 5-bromo-2-metilpiridina se usó en lugar de 5-bromo-3-picolina en la etapa 1, y las escalas

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de reacción se alteraron por las Etapas 2 y 3. Dos compuestos isoméricos se aislaron de la Etapa 3: el isómero primero en eluir de una columna HPLC preparativa fue el compuesto 26A (0.111 g) aislado como una sal bis-TFA del sólido ligeramente blanco opaco y el segundo isómero en eluir de la columna HPLC preparativa fue el compuesto 26B (0.0944 g) aislado como una sal bis-TFA ligeramente amarillo. El rendimiento combinado para ambos compuestos 26A y 26B fue 12.2% durante tres etapas.

Producto de la etapa 1, Ejemplo 26: Sólido ceroso color carne; ^{1}H RMN (500 MHz, CLOROFORMO-D) δ ppm 1.06 (s, 9 H) 1.40 (s, 9 H) 2.42 (s, 3 H) 3.59 (d, *J*=10.38 Hz, 1 H) 4.02 (d, *J*=10.38 Hz, 1 H) 6.87 (dd, 1 H) 6.93 (d, 1 H) 7.99 (d, *J*=2.75 Hz, 1 H); LC-MS, MS m/z 279 (M^+ + H).

Producto de la etapa 2, Ejemplo 26: Sólido amarillo; 1H RMN (500 MHz, DMSO-D_6) δ ppm 1.05 (s, 9 H) 2.52 (s, 3 H) 3.98 (d, *J*=9.16 Hz, 1 H) 6.84 (d, *J*=9.77 Hz, 1 H) 7.59 (d, *J*=9.16 Hz, 1 H) 7.81 (dd, *J*=9.00, 2.59 Hz, 1 H) 8.05 (d, *J*=2.75 Hz, 1 H); LC-MS, MS m/z 223 (M^+ + H).

Compuesto 26A: ^{1}H RMN (500 MHz, CD_3OD) δ ppm 1.07 - 1.18 (m, 11 H) 1.25 - 1.32 (m, 2 H) 1.45 (dd, *J*=9.46, 5.49 Hz, 1 H) 1.93 (dd, *J*=7.93, 5.49 Hz, 1 H) 2.22 - 2.31 (m, 4 H) 2.46 (s, 3 H) 2.60 (dd, *J*=13.43, 6.71 Hz, 1 H) 2.96 - 3.04 (m, 1 H) 4.00 (dd, *J*=12.36, 2.90 Hz, 1 H) 4.05 (s, 3 H) 4.23 (s, 1 H) 4.37 (d, *J*=12.21 Hz, 1 H) 4.65 (dd, *J*=10.07, 7.32 Hz, 1 H)

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5.14 - 5.19 (m, 1 H) 5.34 (d, *J*=17.09 Hz, 1 H) 5.77 (ddd, *J*=17.17, 10.15, 9.00 Hz, 1 H) 5.88 (s, 1 H) 7.05 (d, *J*=8.85 Hz, 1 H) 7.53 (dd, *J*=8.85, 2.75 Hz, 1 H) 7.62 (s, 1 H) 7.73 (dd, *J*=8.85, 2.14 Hz, 1 H) 7.84 (d, *J*=1.83 Hz, 1 H) 7.93 (d, *J*=2.75 Hz, 1 H) 8.14 (d, *J*=8.85 Hz, 1 H) 9.25 (s, 1 H); LC-MS, MS m/z 740 (M^+ + H).

Compuesto 26B: ^{1}H RMN (500 MHz, CD_3OD) δ ppm 0.97 (s, 9 H) 1.07 - 1.14 (m, 2 H) 1.18 - 1.24 (m, 1 H) 1.28 - 1.34 (m, 1 H) 1.41 (dd, *J*=9.46, 5.49 Hz, 1 H) 1.90 (dd, *J*=8.09, 5.34 Hz, 1 H) 2.30 (c, *J*=8.75 Hz, 1 H) 2.37 (ddd, *J*=13.89, 9.92, 4.27 Hz, 1 H) 2.58 (s, 3 H) 2.65 (dd, *J*=13.89, 7.48 Hz, 1 H) 2.93 - 3.00 (m, 1 H) 4.04 (s, 3 H) 4.09 (dd, *J*=12.21, 3.36 Hz, 1 H) 4.34 (s, 1 H) 4.50 (d, *J*=11.90 Hz, 1 H) 4.65 (dd, *J*=9.46, 7.32 Hz, 1 H) 5.16 (d, *J*=10.07 Hz, 1 H) 5.36 (d, *J*=17.40 Hz, 1 H) 5.75 - 5.86 (m, 1 H) 5.89 (s, 1 H) 7.57 (d, *J*=9.16 Hz, 1 H) 7.62 (s, 1 H) 7.75 (dd, *J*=8.85, 2.14 Hz, 1 H) 7.85 (dd, *J*=9.00, 2.90 Hz, 1 H) 8.05 (dd, *J*=4.12, 2.59 Hz, 2 H) 8.15 (d, *J*=9.16 Hz, 1 H) 9.56 (s, 1 H); LC-MS, MS m/z 740 (M^+ + H).

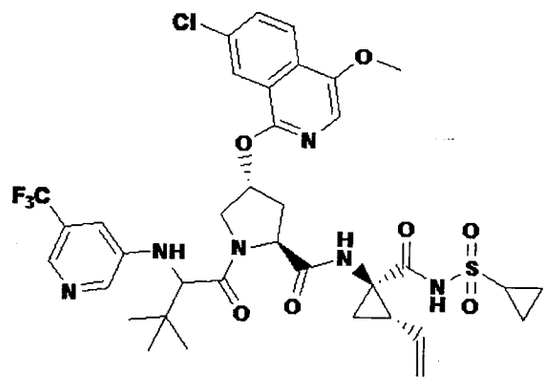
Isómeros del Compuesto 27:

3-metil-N-(5-(trifluorometil)-3-piridinil)-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

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3-metil-N-(5-(trifluorometil)-3-piridinil)-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

Ejemplo 27: Preparación de los compuestos 27A y 27B



Compuestos 27A y 27B

Los compuestos 27A y 27B se preparan por un procedimiento similar como aquel descrito para la preparación del Compuesto 25, excepto que 3-bromo-5-trifluorometilpiridina se usó en lugar de 5-bromo-3-picolina en la etapa 1, y las escalas de reacción fueron diferentes. También, el producto de la Etapa 2 no se aisló como la sal HCl pero se llevó a cabo en lugar de la Etapa 3 directamente como una sal TFA. Dos compuestos isoméricos se aislaron de la Etapa 3: el isómero primero en eluir de una columna HPLC preparativa fue el compuesto 27A (0.128 g) aislado como una sal bis-TFA sólida ligeramente blanca

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opaca y el segundo isómero en eluir de la columna HPLC preparativa fue el compuesto 27B (0.0564 g) aislado como una sal bis-TFA sólida ligeramente blanca opaca. El rendimiento combinado para ambos compuestos 27A y 27B fue 17.9% durante tres etapas.

Producto de la etapa 1, Ejemplo 27: Sólido ceroso anaranjado; ^{1}H RMN (500 MHz, CLOROFORMO-D) δ ppm 1.08 (s, 9 H) 1.43 (s, 9 H) 3.66 (d, *J*=10.07 Hz, 1 H) 4.45 (d, *J*=10.07 Hz, 1 H) 7.06 (s, 1 H) 8.22 (s, 1 H) 8.24 (d, *J*=2.75 Hz, 1 H); LC-MS, MS m/z 333 (M^+ + H).

Producto de la etapa 2, Ejemplo 27: Sólido cristalino café; ^{1}H RMN (500 MHz, DMSO-D_6) δ ppm 1.06 (s, 9 H) 3.90 (s, 1 H) 3.92 (s, 1 H) 6.56 (s, 1 H) 7.42 (s, 1 H) 8.16 (s, 1 H) 8.40 (s, 1 H); LC-MS, MS m/z 277 (M^+ + H).

Compuesto 27A: ^{1}H RMN (500 MHz, CD_3OD) δ ppm 1.10 - 1.13 (m, 2 H) 1.15 (s, 9 H) 1.27 - 1.31 (m, 2 H) 1.45 (dd, *J*=9.46, 5.49 Hz, 1 H) 1.92 (dd, *J*=7.93, 5.49 Hz, 1 H) 2.23 - 2.32 (m, 2 H) 2.57 (dd, *J*=13.58, 7.17 Hz, 1 H) 2.91 (d, *J*=14.04 Hz, 1 H) 2.97 - 3.03 (m, 1 H) 4.02 (s, 3 H) 4.11 (dd, *J*=12.21, 3.36 Hz, 1 H) 4.29 - 4.35 (m, 2 H) 4.60 (dd, *J*=10.22, 7.17 Hz, 1 H) 5.15 (dd, *J*=10.38, 1.53 Hz, 1 H) 5.33 (d, *J*=17.09 Hz, 1 H) 5.73 - 5.83 (m, 1 H) 5.87 (s, 1 H) 7.54 (s, 1 H) 7.55 (s, 1 H) 7.66 (dd, *J*=8.85, 2.14 Hz, 1 H) 7.82 (d, *J*=1.83 Hz, 1 H) 8.04 (s, 1

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H) 8.08 (d, *J*=8.85 Hz, 1 H) 8.23 (s, 1 H) 9.23 (s, 1 H); LC-MS, MS m/z 794 (M^+ + H).

Compuesto 27B: ^{1}H RMN (500 MHz, CD_3OD) δ ppm 0.97 (s, 9 H) 1.04 - 1.12 (m, 2 H) 1.21 - 1.28 (m, 2 H) 1.40 (dd, *J*=9.46, 5.19 Hz, 1 H) 1.91 (dd, *J*=8.09, 5.34 Hz, 1 H) 2.30 (c, *J*=8.65 Hz, 1 H) 2.38 (ddd, *J*=13.81, 9.84, 4.12 Hz, 1 H) 2.65 (dd, *J*=13.89, 7.17 Hz, 1 H) 2.87 - 2.98 (m, 1 H) 4.04 (s, 3 H) 4.09 (dd, *J*=12.21, 3.36 Hz, 1 H) 4.46 (s, 1 H) 4.55 (d, *J*=12.21 Hz, 1 H) 4.65 (dd, *J*=9.46, 7.32 Hz, 1 H) 5.16 (d, *J*=10.38 Hz, 1 H) 5.36 (d, *J*=17.40 Hz, 1 H) 5.76 - 5.85 (m, 1 H) 5.89 (s, 1 H) 7.63 (s, 1 H) 7.75 (dd, *J*=8.85, 2.14 Hz, 1 H) 7.78 (s, 1 H) 8.05 (d, *J*=1.83 Hz, 1 H) 8.15 (d, *J*=9.16 Hz, 1 H) 8.19 (s, 1 H) 8.37 (s, 1 H) 9.56 (s, 1 H); LC-MS, MS m/z 794 (M^+ + H).

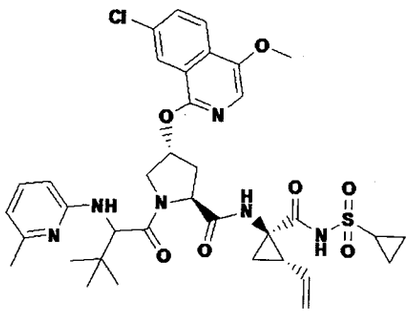
Isómeros del Compuesto 28:

3-metil-N-(6-metil-2-piridinil)-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

3-metil-N-(6-metil-2-piridinil)-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

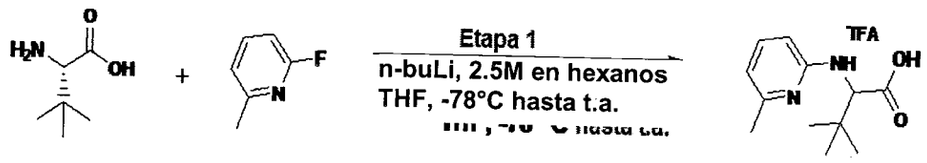
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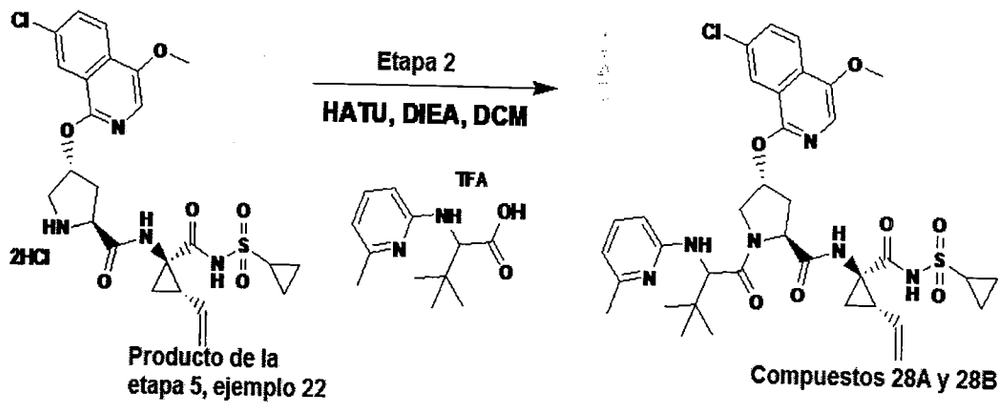
Ejemplo 28: Preparación de los compuestos 28A y 28B



Compuestos 28A y 28B

Esquema de reacción 1





Etapa 1:

La L-terc-leucina (0.734 g, 5.60 mmol) se suspendió con agitación en THF seco (10 mL). La suspensión se enfrió a -78°C, y n-buLi, 2.5M en hexanos (4.48 mL, 11.2 mmol) se agregó gota a gota. La mezcla amarilla se agitó a -78°C durante 30 min, luego el baño de

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enfriamiento se removió y la suspensión se permitió calentar a t.a. durante 25 min. La mezcla se volvió a enfriar a -78°C, y 2-fluoro-6-metilpiridina (0.311 g, 2.80 mmol) se agregó gota a gota. El color cambió de amarillo hasta anaranjado oscuro y finalmente café durante este tiempo. El baño de enfriamiento se removió y la mezcla se agitó a t.a. durante la noche. La mezcla sin refinar se vació en una solución de cloruro de amonio acuosa saturada agitada rápidamente (100 mL) y EtOAc (50 mL) se agregó. Las fases se separaron, y la fase acuosa se extrajo con EtOAc (2 x 50 mL). La fase acuosa tiene se saturó con NaCl y luego se extrajo con DCM (4 x 100 mL) para remover el producto. Los materiales orgánicos se combinaron y se concentró *in vacuo* hasta un residuo. La purificación del residuo por HPLC preparativa de fase inversa dio el producto como un aceite amarillo espeso (0.279 g, 44.8% de rendimiento) sal TFA. ^{1}H RMN (300 MHz, CLOROFORMO-D) δ ppm 1.02 (s, 9 H) 2.49 (s, 3 H) 3.94 (s, 1 H) 3.96 - 4.16 (m, 1 H) 6.54 (d, *J*=7.32 Hz, 1 H) 6.70 (d, *J*=8.78 Hz, 1 H) 7.63 - 7.73 (m, 1 H); LC-MS, MS m/z 223 (M^+ + H).

Etapa 2:

Una mezcla del producto de la Etapa 1, Ejemplo 28, (0.111 g, 0.329 mmol), el producto de la Etapa 5, Ejemplo

22, (0.200 g, 0.329 mmol) y HATU (0.163 g, 0.428 mmol) se suspendió en DCM (2 mL) se trató con NMM (0.167 g, 1.65 mmol). La mezcla se agitó a temperatura ambiente durante 20 horas. El solvente se removió por concentración bajo una corriente de nitrógeno, y la mezcla sin refinar se purificó por HPLC preparativa de fase inversa. El Compuesto 28A (0.0916 g, 28.8% de rendimiento) fue el primero de dos isómeros en eluir de la columna HPLC preparativa y se aisló como una sal bis-TFA de polvo blanco opaco. El Compuesto 28B (0.0353 g, 11.1% de rendimiento) fue el segundo de dos isómeros en eluir de la columna HPLC preparativa y se aisló también como una sal bis-TFA de polvo blanco opaco.

Compuesto 28A: ^{1}H RMN (500 MHz, CD_3OD) δ ppm 1.09 - 1.14 (m, 2 H) 1.15 (s, 9 H) 1.25 - 1.30 (m, 2 H) 1.46 (dd, *J*=9.46, 5.49 Hz, 1 H) 1.94 (dd, *J*=8.24, 5.49 Hz, 1 H) 2.25 - 2.37 (m, 2 H) 2.45 (s, 3 H) 2.66 (dd, *J*=13.89, 7.17 Hz, 1 H) 2.99 (ddd, *J*=12.82, 8.09, 4.73 Hz, 1 H) 4.05 (s, 3 H) 4.09 (dd, *J*=12.21, 3.36 Hz, 1 H) 4.40 (d, *J*=11.90 Hz, 1 H) 4.53 (s, 1 H) 4.69 (dd, *J*=10.07, 7.32 Hz, 1 H) 5.17 (dd, *J*=10.38, 1.53 Hz, 1 H) 5.34 (dd, *J*=17.24, 1.37 Hz, 1 H) 5.77 (ddd, *J*=17.17, 10.15, 9.00 Hz, 1 H) 5.92 (s, 1 H) 6.67 (d, *J*=7.32 Hz, 1 H) 6.77 (d, *J*=8.85 Hz, 1 H) 7.43 (dd, *J*=9.00, 7.48 Hz, 1 H) 7.64 (s, 1 H) 7.71 (dd, *J*=8.85, 2.14 Hz, 1 H) 7.90 (d, *J*=1.83 Hz, 1 H) 8.13 (d, *J*=8.85 Hz,

1 H); LC-MS, MS m/z 740 (M^+ + H).

Compuesto 28B: ^{1}H RMN (500 MHz, CD_3OD) δ ppm 0.97 (s, 9 H) 1.03 - 1.12 (m, 2 H) 1.13 - 1.20 (m, 1 H) 1.22 - 1.29 (m, 1 H) 1.41 (dd, *J*=9.46, 5.19 Hz, 1 H) 1.91 (dd, *J*=8.24, 5.19 Hz, 1 H) 2.31 (c, *J*=8.75 Hz, 1 H) 2.43 (ddd, *J*=13.96, 9.54, 4.27 Hz, 1 H) 2.54 (s, 3 H) 2.69 (dd, *J*=14.04, 7.32 Hz, 1 H) 2.86 - 2.96 (m, 2 H) 4.04 (s, 3 H) 4.20 (dd, *J*=12.21, 3.36 Hz, 1 H) 4.50 (d, *J*=11.90 Hz, 1 H) 4.65 - 4.71 (m, 2 H) 5.13 - 5.19 (m, 1 H) 5.36 (dd, *J*=17.24, 1.37 Hz, 1 H) 5.79 (ddd, *J*=17.24, 10.22, 8.85 Hz, 1 H) 5.92 (s, 1 H) 6.84 (d, *J*=7.32 Hz, 1 H) 7.06 (d, *J*=8.85 Hz, 1 H) 7.63 (s, 1 H) 7.76 (dd, *J*=9.16, 2.14 Hz, 1 H) 7.96 (dd, *J*=8.85, 7.32 Hz, 1 H) 8.06 (d, *J*=2.14 Hz, 1 H) 8.16 (d, *J*=8.85 Hz, 1 H) 9.56 (s, 1 H); LC-MS, MS m/z 740 (M^+ + H).

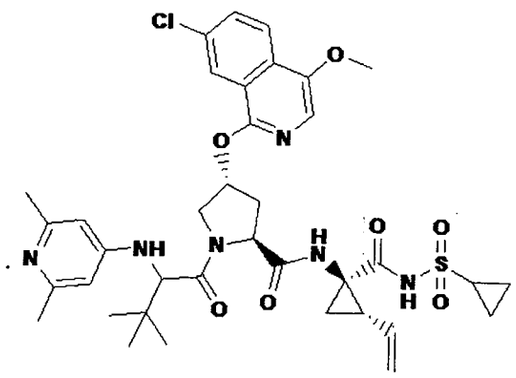
Isómeros del Compuesto 29:

N-(2,6-dimetil-4-piridinil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

N-(2,6-dimetil-4-piridinil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

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Ejemplo 29: Preparación de los compuestos 29A y 29B



Compuestos 29A y 29B

Los compuestos 29A y 29B se prepararon por un procedimiento similar como aquel descrito para la preparación del Compuesto 25, excepto que bromohidrato de 4-bromo-2,6-dimetilpiridina 1.06 (0.980 g, 3.61 mmol) se usó en lugar de 5-bromo-3-picolina en la etapa 1, y las escalas de reacción fueron diferentes. También, el producto de la Etapa 2 no se aisló como la sal HCl sino que en lugar de esto se llevó a la Etapa 3 directamente como una sal TFA. Dos compuestos isoméricos se aislaron de la Etapa 3: el isómero primero en eluir de una columna HPLC preparativa fue el compuesto 29A (0.127 g) aislado como una sal bis-TFA de sólido blanco, y el segundo isómero en eluir de la columna HPLC preparativa fue el compuesto 29B (0.103 g) aislado como una sal bis-TFA sólida blanca. El rendimiento combinado para ambos compuestos 29A y 29B fue 47.8% durante tres etapas.

Producto de la etapa 1, Ejemplo 29: Sólido ceroso café claro; ^{1}H RMN (500 MHz, CLOROFORMO-D) δ ppm 1.04 (s, 9 H) 1.43 (s, 9 H) 2.37 (s, 6 H) 3.71 (d, *J*=9.77 Hz, 1 H) 4.46 (d, *J*=9.77 Hz, 1 H) 6.20 (s, 2 H); LC-MS, MS m/z 293 (M^+ + H).

Producto de la etapa 2, Ejemplo 29: Sólido cristalino café; ^{1}H RMN (500 MHz, DMSO-D_6) δ ppm 1.03 (s, 9 H) 2.38 (s, 3 H) 2.42 (s, 3 H) 4.17 (d, *J*=9.77 Hz, 1 H) 6.79 (s, 1 H) 6.88 (s, 1 H) 8.23 (d, *J*=9.77 Hz, 1 H) 13.11 (s, 1 H); LC-MS, MS m/z 237 (M^+ + H).

Compuesto 29A: ^{1}H RMN (500 MHz, CD_3OD) δ ppm 0.99 (s, 1 H) 1.05 (s, 9 H) 1.07 - 1.13 (m, 2 H) 1.21 - 1.27 (m, 2 H) 1.42 (dd, *J*=9.61, 5.34 Hz, 1 H) 1.46 (s, 1 H) 1.90 (dd, *J*=8.09, 5.34 Hz, 1 H) 2.12 (s, 3 H) 2.21 - 2.29 (m, 2 H) 2.31 (s, 3 H) 2.60 (dd, *J*=13.89, 7.48 Hz, 1 H) 2.92 - 3.00 (m, 1 H) 4.01 (s, 3 H) 4.24 (d, *J*=11.60 Hz, 1 H) 4.35 (d, *J*=9.77 Hz, 1 H) 4.66 (dd, *J*=10.07, 7.32 Hz, 1 H) 5.13 (dd, *J*=10.38, 1.53 Hz, 1 H) 5.31 (dd, *J*=17.09, 1.22 Hz, 1 H) 5.74 (ddd, *J*=17.17, 10.15, 9.00 Hz, 1 H) 5.87 (s, 1 H) 6.49 (d, *J*=13.12 Hz, 2 H) 7.58 (s, 1 H) 7.66 (dd, *J*=8.85, 2.14 Hz, 1 H) 7.80 (d, *J*=1.83 Hz, 1 H) 7.92 (d, *J*=9.77 Hz, 1 H) 8.07 (d, *J*=8.85 Hz, 1 H) 9.22 (s, 1 H); LC-MS, MS m/z 754 (M^+ + H).

Compuesto 29B: ^{1}H RMN (500 MHz, CD_3OD) δ ppm

000557

0.92 (s, 9 H) 1.03 - 1.11 (m, 2 H) 1.19 - 1.26 (m, 2 H) 1.39 (dd, *J*=9.46, 5.49 Hz, 1 H) 1.88 (dd, *J*=8.24, 5.19 Hz, 1 H) 2.28 (c, *J*=8.95 Hz, 1 H) 2.36 (ddd, *J*=14.04, 9.77, 4.27 Hz, 1 H) 2.44 (s a, 6 H) 2.63 (dd, *J*=14.04, 7.32 Hz, 1 H) 2.93 (ddd, *J*=12.74, 8.01, 4.58 Hz, 1 H) 4.01 (s, 3 H) 4.06 (dd, *J*=12.21, 3.36 Hz, 1 H) 4.47 (d, *J*=12.21 Hz, 1 H) 4.52 (d, *J*=9.16 Hz, 1 H) 4.63 (dd, *J*=9.77, 7.32 Hz, 1 H) 5.13 (dd, *J*=10.38, 1.53 Hz, 1 H) 5.33 (dd, *J*=17.09, 1.53 Hz, 1 H) 5.78 (ddd, *J*=17.09, 10.38, 8.85 Hz, 1 H) 5.87 (s, 1 H) 6.71 (s a, 1 H) 6.87 (s a, 1 H) 7.14 (d, *J*=9.16 Hz, 1 H) 7.58 (s, 1 H) 7.72 (dd, *J*=8.85, 2.14 Hz, 1 H) 8.01 (d, *J*=2.14 Hz, 1 H) 8.12 (d, *J*=9.16 Hz, 1 H) 9.54 (s, 1 H); LC-MS, MS m/z 754 (M^+ + H).

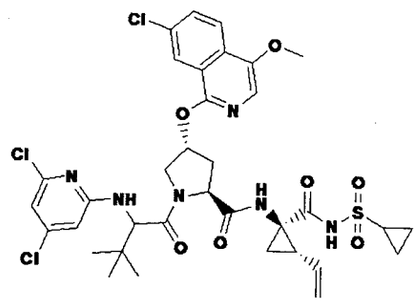
Isómeros del Compuesto 32:

N-(4,6-dicloro-2-piridinil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

N-(4,6-dicloro-2-piridinil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

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Ejemplo 32: Preparación de los compuestos 32A y 32B



Compuestos 32A y 32B

Los Compuestos 32A y 32B se preparan por un procedimiento similar como aquel descrito para la preparación del Compuesto 7, excepto que 2,4,6-tricloropiridina (0.658 g, 3.61 mmol) se usó en lugar de 2-cloropiridina en la etapa 1, y las escalas de reacción fueron diferentes. También, en la etapa 3, el producto de la Etapa 5, Ejemplo 22, se usó en lugar del producto de la Etapa 5, Ejemplo 1. Dos compuestos isoméricos se aislaron de la Etapa 3: el isómero primero en eluir de una columna HPLC preparativa fue el compuesto 32A (0.0783 g) aislado como una sal bis-TFA sólida blanca opaca, y el segundo isómero en eluir de la columna HPLC preparativa fue el compuesto 32B (0.0207 g) aislado como una sal bis-TFA sólida blanca opaca. El rendimiento combinado para ambos compuestos 32A y 32B fue 5.8% durante tres etapas.

Producto de la etapa 1, Ejemplo 32: Aceite amarillo; ^{1}H RMN (500 MHz, CLOROFORMO-D) δ ppm 1.03 (s, 9 H) 1.46 (s, 9 H) 4.10 (d, *J*=8.85 Hz, 1 H) 5.13 (d, *J*=9.16 Hz, 1 H) 6.33 (d,

000559

J=1.22 Hz, 1 H) 6.60 (d, *J*=1.22 Hz, 1 H); LC-MS, MS m/z 334 (M^+ + H).

Producto de la etapa 2, Ejemplo 32: Aceite café espeso; LC-MS, MS m/z 278 (M^+ + H).

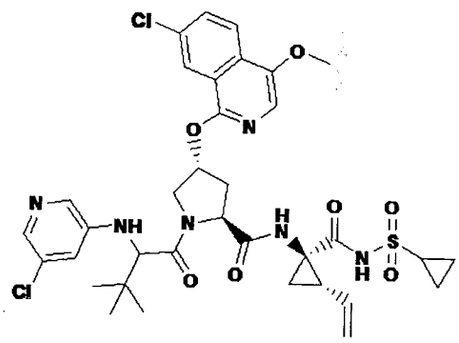
Compuesto 32A: ^{1}H RMN (500 MHz, CD_3OD) δ ppm 1.04 - 1.08 (m, 2 H) 1.09 (s, 9 H) 1.21 - 1.29 (m, 2 H) 1.41 (dd, *J*=9.61, 5.34 Hz, 1 H) 1.87 (dd, *J*=8.09, 5.34 Hz, 1 H) 2.19 - 2.31 (m, 2 H) 2.54 (dd, *J*=13.58, 6.87 Hz, 1 H) 2.92 - 2.98 (m, *J*=8.09, 8.09, 4.73, 4.73 Hz, 1 H) 4.00 (s, 3 H) 4.12 (dd, *J*=11.75, 3.81 Hz, 1 H) 4.53 (dd, *J*=10.53, 6.87 Hz, 1 H) 4.68 (d, *J*=11.60 Hz, 1 H) 4.72 (s, 1 H) 5.11 (dd, *J*=10.22, 1.68 Hz, 1 H) 5.28 (dd, *J*=17.24, 1.37 Hz, 1 H) 5.74 (ddd, *J*=17.09, 10.22, 9.00 Hz, 1 H) 5.88 (t, *J*=3.36 Hz, 1 H) 6.26 (d, *J*=1.22 Hz, 1 H) 6.48 (d, *J*=1.22 Hz, 1 H) 7.54 (s, 1 H) 7.64 (dd, *J*=8.85, 2.14 Hz, 1 H) 7.82 (d, *J*=2.14 Hz, 1 H) 8.05 (d, *J*=8.85 Hz, 1 H) 9.14 (s, 1 H); LC-MS, MS m/z 795 (M^+ + H).

Compuesto 32B: ^{1}H RMN (500 MHz, CD_3OD) δ ppm 0.90 (s, 9 H) 0.97 - 1.11 (m, 3 H) 1.26 - 1.37 (m, 2 H) 1.85 (dd, *J*=8.24, 5.19 Hz, 1 H) 2.23 (c, *J*=8.95 Hz, 1 H) 2.35 (ddd, *J*=13.96, 9.84, 4.27 Hz, 1 H) 2.58 (dd, *J*=13.73, 7.32 Hz, 1 H) 2.81 - 2.88 (m, 1 H) 4.01 (s, 3 H) 4.23 (dd, *J*=12.05, 3.51 Hz, 1 H) 4.38 (d, *J*=12.21 Hz, 1 H) 4.56 (dd, *J*=9.92, 7.17 Hz, 1 H) 4.90

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(s, 1 H) 5.12 (dd, *J*=10.22, 1.68 Hz, 1 H) 5.31 (dd, *J*=17.24, 1.37 Hz, 1 H) 5.77 (ddd, *J*=17.09, 10.38, 8.85 Hz, 1 H) 5.83 (s, 1 H) 6.56 (d, *J*=1.53 Hz, 1 H) 6.58 (d, *J*=1.53 Hz, 1 H) 7.61 (s, 1 H) 7.71 (dd, *J*=8.85, 2.14 Hz, 1 H) 8.02 (d, *J*=2.14 Hz, 1 H) 8.11 (d, *J*=8.85 Hz, 1 H) 9.35 (s, 1 H); LC-MS, MS m/z 795 (M^+ + H).

Ejemplo 33: Preparación del Compuesto 33: N-(5-cloro-3-piridinil)-3-metilvalil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida



Compuesto 33

El Compuesto 33 se preparó por un procedimiento similar como aquel descrito para la preparación del Compuesto 7, excepto que 3,5-dicloropiridina (0.534 g, 3.61 mmol) se usó en lugar de 2-cloropiridina en la etapa 1, y las escalas de reacción fueron

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diferentes. También, en la etapa 3, el producto de la Etapa 5, Ejemplo 22, se usó en lugar del producto de la Etapa 5, Ejemplo 1. El Compuesto 33 (0.187 g, 9.0% de rendimiento durante 3 etapas) se aisló como una sal bis-TFA sólida beige.

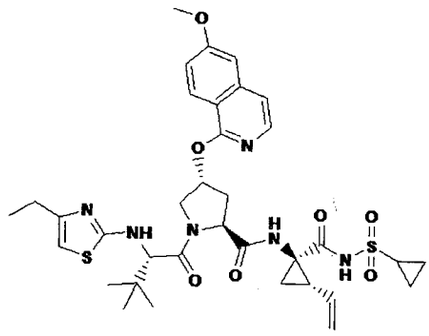
Producto de la etapa 1, Ejemplo 33: Aceite amarillo; ^{1}H RMN (500 MHz, CLOROFORMO-D) δ ppm 1.06 (s, 9 H) 1.44 (s, 9 H) 3.61 (d, *J*=10.07 Hz, 1 H) 4.30 (d, *J*=10.07 Hz, 1 H) 6.91 (t, *J*=2.29 Hz, 1 H) 7.92 (d, *J*=1.83 Hz, 1 H) 7.95 (d, *J*=2.44 Hz, 1 H); LC-MS, MS m/z 299 (M^+ + H).

Producto de la etapa 2, Ejemplo 33: Aceite café espeso; LC-MS, MS m/z 243 (M^+ + H).

Compuesto 33: ^{1}H RMN (500 MHz, CD_3OD) δ ppm 1.03 - 1.08 (m, 2 H) 1.09 (s, 9 H) 1.22 - 1.27 (m, 2 H) 1.42 (ddd, *J*=9.54, 5.42, 0.92 Hz, 1 H) 1.89 (dd, *J*=8.24, 5.49 Hz, 1 H) 2.19 - 2.29 (m, 2 H) 2.56 (dd, *J*=13.73, 7.02 Hz, 1 H) 2.92 - 2.99 (m, 1 H) 3.96 - 4.05 (m, 4 H) 4.21 (s, 1 H) 4.29 (d, *J*=12.21 Hz, 1 H) 4.60 (dd, *J*=10.22, 7.17 Hz, 1 H) 5.12 (dd, *J*=10.38, 1.53 Hz, 1 H) 5.30 (dd, *J*=17.09, 1.53 Hz, 1 H) 5.74 (ddd, *J*=17.09, 10.38, 8.85 Hz, 1 H) 5.84 (s, 1 H) 7.33 (s, 1 H) 7.54 (s, 1 H) 7.65 (dd, *J*=8.85, 2.14 Hz, 1 H) 7.72 (s, 1 H) 7.81 (d, *J*=1.83 Hz, 1 H) 7.94 (s, 1 H) 8.07 (d, *J*=8.85 Hz, 1 H) 9.20 (s, 1 H); LC-MS, MS m/z 760 (M^+ + H).

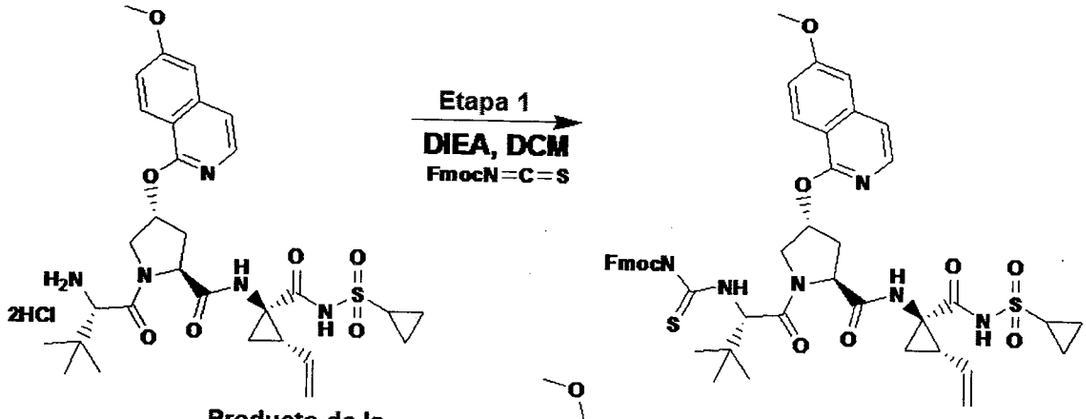
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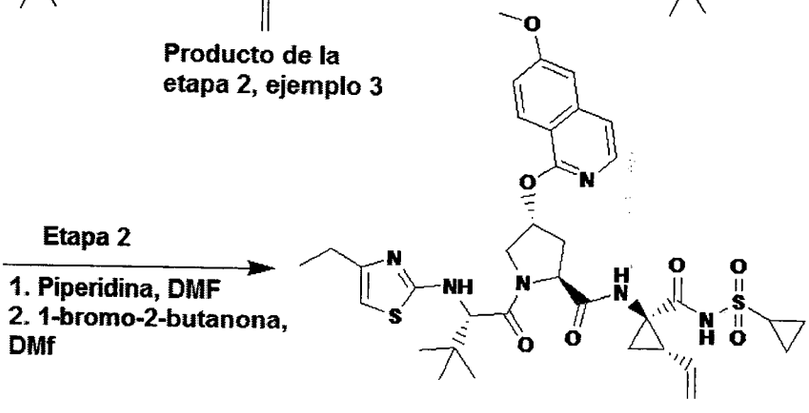
Ejemplo 35: Preparación del Compuesto 35: N-(4-etil-1,3-tiazol-2-il)-3-metil-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida



Compuestos 35

Esquema de reacción 1





Compuesto 35

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Etapa 1:

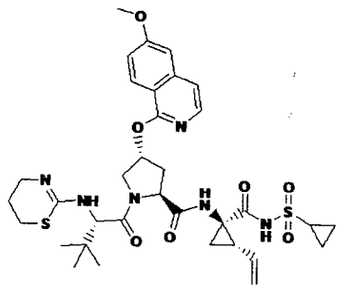
A una solución mezclada del producto de la etapa 2, Ejemplo 3 (1.5g, 2.18 mmol) y DIEA (0.707 g, 5.46 mmol) en DCM (20 mL) se agregó Fmoc-tioisocianato (0.799, 2.84 mmol). La mezcla de reacción se agitó a durante 48 h. La reacción no se completó como se determina por CL/EM, luego se agregó más Fmoc-tioisocianato (0.307 g, 1.09 mmol). La mezcla de reacción se permitió agitar a t.a. durante 24 h adicionales. El sub-producto de precipitación sólido blanco se removió por filtración al vacío y se lavó con EtOAc. El filtrado líquido se concentró, el residuo resultante se volvió a disolver en EtOAc (100 mL) y se lavó con 2 x 25 mL H_2O. Las capas acuosas se combinaron y luego se extrajeron con EtOAc (50 mL). La capa orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$, se filtró y se concentró hasta un sólido amarillo. Más de los sub-productos no identificados se removieron por trituración con EtOAc, se enfriaron a 0°C; el sólido precipitado se filtró y se descartó. La filtración líquida se concentró y el residuo se purificó a través de una Columna de SiO_2 la cual se diluyó con 3:1, 1:1 luego 1:3 hexanos:EtOAc para dar el producto de la Etapa 1, Ejemplo 35 (0.798 g, 41% de rendimiento) como un sólido espumoso amarillo claro. LC-MS, MS m/z 895 (M^+ + H).

Etapa 2:

A una solución amarilla del producto formado de la etapa 1, Ejemplo 35 (0.489 g, 0.546 mmol) en DMF (4 mL) se agregó piperidina (1 mL). La reacción se agitó a t.a. Después de 5h El solvente se removió bajo vacío y se secó para dar un producto sin refinar cristalino sólido el cual se tomó en DMF (5 mL) y se trató con 1-bromo-2-butanona (0.275 g, 1.64 mmol). La mezcla de reacción se agitó a t.a. durante la noche. Después de 14h, El solvente se removió bajo vacío para dar el aceite rojo viscoso el cual se volvió a disolver en MeOH y se filtró para remover la sustancia tipo gel café. El filtrado líquido se concentró y el residuo restante se purificó por HPLC de fase inversa para dar el Ejemplo 35 (139.7, 35% de rendimiento) como un sólido amarillo claro. ^{1}H RMN (500 MHz) δ ppm 0.81 (t, *J*=7.5 Hz, 3 H), 1.06 - 1.12 (m, 3 H), 1.14 (s, 9 H), 1.25 - 1.30 (m, 2 H), 1.46 (dd, *J*=9.6, 5.3 Hz, 1 H), 1.91 (dd, *J*=8.1, 5.3 Hz, 1 H), 1.93 - 1.97 (m, 1 H), 1.99 - 2.07 (m, 1 H), 2.23 - 2.29 (m, 1 H), 2.30 - 2.36 (m, 1 H), 2.59 (dd, *J*=13.4, 6.7 Hz, 1 H), 3.96 (s, 3 H), 4.15 (dd, *J*=11.7, 3.8 Hz, 1 H), 4.46 (s, 1 H), 4.57 (dd, *J*=10.5, 6.9 Hz, 1 H), 4.68 (d, *J*=11.6 Hz, 1 H), 5.15 (d, *J*=10.4 Hz, 1 H), 5.32 (d, *J*=17.1 Hz, 1 H), 5.75 (s, 1 H), 5.76 - 5.82 (m, 1 H), 5.90 (s, 1 H), 7.09 (dd, *J*=8.9, 2.4 Hz, 1 H), 7.23 (d, *J*=2.4 Hz, 1 H), 7.29 (d, *J*=5.8 Hz, 1 H), 7.89 (d, *J*=9.2 Hz, 1 H), 7.93 (d, *J*=6.1 Hz, 1 H). LC-MS, MS m/z 725 (M^+ + H).

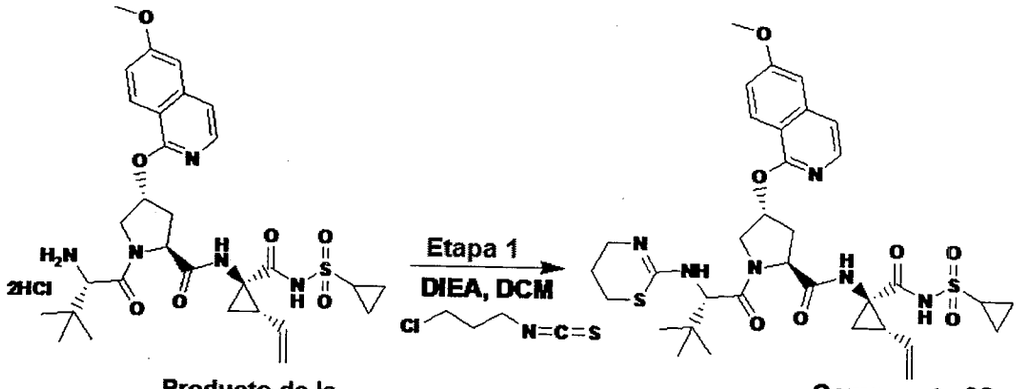
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Ejemplo 36: Preparación del Compuesto 36: N-(5,6-dihidro-4H-1,3-tiazin-2-il)-3-metil-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida



Compuesto 36

Esquema de reacción 1



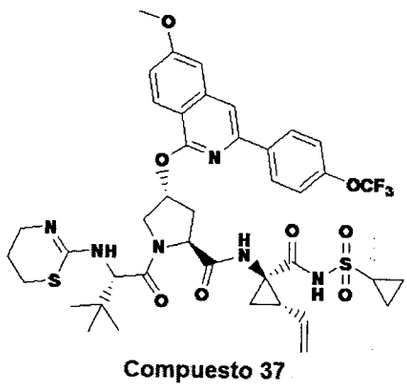
Etapa 1:

A una solución mezclada del producto de la Etapa 2, ejemplo 3 (0.267 g, 0.389 mmol) y DIEA (0.101 g, 0.778 mmol) en DCM (4 mL) se agregó isotiocianato de 3-cloropropilo (0.053 g, 0.389 mmol) y se calentó a 45°C. Después de 3 h, el solvente se removió y el residuo se volvió a disolver en EtOAc caliente con DCM mínimo, Et_2O se agregó para efectuar

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la precipitación verde clara la cual se obtuvo por filtración. El producto se purificó por HPLC de fase inversa para dar el Ejemplo 36 (0.166 g, 54%) como un sólido bis-HCl amarillo claro. ^{1}H RMN (500 MHz, *CD_3OD*) δ ppm 1.12 (s, 9 H), 1.24 - 1.28 (m, 3 H), 1.47 (dd, *J*=9.5, 5.5 Hz, 1 H), 1.94 (dd, *J*=8.2, 5.5 Hz, 1 H), 2.27 - 2.38 (m, 2 H), 2.70 (dd, *J*=13.7, 7.0 Hz, 1 H), 2.94 - 3.01 (m, 1 H), 3.97 (s, 3 H), 4.05 - 4.10 (m, 1 H), 4.12 (c, *J*=7.3 Hz, 1 H), 4.39 (d, *J*=11.9 Hz, 1 H), 4.73 (dd, *J*=10.2, 7.5 Hz, 1 H), 5.17 (dd, *J*=10.4, 1.5 Hz, 1 H), 5.35 (d, *J*=17.1 Hz, 1 H), 5.74 - 5.83 (m, 1 H), 5.91 (s, 1 H), 7.26 (dd, *J*=9.2, 2.4 Hz, 1 H), 7.30 (d, *J*=2.1 Hz, 1 H), 7.35 (d, *J*=6.1 Hz, 1 H), 7.97 (d, *J*=5.8 Hz, 1 H), 8.11 (d, *J*=9.2 Hz, 1 H). LC-MS, MS m/z 713 (M^+ + H).

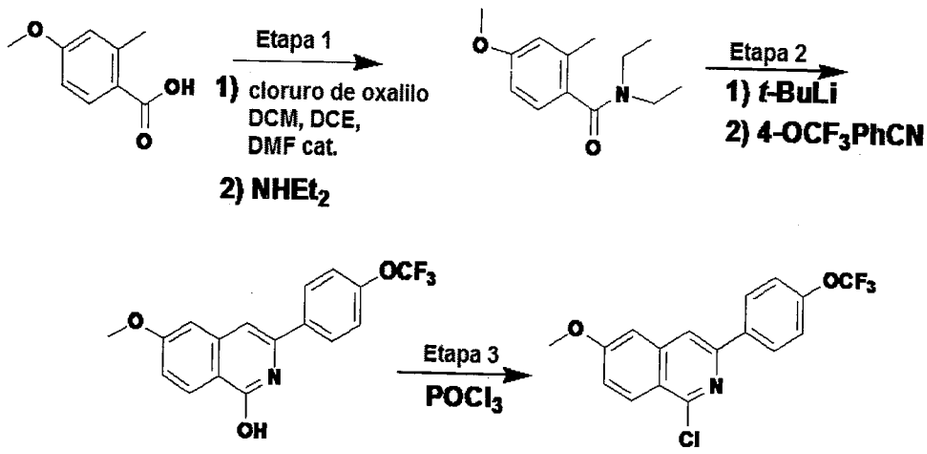
Ejemplo 37: Preparación del Compuesto 37: N-(5,6-dihidro-4H-1,3-tiazin-2-il)-3-metil-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-3-(4-(trifluorometoxi)fenil)-1-isoquinolinil)oxi)-L-prolinamida



Compuesto 37

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Esquema de reacción 1



Etapa 1:

Una mezcla de ácido 4-metoxi-2-metil-benzoico (25.3 g, 152 mmol) en 1:1 DCM:DCE se trató con cloruro de oxalilo (38.6 g, 304 mmol), seguido por la adición de DMF (0.111 g, 1.50 mmol). La evolución de gas vigorosa es un resultado, y la reacción eventualmente se volvió clara después de 1 h. Los materiales volátiles se removieron *in vacuo* y el residuo sólido blanco se colocó bajo vacío durante 2 h. El material sin refinar se volvió a disolver en DCM (200 mL) y la mezcla se enfrió a 0°C. Dietilamina (22.8 g, 312 mmol) se agregó gota a gota con agitación. La mezcla se permitió calentar a t.a. durante 1 h con agitación. La mezcla se concentró *in vacuo* hasta aproximadamente 1/3 de volumen, y Et_2O (300 mL) se agregó y la mezcla se enfrió. El precipitado sólido el cual se formó se removió por filtración. El filtrado se concentró para dar un aceite café viscoso el cual se volvió a

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disolver en DCM (200 mL) y se lavó con 0.1M HCl (2 x 50 mL). La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró *in vacuo* para dar el producto deseado (33.1 g, 98% de rendimiento). LC-MS, MS m/z 222 (M^++H).

Etapa 2:

A una solución agitada de N,N-dietil-4-metoxi-2-metil-benzamida (10.0 g, 45.2 mmol) en THF (150 mL) a -78°C bajo una atmósfera de nitrógeno se agregó *t*-BuLi (29.2 mL de 1.7M en pentano, 49.7 mmol) gota a gota. La solución roja resultante se mantuvo a esta temperatura durante 10 min adicionales antes de la adición gota a gota de 4-(trifluorometoxi)-benzonitrilo (9.49 g, 49.7 mmol). La solución café se agitó a -78°C durante 2 h; las pruebas por LCMS mostraron que la reacción fue incompleta. Así a la mezcla se agregó una cantidad adicional de 4-(trifluorometoxi)-benzonitrilo (3.38 g, 18.1 mmol) y la mezcla resultante se agitó durante 1 h adicional. La mezcla luego se permitió calentar a t.a. y se apagó por vaciado en HCl acuoso 1.0M (50 mL). EtOAc (100 mL) se agregó y la mezcla se agitó y las fases se separaron. Un precipitado se presentó dentro de la fase de EtOAc la cual se aisló por filtración y se permitió secar (3.0 g). Estos 3.0 g del sólido aislado se determinó que son del producto impuro y se dejaron para

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purificación adicional. El filtrado EtOAc se dejó a un lado. Los ácidos acuosos lavados se combinaron y luego se extrajeron con DCM (3 x 100 mL). Los extractos DCM se combinaron, se lavaron con salmuera, se secaron sobre $MgSO_4$, se filtraron y se concentraron *in vacuo*. Este residuo se combinó con el filtrado EtOAc original y los orgánicos combinados se concentraron hasta una mezcla espesa. Un sólido se aisló por filtración para dar el producto deseado (8.84 g, 58.0% de rendimiento). LC-MS, MS m/z 336 (M^++H).

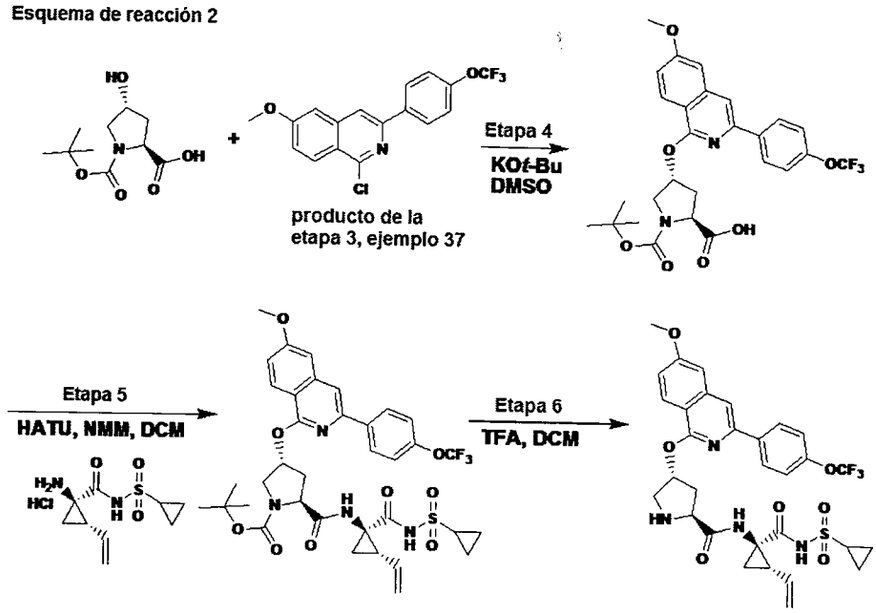
Etapa 3:

El producto sólido de la Etapa 2, Ejemplo 37 (8.84 g, 26.4 mmol) se disolvió en $POCl_3$ (100 mL) y la mezcla se calentó a reflujo durante 3 h. La mezcla se concentró *in vacuo*, y al residuo resultante se agregó agua (100 mL) y EtOAc (100 mL). La mezcla agitada rápidamente se trató lentamente con bicarbonato de sodio sólido hasta que se alcanzó pH = 7. Las fases se separaron, y la fase acuosa se extrajo con EtOAc (2 x 40 mL). Los extractos orgánicos se combinaron y se lavaron con bicarbonato de sodio acuoso saturado (40 mL) y luego con salmuera (40 mL), se secaron sobre $MgSO_4$, se filtraron y se concentraron *in vacuo*. El producto (9.21 g, 98.7% de rendimiento) se aisló sin cromatografía como un aceite viscoso ligeramente amarillo. ^1H RMN (500 MHz, CLOROFORMO-D) δ ppm 3.97 (s, 3 H) 7.11 (d,

000577

J=2.44 Hz, 1 H) 7.26 (dd, *J*=9.46, 2.44 Hz, 1 H) 7.31 (d, *J*=8.85 Hz, 2 H) 7.84 (s, 1 H) 8.10 (d, *J*=8.85 Hz, 2 H) 8.20 (d, *J*=9.46 Hz, 1 H); LC-MS, MS m/z 354 (M^++H).

Esquema de reacción 2



Etapa 4:

A una solución agitada mecánicamente de Boc-Hyp-OH (6.31 g, 27.3 mmol) en DMSO (100 mL) se agregó terc-butóxido de potasio sólido (8.05 g, 68.2 mmol). La mezcla se agitó durante 1.5 h, y el producto de la Etapa 3, Ejemplo 37 (20.0 g, g, 74.2 mmol) se agregó en dos porciones durante 15 min. La suspensión resultante se agitó durante 3 h a t.a. La suspensión luego se diluyó con una mezcla de pH = 4 solución amortiguadora (500 mL) y 1.0 M HCl (41 mL) y luego se extrajo con EtOAc (3 x 150 mL). Los extractos orgánicos se combinaron y se lavaron con pH = 4 solución amortiguadora (75 mL) y luego con salmuera (50 mL). El material orgánico luego se

000571

extrajo con una mezcla de NaOH 1.0M (30 mL) y agua (50 mL) dos veces, y los extractos básicos combinados se lavaron con EtOAc (30 mL). Los extractos básicos acuosos se trataron con HCl 1.0M (aproximadamente 60 mL) hasta que se logró pH = 4, y el producto deseado luego se extrajo en EtOAc (3 x 100 mL). Los extractos se combinaron, se secaron sobre $MgSO_4$ y se filtraron. El filtrado se evaporó *in vacuo* hasta secarse para dar un sólido espumoso. El producto deseado (13.2 g, 92.7% de rendimiento) se aisló después de la purificación por cromatografía en columna de gel de sílice (etapa de gradiente DCM, luego 40:1 DCM:MeOH, luego 10:1 DCM:MeOH) como un sólido cristalino. LC-MS, MS m/z 549 (M^++H).

Etapa 5:

Una mezcla del producto de la Etapa 4, Ejemplo 37 (12.3 g, 22.4 mmol), NMM (6.80 g, 67.3 mmol) y sal HCl de (1-(R)-amino-2-(S)-vinil-ciclopropanocarbonil)-amida del ácido ciclopropanosulfónico (6.28 g, 23.5 mmol) en DCM (250 mL) se trató con HATU (10.23 g, 26.9 mmol), y la solución resultante se agitó a t.a. durante la noche. El solvente se removió *in vacuo*, y el residuo se tomó hasta en EtOAc (700 mL) y se lavó con solución amortiguadora pH = 4 (4 x 200 mL) y con salmuera (75 mL). El material orgánico se secó sobre $MgSO_4$, se filtró y se concentró *in vacuo*. El producto (13.5 g, 79.1% de rendimiento) se aisló después de la purificación por columna

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de cromatografía de gel de sílice (1:1 hexanos:EtOAc) como una sólido cristalino blanco. LC-MS, MS m/z 761 (M^++H).

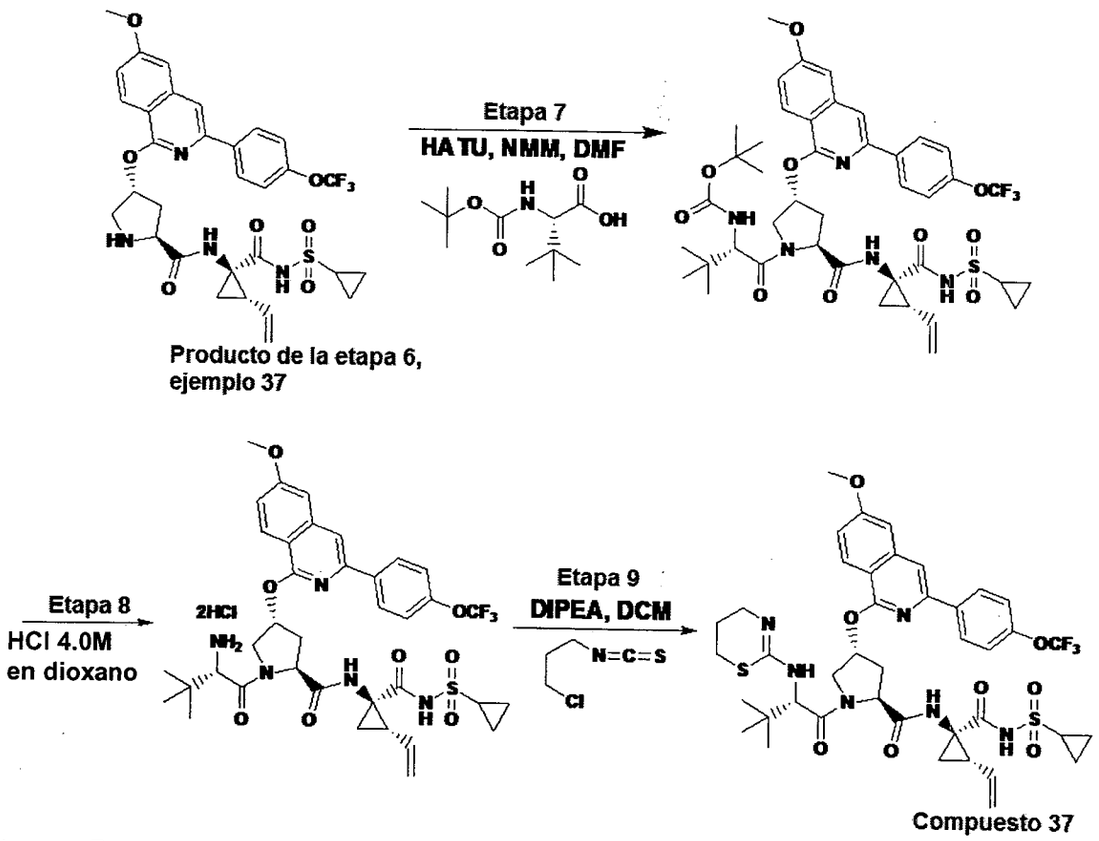
Etapa 6:

A una solución del producto de la Etapa 5, Ejemplo 37 (15.0g, 19.6 mmol) en una mezcla de DCM (50 mL) y 1,2-DCE (50 mL) se agregó TFA (100 mL). La mezcla se agitó a t.a. durante 1.5 h y luego se concentró *in vacuo*. El residuo se determinó que era menor de 85% puro por LCMS. El producto sin refinar (15.1 g) se purificó por columna de cromatografía de gel de sílice (etapa de gradiente DCM + 0.5% TEA seguido por 50 :1 DCM:MeOH + 0.5% TEA seguido por 40:1 DCM:MeOH + 0.5% TEA). Las fracciones del producto puro se combinaron para dar el producto deseado (9.13 g, 54% de rendimiento) el cual se determinó que tiene 2.0 equivalentes de TEA asociado con este. Las fracciones mezcladas se combinaron y se concentraron para dar 5.27 g del material el cual se dejó para purificación en una fecha posterior. ^{1}H RMN (500 MHz, MeOD) δ ppm 0.81 - 0.91 (m, 2 H) 1.02 - 1.13 (m, 2 H) 1.33 (t, *J*=7.32 Hz, 18 H) 1.88 (dd, *J*=7.63, 4.88 Hz, 1 H) 2.11 (dd, 1 H) 2.48 (ddd, *J*=14.19, 9.31, 5.19 Hz, 1 H) 2.77 (dd, *J*=14.34, 7.63 Hz, 1 H) 2.88 (tt, *J*=8.24, 4.88 Hz, 1 H) 3.22 (c, *J*=7.32 Hz, 12 H) 3.66 (d, *J*=13.12 Hz, 1 H) 3.79 (dd, *J*=12.97, 4.43 Hz, 1 H) 3.96 (s, 3 H) 4.44 (dd, *J*=9.31, 7.78 Hz, 1 H) 5.03 (dd, *J*=10.38, 1.83 Hz, 1 H) 5.24 (dd, *J*=17.09,

001573

1.83 Hz, 1 H) 5.88 (ddd, *J*=17.17, 10.15, 9.31 Hz, 1 H) 5.99 (t, *J*=4.73 Hz, 1 H) 7.19 (dd, *J*=9.16, 2.44 Hz, 1 H) 7.28 (d, *J*=2.44 Hz, 1 H) 7.38 (d, *J*=8.24 Hz, 2 H) 7.82 (s, 1 H) 8.19 (d, *J*=9.16 Hz, 1 H) 8.22 - 8.27 (m, 2 H); LC-MS, MS m/z 661 (M^++H).

Esquema de reacción 3



Etapa 7:

El producto de la Etapa 6, Ejemplo 37 (6.00 g, 6.95 mmol) se combinó con N-Boc-terc-leucina (1.77 g, 7.65 mmol) y HATU (3.17 g, 8.34 mmol) en DCM (75 mL), y la suspensión resultante se trató con NMM (1.48 g, 14.6 mmol), y la mezcla se agitó a t.a. durante 3 días. La mezcla de reacción se concentró *in*

- 60157

vacuo hasta un residuo, se volvió a disolver en EtOAc (250 mL) y se lavó con una mezcla 1:1 de solución amortiguadora pH = 4 y salmuera (4 x 100 mL). Los orgánicos combinados se secaron sobre $MgSO_4$ anhidro, se filtraron y se concentraron *in vacuo* hasta una espuma beige. La purificación por cromatografía en columna de gel de sílice (1:1 hexanos: EtOAc) proporcionó el producto puro como una espuma blanca opaca (4.62 g, 76.1% de rendimiento). LC-MS, MS m/z 874 (M^++H).

Etapa 8:

El producto de la Etapa 7, Ejemplo 37 (4.61 g, 5.28 mmol) se trató con una mezcla de 1,4-dioxano (50 mL) y 4.0M HCl en 1,4-dioxano (50 mL) durante 2.5h, conduciendo a un gel espeso asentado en el fondo del matraz. La mezcla se concentró in vacuo, luego el sólido espumoso resultante se volvió a disolver con DCM (25 mL) y la solución se agregó gota a gota a una mezcla agitada rápidamente de éter dietílico (100 mL) y HCl 2.0M en éter (100 mL). Un polvo blanco se precipitó y se aisló por filtración, se enjuagó con éter y se secó bajo alto vacío. La recuperación total fue 3.95 g (88.4% de rendimiento) del producto de sal bis-HCl en polvo blanco. ^{1}H RMN (500 MHz, MeOD) δ ppm 1.09 - 1.15 (m, 2 H) 1.20 (s, 9 H) 1.23 - 1.32 (m, 2 H) 1.46 (dd, *J*=9.46, 5.49 Hz, 1 H) 1.94 (dd, *J*=8.24, 5.49 Hz, 1 H) 2.31 (c, *J*=8.75 Hz, 1 H) 2.42 (ddd, *J*=13.96, 10.15, 4.27 Hz, 1 H) 2.77 (dd,

005575

J=13.89, 7.17 Hz, 1 H) 2.98 (ddd, *J*=12.67, 8.09, 4.88 Hz, 1 H) 3.99 (s, 3 H) 4.12 (s, 1 H) 4.25 (dd, 1 H) 4.32 (d, 1 H) 4.74 (dd, *J*=10.22, 7.17 Hz, 1 H) 5.17 (dd, *J*=10.68, 1.22 Hz, 1 H) 5.33 (dd, *J*=16.94, 1.07 Hz, 1 H) 5.77 (ddd, *J*=17.17, 10.15, 9.00 Hz, 1 H) 6.15 (s, 1 H) 7.21 (dd, *J*=9.16, 2.44 Hz, 1 H) 7.34 (d, *J*=2.14 Hz, 1 H) 7.40 (d, *J*=8.24 Hz, 2 H) 7.88 (s, 1 H) 8.15 (d, *J*=9.16 Hz, 1 H) 8.29 (d, *J*=8.55 Hz, 2 H) 9.25 (s, 1 H); LC-MS, MS m/z 774 (M^++H).

Etapa 9:

A una mezcla del producto de la Etapa 8, ejemplo 37 (0.271 g, 0.320 mmol) y DIEA (0.083 g, 0.641 mmol) en DCM (5 mL) se agregó isotiocianato de 3-cloropropilo (0.046 g, 0.336 mmol). La mezcla se calentó a 45°C durante 3h luego se dejó reposar a t.a. durante la noche. La mezcla de reacción se diluyó con DCM (50 mL) y se lavó con 0.1N HCl (3 mL). La capa acuosa se extrajo con DCM (25 mL) y la capa orgánica combinada se lavó con 10% acuoso Na_2CO_3 (3 mL), salmuera, se secó sobre $MgSO_4$ y se concentró hasta un sólido espumoso amarillo. El producto se purificó por HPLC preparativa de fase inversa para dar el Compuesto 37 como un sólido bis-HCl amarillo claro. ^{1}H RMN (500 MHz, *MeOD*) δ ppm 1.11 (s, 9 H), 1.15 (d, *J*=1.8 Hz, 1 H), 1.22 - 1.29 (m, 2 H), 1.45 - 1.51 (m, 1 H), 1.78 - 1.87 (m, *J*=8.9 Hz, 1 H), 1.91 - 1.98 (m, 2 H), 2.31 (c, *J*=8.6 Hz, 1 H), 2.37 - 2.45 (m, 1 H), 2.70

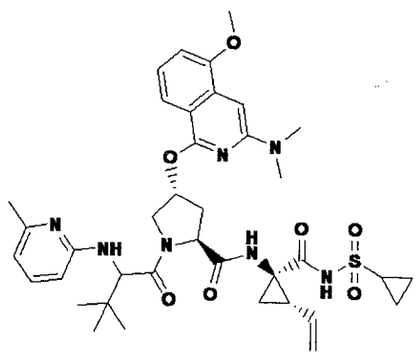
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- 2.84 (m, 2 H), 2.93 - 3.01 (m, 1 H), 3.98 - 4.02 (m, *J*=1.5 Hz, 3 H), 4.18 (d, *J*=11.3 Hz, 1 H), 4.28 (s, 1 H), 4.34 - 4.42 (m, 1 H), 4.71 - 4.78 (m, 1 H), 5.17 (d, *J*=10.4 Hz, 1 H), 5.35 (d, *J*=17.1 Hz, 1 H), 5.75 - 5.83 (m, 1 H), 6.15 (s, 1 H), 7.24 (d, *J*=9.2 Hz, 1 H), 7.37 (s, 1 H), 7.42 (d, *J*=7.9 Hz, 1 H), 7.91 (s, 1 H), 8.10 (d, *J*=9.2 Hz, 1 H), 8.31 (dd, *J*=8.9, 1.8 Hz, 2 H); LC-MS, MS m/z 873 (M^+ + H).

Isómeros del Compuesto 38:

3-metil-N-(6-metil-2-piridinil)-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((3-(dimetilamino)-5-metoxi-1-isoquinolinil)oxi)-L-prolinamida y 3-metil-N-(6-metil-2-piridinil)-D-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((3-(dimetilamino)-5-metoxi-1-isoquinolinil)oxi)-L-prolinamida

Ejemplo 38: Preparación de los compuestos 38A y 38B



Compuestos 38A y 38B

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Los compuestos 38A y 38B se prepararon por un procedimiento similar como aquel descrito para la preparación del Compuesto 17, pero con las siguientes excepciones: En la etapa 1, ácido 3-metoxi-2-metilbenzoico se usó en lugar de ácido 4-metoxi-2-metilbenzoico. En la etapa 2, el LDA se reemplazó con KHMDS. Y en la etapa 7, el producto de la Etapa 1, ejemplo 28 se usó en lugar de ácido 2-(4,6-dimetilpiridin-2-ilamino)-3-metil butanoico comercialmente disponible. Dos compuestos isoméricos se aislaron de la Etapa 7: el isómero primero en eluir de una columna HPLC preparativa fue el compuesto 38A, y el segundo isómero en eluir de la columna HPLC preparativa fue el compuesto 38B.

Producto de la etapa 1, Ejemplo 38: Sólido ligeramente amarillo (100% de rendimiento). ^{1}H RMN (500 MHz, CLOROFORMO-D) δ ppm 2.42 (s, 3 H) 2.96 (s, 12 H) 3.80 (s, 3 H) 6.81 (d, *J*=7.93 Hz, 1 H) 7.11 (t, *J*=7.93 Hz, 1 H) 7.25 (d, *J*=6.71 Hz, 1 H); LC-MS, MS m/z 264 (M^+ + H).

Producto de la etapa 2, Ejemplo 38: Sólido amarillo (89% de rendimiento). ^{1}H RMN (500 MHz, CLOROFORMO-D) δ ppm 3.04 (s, 6 H) 3.92 (s, 3 H) 5.89 (s, 1 H) 6.92 (d, *J*=7.63 Hz, 1 H) 7.09 (t, *J*=7.93 Hz, 1 H) 7.82 (d, *J*=7.93 Hz, 1 H) 10.69 (s, 1 H); LC-MS, MS m/z 219 (M^+ + H).

000578

Producto de la etapa 3, Ejemplo 38: Sólido amarillo (95% de rendimiento). ^{1}H RMN (300 MHz, CLOROFORMO-D) δ ppm 3.12 (s, 6 H) 3.93 (s, 3 H) 6.77 (d, *J*=7.32 Hz, 1 H) 6.83 (s, 1 H) 7.09 (dd, *J*=8.42, 7.68 Hz, 1 H) 7.62 (d, *J*=8.42 Hz, 1 H); LC-MS, MS m/z 237 (M^+ + H).

Producto de la etapa 4, Ejemplo 38: Sólido amarillo (92% de rendimiento). LC-MS, MS m/z 432 (M^+ + H).

Producto de la etapa 5, Ejemplo 38: Sólido amarillo/verde (73% de rendimiento). LC-MS, MS m/z 644 (M^+ + H).

Producto de la etapa 6, Ejemplo 38: Sólido amarillo (95% de rendimiento). LC-MS, MS m/z 544 (M^+ + H).

Compuesto 38A (Producto de la etapa 7, Ejemplo 38): ^{1}H RMN (500 MHz, *MeOD*) δ ppm 1.07 - 1.14 (m, 2 H), 1.15 (s, 9 H), 1.27 (dd, *J*=4.6, 2.7 Hz, 2 H), 1.43 - 1.49 (m, 1 H), 1.94 (dd, *J*=8.1, 5.3 Hz, 1 H), 2.25 - 2.36 (m, 2 H), 2.41 (s, 3 H), 2.67 (dd, *J*=13.9, 7.5 Hz, 2 H), 2.95 - 3.02 (m, 2 H), 3.16 (s, 6 H), 3.18 - 3.20 (m, 1 H), 3.99 (s, 3 H), 4.10 (dd, *J*=12.1, 3.2 Hz, 1 H), 4.38 (d, *J*=11.9 Hz, 1 H), 4.50 (s, 1 H), 4.69 (dd, *J*=10.1, 7.3 Hz, 1 H), 5.17 (dd, *J*=10.4, 1.5 Hz, 1 H), 5.34 (dd, *J*=17.1, 1.2 Hz, 1 H), 5.73 - 5.82 (m, 1 H), 5.98 (s, 1 H), 6.64 (dd, *J*=9.8, 7.3 Hz, 2 H), 6.90 (d, *J*=6.7 Hz, 1 H), 6.95 (t, *J*=7.9 Hz, 1 H), 7.30 (dd, *J*=9.0, 7.5 Hz, 1 H), 7.33 (d, *J*=7.3 Hz, 1 H); LC-MS, MS m/z 748 (M^+ + H).

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601579

Compuesto 38B (Producto de la etapa 7, Ejemplo 38): ^{1}H RMN (500 MHz, *MeOD*) δ ppm 0.98 (s, 9 H), 1.05 - 1.10 (m, 2 H), 1.15 (s, 1 H), 1.15 - 1.19 (m, 1 H), 1.23 - 1.28 (m, 1 H), 1.40 (dd, *J*=9.6, 5.0 Hz, 1 H), 1.91 (dd, *J*=8.1, 5.3 Hz, 1 H), 2.31 (c, *J*=8.7 Hz, 1 H), 2.40 - 2.47 (m, 1 H), 2.54 (s, 3 H), 2.68 (dd, *J*=13.9, 7.5 Hz, 2 H), 2.89 - 2.95 (m, 2 H), 3.15 (s, 6 H), 3.18 - 3.20 (m, 1 H), 3.98 (s, 3 H), 4.21 (dd, *J*=12.1, 3.5 Hz, 1 H), 4.44 (d, *J*=12.2 Hz, 1 H), 4.65 (s, 1 H), 4.66 - 4.69 (m, 1 H), 5.16 (dd, *J*=10.4, 1.8 Hz, 1 H), 5.36 (dd, *J*=17.2, 1.4 Hz, 1 H), 5.74 - 5.83 (m, 1 H), 6.02 (s, 1 H), 6.84 (d, *J*=7.3 Hz, 1 H), 6.94 (d, *J*=7.3 Hz, 1 H), 7.04 - 7.09 (m, 2 H), 7.47 (dd, *J*=8.2, 0.9 Hz, 1 H), 7.96 (dd, *J*=9.2, 7.3 Hz, 1 H); LC-MS, MS m/z 748 (M^+ + H).

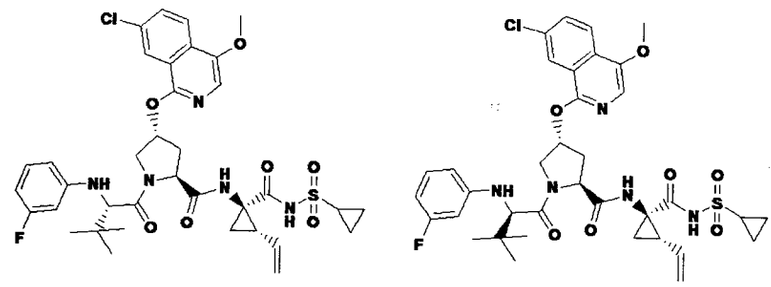
Isómeros del Compuesto 200:

N-(3-fluorofenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

N-(3-fluorofenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

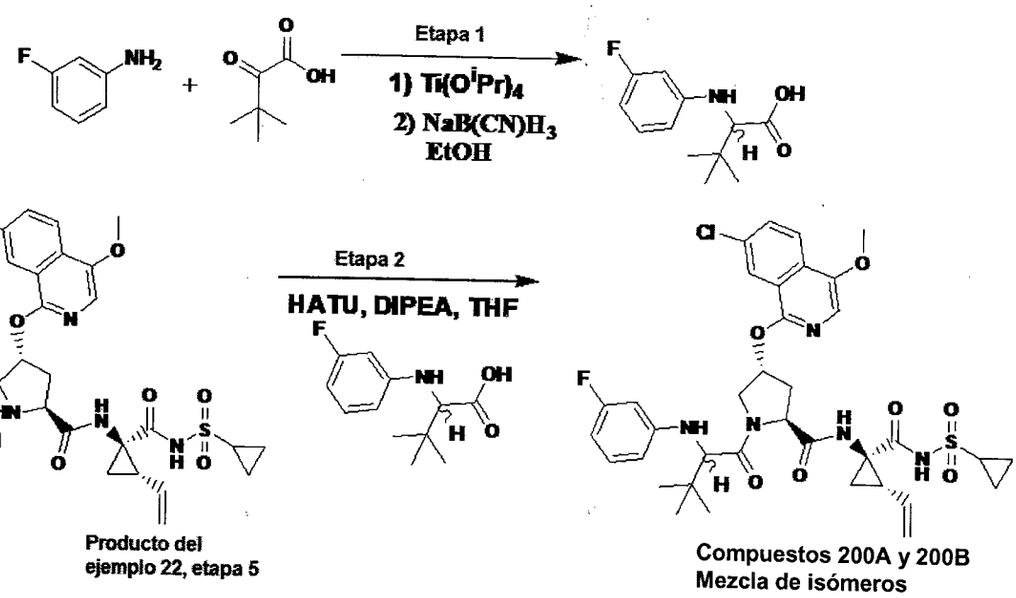
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Ejemplo 200: Preparación de los compuestos 200A y 200B



Compuestos 200A y 200B

Esquema de reacción 1



Etapa 1:

A una mezcla de 3-fluoroanilina (160 mg, 1.299 mmol) y ácido 3,3-dimetil-2-oxobutanoico (220 mg, 1.690 mmol) en un matraz de fondo redondo a 100 mL (RBF) a t.a. se agregó tetraisopropoxititanio (2 ml,) por medio una pipeta. El color de la mezcla cambió pronto a un color canario característico. La solución se calentó a 75°C durante alrededor de 15 minutos y el color se mantiene igual. La solución se diluyó con etanol

absoluto (8 ml) a t.a., seguido por la adición de 1.5x de cianotrihidroborato de sodio (136 mg, 2.16 mmol), y la mitad restante después que la emisión de sonidos y burbujeo se terminó. El color de la solución se volvió claro. La solución se mezcló con 4 mL de agua, formando una suspensión. El PPT blanco se removió por centrifugado, el residuo orgánico se extrajo en acetato de etilo y la fase orgánica se secó sobre Na_2SO_4. La evaporación hasta secarse bajo alto vacío (20-40 microHg) a t.a. dio una espuma blanca la cual se usó en la siguiente etapa sin purificación adicional. LC-MS, MS m/z 226 (M^+ +H).

Etapa 2:

A la solución amarilla del ácido 2-(3-fluorofenilamino)-3,3-dimetilbutanoico (0.20 g, 0.888 mmol, de la etapa 1, ejemplo 200) y (2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-N-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropil)pirrolidina-2-carboxamida (0.10 g, 0.187 mmol, de la etapa 5, ejemplo 22) en THF (4 mL) a 0°C se agregó HATU (0.175 g, 0.46 mmol) seguido por diisopropiletil amina (400 µL, exceso). Una solución amarilla pálida se formó después de la adición de la base. La mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con acetato de etilo (25 ml), se lavó con agua (pH~6), y salmuera. El material orgánico se secó sobre sulfato de sodio, se filtró y se concentró, y el residuo se purificó por HPLC preparativa de fase

000582

inversa para dar dos productos separados con MS idéntico (*m/z* 226 por $[M+H]^+$) como se observó por LCMS. El Compuesto 200A (0.022 g, 16% de rendimiento, no optimizado) fue el primero de dos isómeros en eluir por HPLC preparativa de fase inversa. El Compuesto 200B (0.010 g, 7% de rendimiento, no optimizado) fue el segundo de los dos isómeros en eluir por HPLC preparativa de fase inversa.

Compuesto 200A: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.12 (s, 9 H), 1.26 - 1.31 (m, 2 H), 1.39 (dd, J=6.71, 4.27 Hz, 2 H), 1.45 (dd, J=9.46, 5.49 Hz, 1 H), 1.90 (dd, J=7.93, 5.49 Hz, 1 H), 2.19 - 2.32 (m, 2 H), 2.55 (dd, J=13.73, 7.02 Hz, 1 H), 2.93 - 3.03 (m, 1 H), 3.69 - 3.78 (m, 1 H), 4.04 (s, 3 H), 4.05 (dd, J=8.85, 3.35 Hz, 1 H), 4.31 (d, J=12.21 Hz, 1 H), 4.55 (dd, J=10.38, 7.02 Hz, 1 H), 5.14 (d, J=10.38 Hz, 1 H), 5.32 (d, J=17.09 Hz, 1 H), 5.71 - 5.83 (m, 2 H), 5.89 - 5.98 (m, 1 H), 6.21 (dd, J=8.09, 1.98 Hz, 1 H), 6.25 - 6.32 (m, 1 H), 6.42 - 6.50 (m, 1 H), 7.57 (s, 1 H), 7.70 (dd, J=8.85, 2.14 Hz, 1 H), 7.83 (d, J=1.83 Hz, 1 H), 8.11 (d, J=8.85 Hz, 1 H), 9.19 (br. s, 1 H); LC-MS, MS m/z 743 $[M+H]^+$.

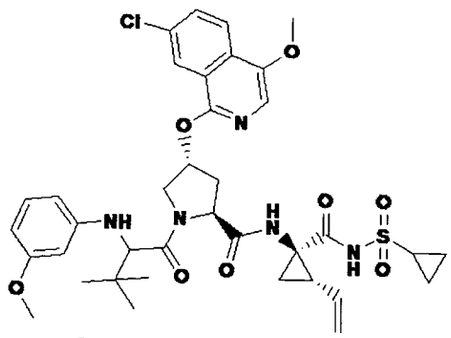
Compuesto 200B: LC-MS, MS m/z 743 $[M+H]^+$.

Isómeros del Compuesto 201:

N-(3-metoxifenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

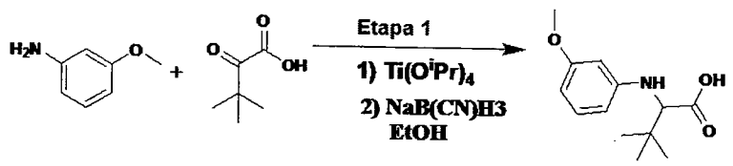
N-(3-metoxifenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

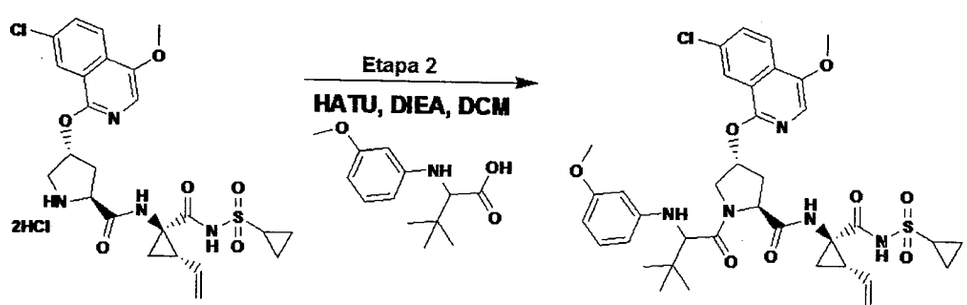
Ejemplo 201: Preparación de los compuestos 201A y 201B



Compuestos 201A y 201B

Esquema de reacción 1





Producto del ejemplo 22, etapa 5

Compuestos 201A y 201B
Mezcla de isómeros

- 000534

Etapa 1:

A una mezcla de 3-metoxianilina (160 mg, 1.299 mmol) y ácido 3,3-dimetil-2-oxobutanoico (220 mg, 1.690 mmol) en 100 mL de RBF a t.a. se agregó tetraisopropoxititanio (2 ml) por medio de una pipeta. El color de la mezcla se cambió pronto a un color canario característico. La solución se calentó a 75°C durante alrededor de 15 minutos y el color se mantiene igual. La solución se diluyó con etanol absoluto (8 ml) a t.a., seguido por la adición de 1.5x de cianotrihidroborato de sodio (245 mg, 3.90 mmol), y la mitad restante después que la emisión de sonidos y burbujeo se terminó. El color de la solución se volvió más transparente. La solución se mezcló con 4 mL de agua, formando una suspensión, el PPT blanco se removió por centrifuga. El material orgánico se extrajo en acetato de etilo, y la fase orgánica se secó sobre Na_2SO_4, se filtró y se evaporó hasta secarse para dar una espuma blanca. Este material se llevó a cabo en la siguiente etapa sin purificación adicional. LC-MS, MS m/z 238 (M^+ +H).

Etapa 2:

A la solución amarilla del ácido de 2-(3-metoxifenilamino)-3,3-dimetilbutanoico (0.045 g, 0.189 mmol, etapa 1, ejemplo 201) y (2S,4R)-4-(7-cloro-4-

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metoxiisoquinolin-1-iloxi)-N-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropil)pirrolidina-2-carboxamida (0.101 g, 0.189 mmol, etapa 5, ejemplo 22) en CH_2Cl_2 a 0°C se agregó HATU (0.144 g, 0.378 mmol) seguido por diisopropiletil amina (0.061 g, 0.473 mmol). Una solución amarilla clara se formó después de la adición de la base. La mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con acetato de etilo (25 ml) y luego se lavó con agua (pH~6) y salmuera. El material orgánico se secó sobre sulfato de sodio, se concentró, y el residuo se purificó por HPLC preparativa de fase inversa para dar dos productos separados con MS m/z idéntico como se observó por LCMS. El Compuesto 201A (0.045 g, 32% de rendimiento) fue el primero de dos isómeros en eluir por HPLC preparativa de fase inversa. El compuesto 201B (0.024 g, 16.2% de rendimiento) fue el segundo de los dos isómeros en eluir por HPLC preparativa de fase inversa.

Compuesto 201A: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.03 - 1.14 (m, 11 H) 1.21 - 1.32 (m, 2 H) 1.41 (dd, *J*=9.44, 5.41 Hz, 1 H) 1.87 (dd, *J*=8.06, 5.54 Hz, 1 H) 2.16 - 2.26 (m, 2 H) 2.48 (dd, *J*=13.60, 6.80 Hz, 1 H) 2.95 (ddd, *J*=12.78, 8.12, 4.78 Hz, 1 H) 3.95 - 4.07 (m, 5 H) 4.48 (dd, *J*=10.58, 7.05 Hz, 1 H) 5.11 (d, *J*=10.32 Hz, 1 H)

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5.29 (d, *J*=17.12 Hz, 1 H) 5.65 - 5.73 (m, 2 H) 5.73 - 5.79 (m, 1 H) 6.15 - 6.21 (m, 1 H) 6.27 (d, *J*=2.01 Hz, 1 H) 6.36 - 6.42 (m, 1 H) 7.50 (s, 1 H) 7.68 (d, *J*=9.06 Hz, 1 H) 7.74 (s, 1 H) 8.08 (d, *J*=8.81 Hz, 1 H); LC-MS, MS m/z 753 (M^+ +H).

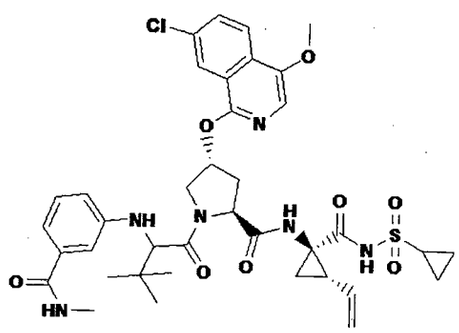
Compuesto 201B: LC-MS, MS m/z 753 (M^+ +H).

Isómeros del Compuesto 202:

3-metil-N-(3-(metilcarbamoil)fenil)-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

3-metil-N-(3-(metilcarbamoil)fenil)-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

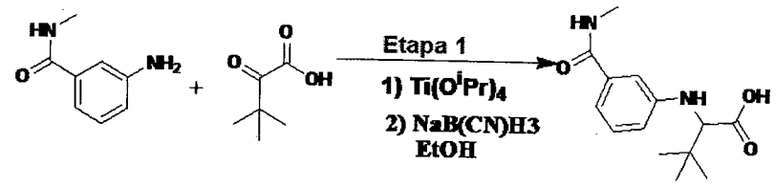
Ejemplo 202: Preparación de los compuestos 202A y 202B

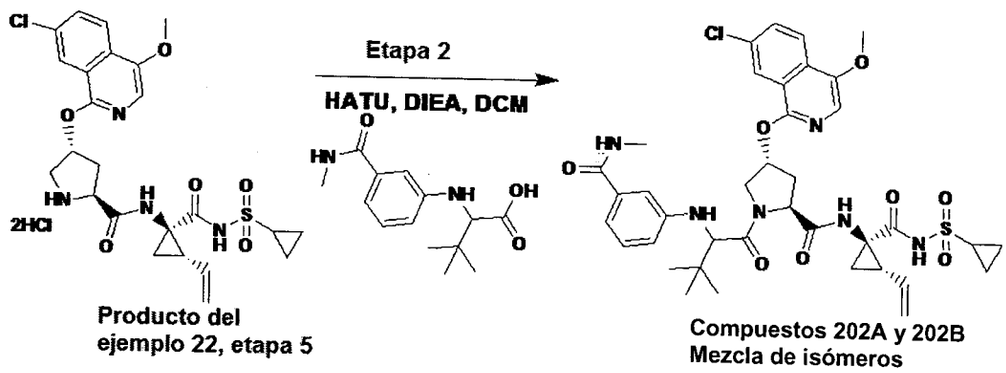


Compuestos 202A y 202B

000557

Esquema de reacción 1





Producto del ejemplo 22, etapa 5

Compuestos 202A y 202B
Mezcla de isómeros

Etapa 1:

A una mezcla de 3-amino-N-metilbenzamida (230 mg, 1.532 mmol) y ácido 3,3-dimetil-2-oxobutanoico (199 mg, 1.532 mmol) en 100 mL de RBF a t.a. se agregó tetraisopropoxititanio (2 ml,) por medio de una pipeta, el color de la mezcla cambió pronto a un color canario característico. La solución se calentó a 75°C durante alrededor de 15 minutos y el color se mantiene igual. La solución se diluyó con etanol absoluto (8 ml) a t.a., seguido por la adición de 1.5X de cianotrihidroborato de sodio (245 mg, 3.90 mmol), y la mitad restante después que la emisión de sonidos y burbujeo se terminó. El color de la solución se volvió claro. La solución se mezcló con 4 mL de agua, formando una suspensión, el PPT

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blanco se removió por centrifugado, el material orgánico se extrajo en acetato de etilo, se secó sobre Na_2SO_4. La evaporación hasta secado dio una espuma blanca que se obtuvo y se usó en la siguiente etapa sin purificación adicional. LC-MS, MS m/z 265 (M^+ +H).

Etapa 2:

A la solución amarilla de ácido (S)-3,3-dimetil-2-(3-(metilcarbamoil)fenilamino)butanoico (0.050 g, 0.189 mmol, etapa 1, ejemplo 202) y (2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-N-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropil)pirrolidina-2-carboxamida (0.101 g, 0.189 mmol, etapa 5, ejemplo 22) en CH_2Cl_2 a 0°C se agregó HATU (0.144 g, 0.378 mmol) seguido por diisopropiletil amina (0.061 g, 0.473 mmol). Una solución amarilla clara se formó después de la adición de la base. La mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con acetato de etilo (25 ml) y se lavó con agua (pH~6) y salmuera. El material orgánico se secó sobre sulfato de sodio, luego se concentró, y el residuo se purificó por HPLC preparativa de fase inversa para dar dos productos separados con MS m/z idéntico como se observó por LCMS. El Compuesto 202A (0.061 g, 41% de rendimiento) fue el primero de dos isómeros en eluir por HPLC preparativa de fase

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inversa. El Compuesto 202B (0.015 g, 10.2% de rendimiento) fue el segundo de los dos isómeros en eluir por HPLC preparativa de fase inversa.

Compuesto 202A: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.02 - 1.13 (m, 11 H) 1.20 - 1.30 (m, 2 H) 1.42 (dd, *J*=9.44, 5.41 Hz, 1 H) 1.87 (dd, *J*=8.06, 5.54 Hz, 1 H) 2.14 - 2.25 (m, 2 H) 2.47 (dd, *J*=13.72, 6.92 Hz, 1 H) 2.77 (s, 3 H) 2.95 (ddd, *J*=12.65, 7.99, 4.78 Hz, 1 H) 3.94 (dd, *J*=12.21, 3.15 Hz, 1 H) 3.98 (s, 4 H) 4.22 (d, *J*=12.09 Hz, 1 H) 4.51 (dd, *J*=10.32, 7.05 Hz, 1 H) 5.11 (d, *J*=10.32 Hz, 1 H) 5.28 (d, *J*=17.12 Hz, 1 H) 5.69 - 5.79 (m, 2 H) 6.63 - 6.73 (m, 3 H) 7.01 (s, 1 H) 7.48 (s, 1 H) 7.64 (dd, *J*=8.94, 2.14 Hz, 1 H) 7.71 (d, *J*=2.01 Hz, 1 H) 8.05 (d, *J*=8.81 Hz, 1 H); LC-MS, MS m/z 781 (M^+ +H).

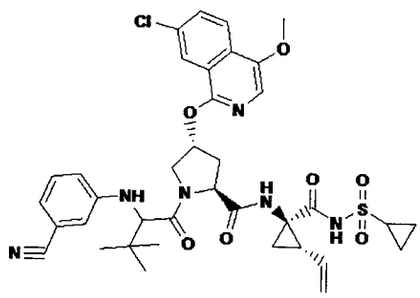
Compuesto 202B: LC-MS, MS m/z 781 (M^+ +H).

Isómeros del Compuesto 203:

N-(3-cianofenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

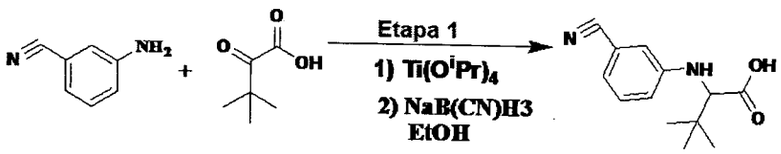
N-(3-cianofenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

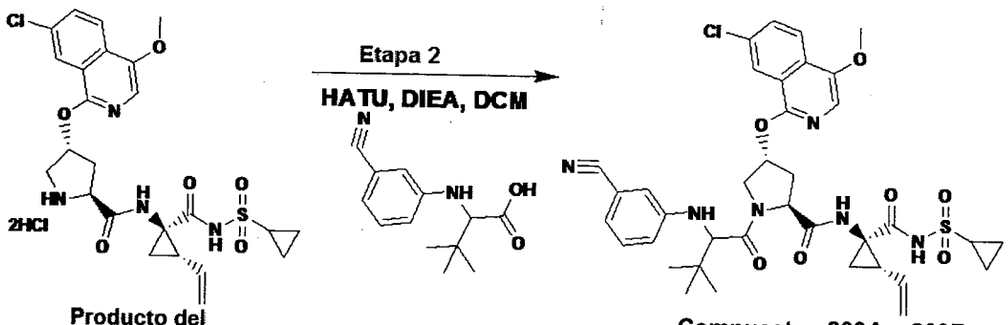
Ejemplo 203: Preparación de los compuestos 203A y 203B



Compuestos 203A y 203B

Esquema de reacción 1





Etapa 1:

A una mezcla de 3-aminobenzonitrilo (180 mg, 1.524 mmol) y ácido 3,3-dimetil-2-oxobutanoico (198 mg, 1.524 mmol) en 100 mL de RBF a t.a. se agregó tetraisopropoxititanio (2 ml,) por medio de una pipeta. El color de la mezcla pronto cambió a un color canario característico. La solución se calentó a 75°C durante

alrededor de 15 minutos y el color se mantiene igual. La solución se diluyó con etanol absoluto (8 ml) a t.a., seguido por la adición de 1.5X de cianotrihidroborato de sodio (245 mg, 3.90 mmol), y la mitad restante después que la emisión de sonidos y burbujeo se terminó. El color de la solución se volvió claro. La solución se mezcló con 4 mL de agua, formando una suspensión, el PPT blanco se removió por centrifugado, el material orgánico se extrajo en acetato de etilo, y la fase orgánica se secó sobre Na_2SO_4, se filtró, y se evaporó hasta secarse. Un aceite amarillo se obtuvo y se usó en la siguiente etapa sin purificación adicional. LC-MS, MS m/z 233 (M^+ +H).

Etapa 2:

A la solución amarilla de ácido (S)-2-(3-cianofenilamino)-3,3-dimetilbutanoico (0.044 g, 0.189 mmol, etapa 1, ejemplo 203) y (2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-N-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropil)pirrolidina-2-carboxamida (0.101 g, 0.189 mmol, etapa 5, ejemplo 22) en CH_2Cl_2 a 0°C se agregó HATU (0.144 g, 0.378 mmol) seguido por diisopropiletil amina (0.061 g, 0.473 mmol). Una solución amarilla clara se formó después de la adición de la base. La mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con acetato de etilo (25 ml) y luego se lavó con agua (pH~6) y salmuera. El material orgánico se secó sobre sulfato de sodio,

se filtró, se concentró, y el residuo se purificó por HPLC preparativa de fase inversa para dar dos productos separados con MS m/z idéntico como se observó por LCMS. El Compuesto 203A (0.025 g, 17.7% de rendimiento) fue el primero de dos isómeros en eluir por HPLC preparativa de fase inversa. El Compuesto 203B (0.014 g, 10.0% de rendimiento) fue el segundo de los dos isómeros en eluir por HPLC preparativa de fase inversa.

Compuesto 203A: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.07 (s, 11 H) 1.19 - 1.31 (m, 2 H) 1.41 (dd, *J*=9.44, 5.41 Hz, 1 H) 1.87 (dd, *J*=8.06, 5.54 Hz, 1 H) 2.17 - 2.26 (m, 2 H) 2.51 (dd, *J*=13.60, 6.80 Hz, 1 H) 2.88 - 2.98 (m, 1 H) 3.95 - 4.02 (m, 4 H) 4.02 - 4.05 (S, 1 H) 4.21 (d, *J*=12.09 Hz, 1 H) 4.53 (dd, *J*=10.32, 7.05 Hz, 1 H) 5.11 (d, *J*=10.32 Hz, 1 H) 5.28 (d, *J*=17.12 Hz, 1 H) 5.68 - 5.78 (m, 2 H) 6.46 (d, *J*=7.30 Hz, 1 H) 6.57 (t, *J*=7.93 Hz, 1 H) 6.63 - 6.68 (m, 1 H) 6.86 (s, 1 H) 7.50 (s, 1 H) 7.64 (dd, *J*=8.94, 1.38 Hz, 1 H) 7.69 (s, 1 H) 8.05 (d, *J*=8.81 Hz, 1 H); LC-MS, MS m/z 749 (M^+ +H).

Compuesto 203B: LC-MS, MS m/z 749 (M^+ +H).

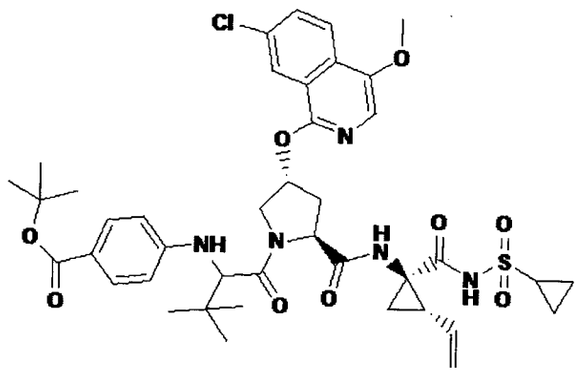
Isómeros del Compuesto 204:

N-(4-(terc-Butoxicarbonil)fenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

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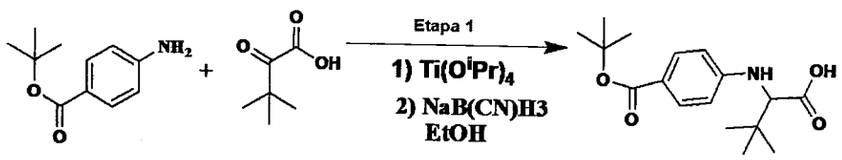
N-(4-(terc-Butoxicarbonil)fenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

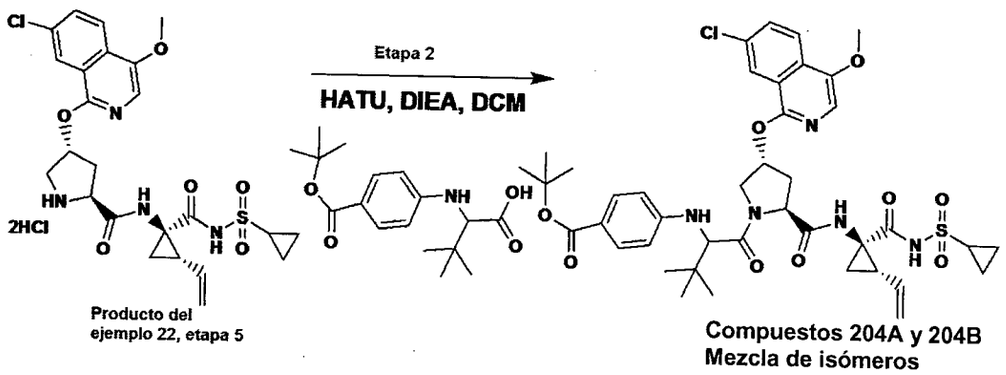
Ejemplo 204: Preparación de los compuestos 204A y 204B



Compuestos 204A y 204B

Esquema de rección 1





Etapa 1:

A una mezcla de 4-aminobenzoato de terc-Butilo (230 mg, 1.190 mmol) y ácido 3,3-dimetil-2-oxobutanoico (155 mg, 1.190 mmol) en 100 mL de RBF a t.a. se agregó tetraisopropoxititanio (2 ml) por medio de una pipeta. El color de la mezcla cambió pronto a un color canario característico. La solución se calentó a 75°C durante alrededor de 15 minutos y el color se mantiene igual. La solución se diluyó con etanol absoluto (8 ml) a t.a., seguido por la adición de 1.5X de cianotrihidroborato de sodio (245 mg, 3.90 mmol), y la mitad restante después que la emisión de sonidos y burbujeo se terminó. El color de la solución se volvió claro. La solución se mezcló con 4 mL de agua, formando una suspensión, el PPT blanco se removió por centrifugado. El material orgánico se extrajo en acetato de etilo, y la fase orgánica se secó sobre Na_2SO_4, se filtró y se evaporó hasta secarse. Un aceite amarillo se obtuvo y se usó en la siguiente etapa sin purificación adicional. LC-MS, MS m/z 308 (M^+ +H).

Etapa 2:

A la solución amarilla de ácido (S)-2-(4-(terc-butoxicarbonil)fenilamino)-3,3-dimetilbutanoico (0.058 g, 0.189 mmol, etapa 1, ejemplo 204) y (2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-N-((1R,2S)-1-

- 000595

(ciclopropilsulfonilcarbamoil)-2-vinilciclopropil)pirrolidina-2-carboxamida (0.101 g, 0.189 mmol, etapa 5, ejemplo 22) en CH_2Cl_2 a 0°C se agregó HATU (0.144 g, 0.378 mmol) seguido por diisopropiletil amina (0.061 g, 0.473 mmol). Una solución amarilla clara se formó después de la adición de la base. La mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con acetato de etilo (25 ml), se lavó con agua (pH~6) y salmuera. El material orgánico se secó sobre sulfato de sodio, se concentró, y el residuo se purificó por HPLC preparativa de fase inversa para dar dos productos separados con MS m/z idéntico como se observó por LCMS. El Compuesto 204A (0.024 g, 15.4% de rendimiento) fue el primero de dos isómeros en eluir por HPLC preparativa de fase inversa. El Compuesto 204B (0.020 g, 12.8% de rendimiento) fue el segundo de los dos isómeros en eluir por HPLC preparativa de fase inversa.

Compuesto 204A: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.02 - 1.11 (m, 11 H) 1.19 - 1.30 (m, 2 H) 1.41 (dd, *J*=9.19, 5.41 Hz, 1 H) 1.46 - 1.54 (S, 9 H) 1.86 (dd, *J*=8.06, 5.54 Hz, 1 H) 2.17 - 2.27 (m, 2 H) 2.54 (dd, *J*=13.60, 6.80 Hz, 1 H) 2.95 (ddd, *J*=12.65, 7.99, 4.78 Hz, 1 H) 3.96 - 4.04 (m, 4 H) 4.12 (s, 1 H) 4.37 (d, *J*=12.09, 1H) 4.55 (dd, *J*=10.07, 7.30 Hz, 1 H) 5.10 (d, *J*=10.58

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Hz, 1 H) 5.28 (d, *J*=17.58 Hz, 1 H) 5.75 (m, 1H) 5.78 (S, 1 H) 6.42 (d, *J*=8.81 Hz, 2 H) 7.28 (d, *J*=8.56 Hz, 2 H) 7.52 (s, 1 H) 7.59 (dd, *J*=8.94, 2.14 Hz, 1 H) 7.75 (d, *J*=1.76 Hz, 1 H) 8.03 (d, *J*=8.81 Hz, 1 H); LC-MS, MS m/z 824 (M^+ +H).

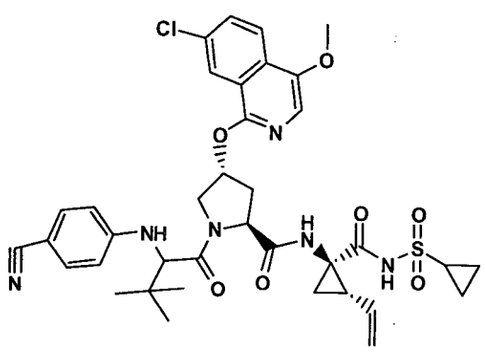
Compuesto 204B: LC-MS, MS m/z 824 (M^+ +H).

Isómeros del compuesto 205:

N-(4-cianofenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

N-(4-cianofenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

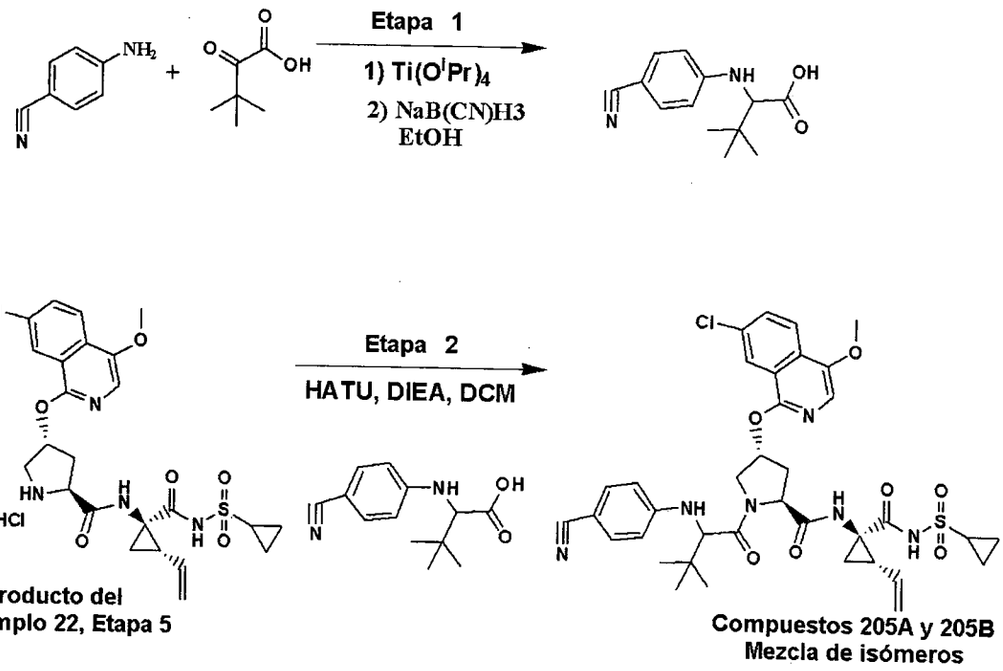
Ejemplo 205: Preparación de los Compuestos 205A y 205B



Compuestos 205A y 205B

006597

Esquema de Reacción 1



Etapa 1:

A una mezcla de 4-aminobenzonitrilo (180 mg, 1.524 mmol) y ácido 3,3-dimetil-2-oxobutanoico (198 mg, 1.524 mmol) en un RBF 100 mL a TA se le agregó tetraisopropoxititanio (2 ml) por medio de una pipeta. El color de la mezcla pronto cambió a un color canario característico. La solución se calentó a 75°C durante alrededor de 15 minutos y el color sigue siendo el mismo. La solución se diluyó con etanol absoluto (8 ml) a TA, seguido por la adición de 1.5 X de cianotrihidroborato de sodio (245 mg, 3.90 mmol), y la mitad restante se terminó después del burbujeo y la emisión de sonidos. El color de la solución se hizo más claro. La solución se mezcló con 4 mL

000598

de agua, formando una suspensión, el PPT blanco se removió por centrifugado. El material orgánico se extrajo en acetato de etilo, y la fase orgánica se secó sobre Na_2SO_4, se filtró, y evaporó hasta secarse. Un aceite amarillo se obtuvo y se usó en la siguiente etapa sin purificación adicional. LC-MS, MS *m/z* 233 (M^++H).

Etapa 2:

A la solución amarilla de ácido 2-(4-cianofenilamino)-3,3-dimetilbutanoico (0.044 g, 0.189 mmol, etapa 1, ejemplo 205) y (2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-N-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropil)pirrolidin-2-carboxamida (0.101 g, 0.189 mmol, etapa 5, ejemplo 22) en CH_2Cl_2 a 0°C se le agregó HATU (0.144 g, 0.378 mmol) seguido por diisopropiletil amina (0.061 g, 0.473 mmol). Una solución color amarillo claro se formó después de la adición de la base. La mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con acetato de etilo (25 ml), se lavó con agua (pH~6) y salmuera. El material orgánico se secó sobre sulfato de sodio, se filtró y se concentró, y el residuo se purificó por HPLC preparativa de fase inversa para dar dos productos separados con MS *m/z* idénticos como se observa por LCMS. El compuesto 205A

000599

(0.052 g, 37% de rendimiento) fue el primero de los dos isómeros en eluir por HPLC preparativa de fase inversa. El compuesto 205B (0.013 g, 9% de rendimiento) fue el segundo de los dos isómeros a eluir por HPLC preparativa de fase inversa.

Compuesto 205A: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 0.99 - 1.09 (m, 11 H) 1.17 - 1.26 (m, 2 H) 1.35 - 1.45 (m, 1 H) 1.87 (dd, *J*=8.06, 5.29 Hz, 1 H) 2.17 - 2.28 (m, 2 H) 2.56 (dd, *J*=13.85, 7.05 Hz, 1 H) 2.94 (ddd, *J*=12.84, 8.06, 4.78 Hz, 1 H) 3.95 - 4.04 (m, 4 H) 4.08 (s, 1 H) 4.28 - 4.37 (m, 1 H) 4.56 (dd, *J*=10.32, 7.05 Hz, 1 H) 5.05 - 5.13 (m, 1 H) 5.28 (d, *J*=17.12 Hz, 1 H) 5.66 - 5.75 (m, 1 H) 5.78 (s, 1 H) 6.44 (d, *J*=8.81 Hz, 2 H) 6.80 (d, *J*=8.56 Hz, 2 H) 7.46 - 7.54 (s, 1 H) 7.63 - 7.73 (m, 1 H) 7.74 - 7.81 (s, 1 H) 8.02 - 8.10 (m, 1 H); LC-MS, MS *m/z* 749 (M^+ +H).

Compuesto 205B: LC-MS, MS *m/z* 749 (M^+ +H).

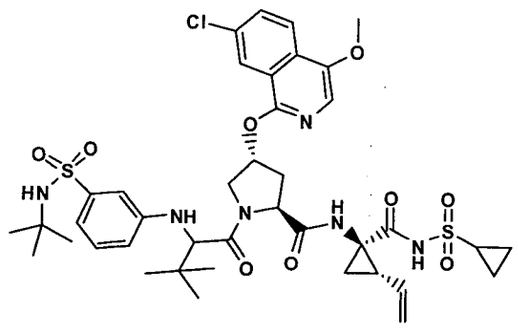
Isómeros del compuesto 206:

N-(3-(terc-Butilsulfamoil)fenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

N-(3-(terc-Butilsulfamoil)fenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

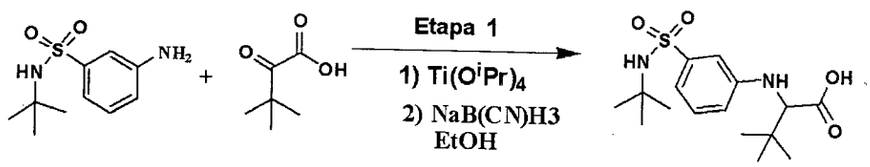
000690

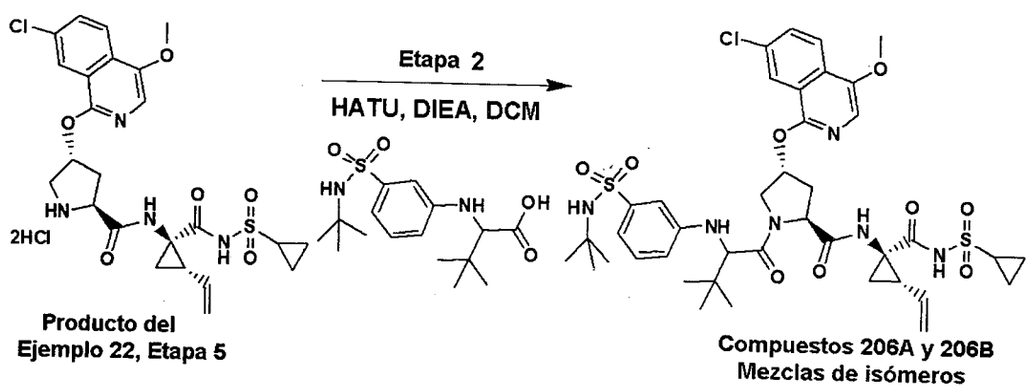
Ejemplo 206: Preparación de los Compuestos 206A y 206B



Compuestos 206A y 206B

Esquema de Reacción 1





Etapa 1:

A una mezcla de 3-amino-N-terc-Butilbencensulfonamida (180 mg, 0.788 mmol) y ácido 3,3-dimetil-2-oxobutanoico (308 mg, 2.365 mmol) en un RBF 100 mL a TA se le agregó

006671

tetraisopropoxititanio (2 ml) por medio de una pipeta. El color de la mezcla pronto cambió a un color canario característico. La solución se calentó a 75°C durante alrededor de 15 minutos y el color sigue siendo el mismo. La solución se diluyó con etanol absoluto (8 ml) a TA, seguido por la adición de 1.5X de cianotrihidroborato de sodio (245 mg, 3.90 mmol), y la mitad restante después que el burbujeo y la emisión de sonidos se terminó. El color de la solución se hizo más claro. La solución se mezcló con 4 mL de agua, formando una suspensión, el PPT blanco se removió por centrifugado. El material orgánico se extrajo en acetato de etilo, y la fase orgánica se secó sobre Na_2SO_4, se filtró, y evaporó hasta secarse. Un aceite amarillo se obtuvo y se usó en la siguiente etapa sin purificación adicional. LC-MS, MS *m/z* 343 (M^+ +H).

Etapa 2:

A la solución amarilla de ácido 2-(3-(N-terc-Butilsulfamoil)fenilamino)-3,3-dimetilbutanoico (0.065 g, 0.189 mmol etapa 1, ejemplo 206) y (2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-N-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropil)pirrolidin-2-carboxamida (0.101 g, 0.189 mmol, etapa 5, ejemplo 22) en CH_2Cl_2 a 0°C se le agregó HATU (0.144 g, 0.378 mmol) seguido por diisopropiletil amina

- 000612

(0.061 g, 0.473 mmol). Una solución color amarillo claro se formó después de la adición de la base. La mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con acetato de etilo (25 ml) y se lavó con agua (pH~6) y salmuera. El material orgánico se secó sobre sulfato de sodio, se filtró, se concentró, y el residuo se purificó por HPLC preparativa de fase inversa para dar dos productos separados con MS *m/z* idéntico como se observa por LCMS. El Compuesto 206A (0.025 g, 15.4% de rendimiento) fue el primero de los dos isómeros en eluir por HPLC preparativa de fase inversa. El Compuesto 206B (0.013 g, 8% de rendimiento) fue el segundo de los dos isómeros a eluir por HPLC preparativa de fase inversa.

Compuesto 206A: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 0.97 - 1.06 (m, 9 H) 1.06 - 1.18 (m, 11 H) 1.18 - 1.29 (m, 2 H) 1.36 - 1.46 (m, 1 H) 1.86 (dd, *J*=8.06, 5.54 Hz, 1 H) 2.18 - 2.29 (m, 2 H) 2.55 (m, 1H) 2.95 (ddd, *J*=12.84, 8.06, 4.78 Hz, 1 H) 3.95 - 4.01 (s, 3 H) 4.02 - 4.12 (m, 2 H) 4.26 (d, *J*=12.09 Hz, 1 H) 4.51 (dd, *J*=10.07, 7.05 Hz, 1 H) 5.10 (dd, *J*=10.32, 1.51 Hz, 1 H) 5.24 - 5.32 (m, 1 H) 5.73 (m, 2 H) 6.52 (m, 1 H) 6.62 (m, 1 H) 6.86 (m, 1 H) 7.15 (d, *J*=2.01 Hz, 1 H) 7.50 - 7.56 (s, 1 H) 7.62 - 7.70 (m, 1 H) 7.83 (s, 1 H) 8.01 - 8.09 (m, 1 H); LC-MS, MS *m/z* 859 (M^+ +H).

Compuesto 206B: LC-MS, MS *m/z* 859 (M^+ +H).

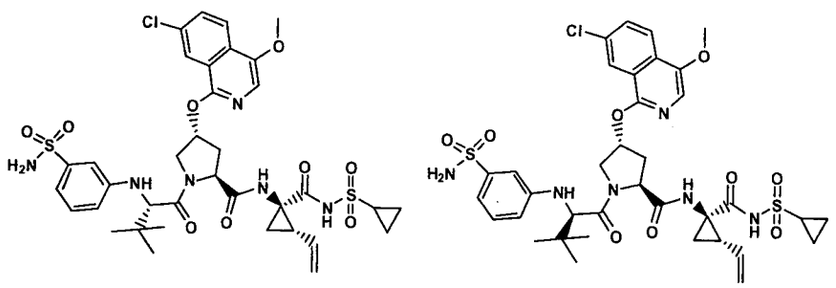
- 00063

Isómeros del compuesto 207:

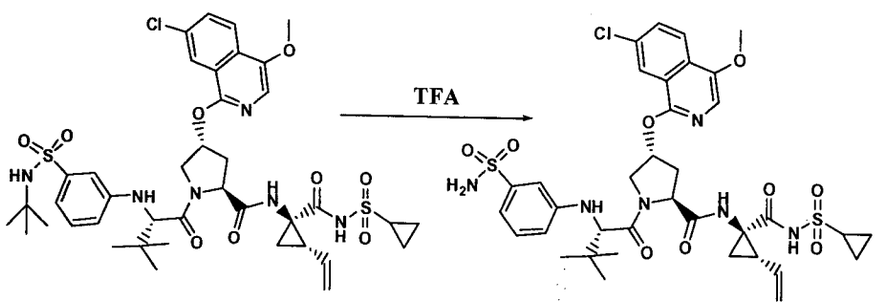
3-metil-N-(3-sulfamoilfenil)-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

3-metil-N-(3-sulfamoilfenil)-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

Ejemplo 207: Preparación de Compuestos 207A y 207B



Compuestos 207A y 207B



(2S,4R)-1-((S)-2-(3-(N-terc-Butilsulfamoil)fenilamino)-3,3-dimetilbutanoil)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-

N-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropil)pirrolidin-2-carboxamida (compuesto 206A) se disolvió en 1 ml de ácido 2,2,2-trifluoroacético a 25°C. La mezcla se agitó durante la noche. El TFA se removió y el residuo se purificó por HPLC preparativa. El Compuesto 207A se obtuvo así como un polvo blanco (0.012 g, 64% de rendimiento). ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.05 - 1.14 (m, 11 H) 1.19 - 1.29 (m, 2 H) 1.41 (dd, *J*=9.44, 5.41 Hz, 1 H) 1.87 (dd, *J*=8.18, 5.41 Hz, 1 H) 2.17 - 2.26 (m, 2 H) 2.52 (dd, *J*=13.85, 7.05 Hz, 1 H) 2.95 (ddd, *J*=12.78, 8.12, 4.78 Hz, 1 H) 3.96 - 4.02 (s, 3 H) 4.02 - 4.10 (m, 2 H) 4.30 (d, *J*=12.09 Hz, 1 H) 4.52 (dd, *J*=10.07, 7.05 Hz, 1 H) 5.11 (dd, *J*=10.32, 1.51 Hz, 1 H) 5.24 - 5.32 (m, 1 H) 5.69 - 5.79 (m, 2 H) 6.49 - 6.55 (m, 1 H) 6.60 (t, *J*=7.81 Hz, 1 H) 6.87 (d, *J*=7.55 Hz, 1 H) 7.16 (s, 1 H) 7.51 - 7.55 (s, 1 H) 7.67 (dd, *J*=8.94, 2.14 Hz, 1 H) 7.85 (d, *J*=2.01 Hz, 1 H) 8.07 (d, *J*=8.81 Hz, 1 H); LC-MS, MS *m/z* 803 (M^+ +H).

Compuesto 207B se hizo del compuesto 206B por el mismo procedimiento como se usó por la preparación del compuesto 207A. LC-MS, MS *m/z* 803 (M^+ +H).

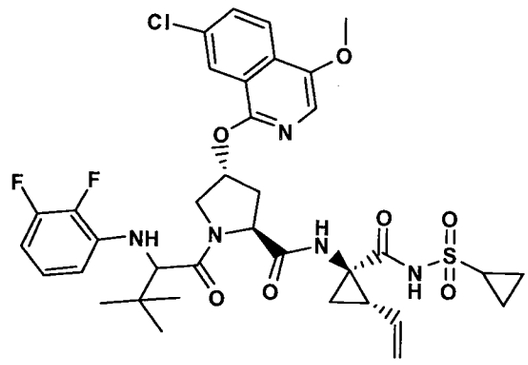
Isómeros del compuesto 208:

N-(2,3-difluorofenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

0006 5

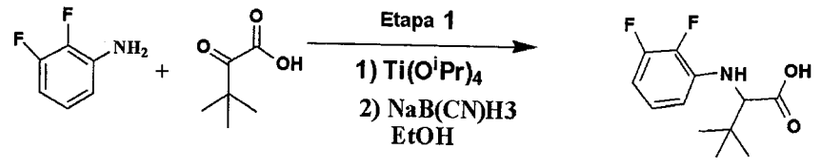
N-(2,3-difluorofenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

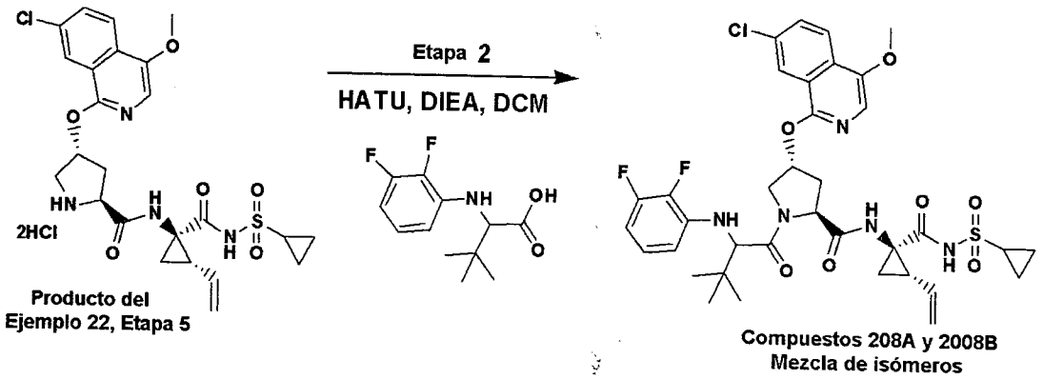
Ejemplo 208: Preparación de Compuestos 208A y 208B



Compuestos 208A y 208B

Esquema de Reacción 1





00696

Etapa 1:

A una mezcla de 2,3-difluoroanilina (180 mg, 1.394 mmol) y ácido 3,3-dimetil-2-oxobutanoico (500 mg, 3.84 mmol) en un RBF 100 mL a TA se le agregó tetraisopropoxititanio (2 ml) por medio de una pipeta. El color de la mezcla pronto cambió a un color canario característico. La solución se calentó a 75°C durante alrededor de 15 minutos y el color sigue siendo el mismo. La solución se diluyó con etanol absoluto (8 ml) a TA, seguido por la adición de 1.5X de cianotrihidroborato de sodio (245 mg, 3.90 mmol), y la mitad restante después del burbujeo y la emisión de sonidos se terminó. El color de la solución se hizo más claro. La solución se mezcló con 4 mL de agua, formando una suspensión, el PPT blanco se removió por centrifugado. El material orgánico se extrajo en acetato de etilo, y la fase orgánica se secó sobre Na_2SO_4, se filtró y evaporó hasta secarse. Un aceite amarillo se obtuvo y se usó en la siguiente etapa sin purificación adicional. LC-MS, MS *m/z* 244 (M^+ +H).

Etapa 2:

A la solución amarilla de ácido 2-(2,3-difluorofenilamino)-3,3-dimetilbutanoico (0.046 g, 0.189 mmol etapa 1, ejemplo 208) y (2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-N-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-

00067

vinilciclopropil)pirrolidin-2-carboxamida (0.101 g, 0.189 mmol, etapa 5, ejemplo 22) en CH_2Cl_2 a 0°C se le agregó HATU (0.144 g, 0.378 mmol) seguido por diisopropiletil amina (0.061 g, 0.473 mmol). Una solución color amarillo claro se formó después de la adición de la base. La mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con acetato de etilo (25 ml), y el material orgánico se lavó con agua (pH~6) y salmuera. El material orgánico se secó sobre sulfato de sodio, se filtró, se concentró, y se purificó por HPLC preparativa de fase inversa para dar dos productos separados con MS *m/z* idéntico como se observa por LCMS. El Compuesto 208A (0.026 g, 18.4% de rendimiento) fue el primero de los dos isómeros a eluir por HPLC preparativa de fase inversa. El Compuesto 208B (0.012 g, 9% de rendimiento) fue el segundo de los dos isómeros a eluir por HPLC preparativa de fase inversa.

Compuesto 208A: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.03 - 1.12 (m, 11 H) 1.21 - 1.26 (m, 2 H) 1.41 (dd, *J*=9.44, 5.41 Hz, 1 H) 1.86 (dd, *J*=8.06, 5.54 Hz, 1 H) 2.17 - 2.28 (m, 2 H) 2.53 (dd, *J*=13.60, 7.05 Hz, 1 H) 2.94 (ddd, *J*=12.72, 8.06, 4.66 Hz, 1 H) 3.96 - 4.02 (m, 4 H) 4.02 - 4.07 (s, 1 H) 4.27 (d, *J*=12.09 Hz, 1 H) 4.53 (dd, *J*=10.45, 7.18 Hz, 1 H) 5.10 (d, *J*=10.32 Hz, 1 H) 5.28 (d, *J*=17.12 Hz, 1 H) 5.68 - 5.75 (m, 1

000638

H) 5.77 (s, 1 H) 6.02 - 6.10 (m, 2 H) 6.21 - 6.28 (m, 1 H) 7.55 (s, 1 H) 7.68 (dd, *J*=8.81, 2.01 Hz, 1 H) 7.76 (d, *J*=2.01 Hz, 1 H) 8.09 (d, *J*=8.81 Hz, 1 H); LC-MS, MS *m/z* 760 (M^+ +H).

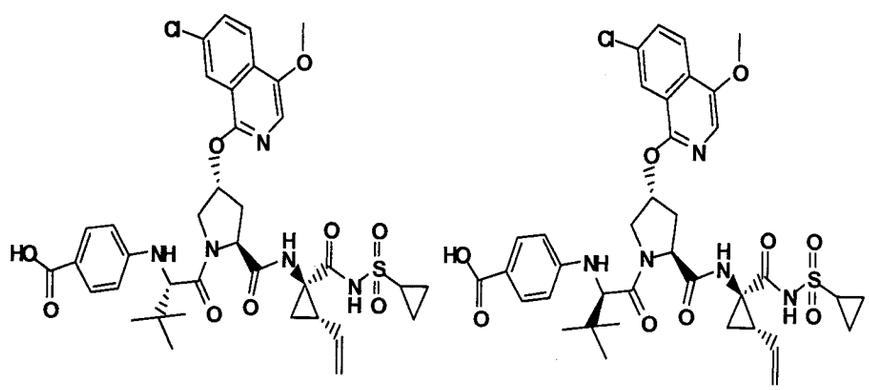
Compuesto 208B: LC-MS, MS *m/z* 760 (M^+ +H).

Isómeros del compuesto 209:

N-(4-carboxifenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

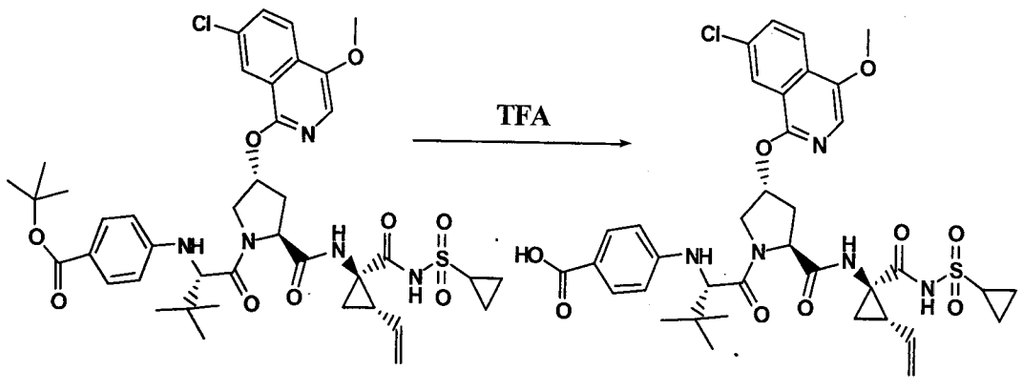
N-(4-carboxifenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

Ejemplo 209: Preparación de Compuestos 209A y 209B



Compuestos 209A y 209B

606639



El 4-((S)-1-((2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-2-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropilcarbamoil)pirrolidin-1-il)-3,3-dimetil-1-oxobutan-2-ilamino)benzoato de terc-butilo (20 mg, 0.024 mmol, compuesto 204A) se disolvió en CH_2Cl_2 (2 ml) a 25°C. TFA (0.019 ml, 0.243 mmol) se agregó gota a gota. La mezcla se agitó durante la noche. El TFA se removió y el residuo se purificó por HPLC preparativa. El Compuesto 209A se obtuvo así como un polvo blanco (0.018 g, 95% de rendimiento). ^1H RMN (400 MHz, CD_3OD) δ ppm 1.05 - 1.14 (m, 11 H) 1.18 - 1.29 (m, 2 H) 1.42 (dd, *J*=9.32, 5.29 Hz, 1 H) 1.87 (dd, *J*=8.06, 5.54 Hz, 1 H) 2.19 - 2.28 (m, 2 H) 2.55 (dd, *J*=13.72, 7.18 Hz, 1 H) 2.95 (ddd, *J*=12.78, 8.12, 4.78 Hz, 1 H) 3.96 - 4.03 (m, 4 H) 4.06 - 4.10 (s, 1 H) 4.36 (d, *J*=12.34 Hz, 1 H) 4.58 (dd, *J*=10.32, 7.05 Hz, 1 H) 5.07 - 5.15 (m, 1 H) 5.29 (d, *J*=17.12 Hz, 1 H) 5.68 - 5.78 (m, 2 H) 6.38 (d,

000610

J=8.81 Hz, 2 H) 7.22 (d, *J*=8.81 Hz, 2 H) 7.51 (s, 1 H) 7.61 (dd, *J*=8.81, 2.27 Hz, 1 H) 7.79 (d, *J*=2.01 Hz, 1 H) 8.04 (d, *J*=9.06 Hz, 1 H); LC-MS, MS *m/z* 768 (M^+ +H).

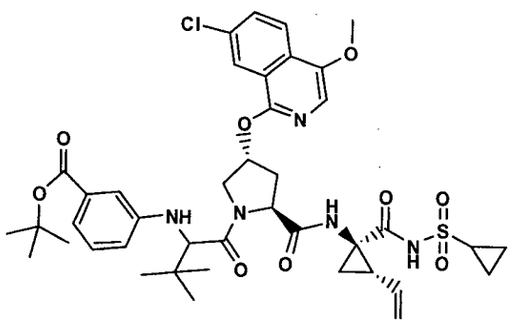
Compuesto 209B se hizo del compuesto 204B por el mismo procedimiento como se usó por la preparación del compuesto 209A. LC-MS, MS *m/z* 768 (M^+ +H).

Isómeros del compuesto 210:

N-(3-(terc-Butoxicarbonil)fenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

N-(3-(terc-Butoxicarbonil)fenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

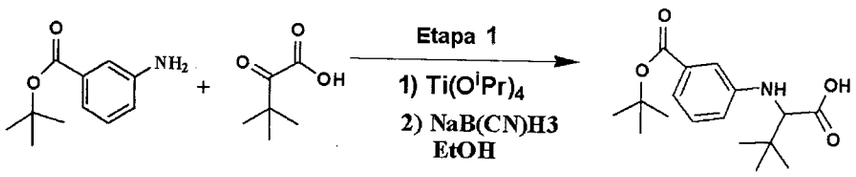
Ejemplo 210: Preparación de Compuestos 210A y 210B

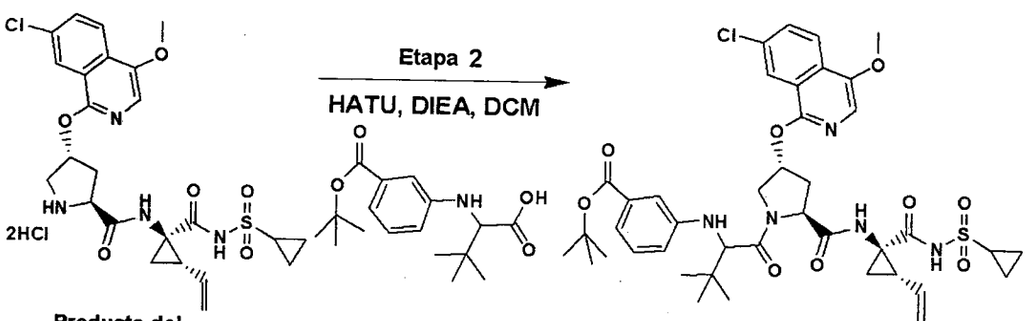


Compuestos 210A y 210B

000611

Esquema de reacción 1





Producto del Ejemplo 22, Etapa 5

Compuestos 210A y 210B Mezcla de isómeros

Etapa 1:

A una mezcla de 3-amino-N-terc-Butilbencensulfonamida (180 mg, 0.788 mmol) y ácido 3,3-dimetil-2-oxobutanoico (308 mg, 2.365 mmol) en un RBF 100 mL a TA se le agregó tetraisopropoxititanio (2 ml) por medio de una pipeta. El color de la mezcla pronto cambió a un color canario característico. La solución se calentó a 75°C durante alrededor de 15 minutos y el color sigue siendo el mismo. La solución se diluyó con etanol absoluto (8 ml) a TA, seguido por la adición de 1.5X de cianotrihidroborato de sodio (245 mg, 3.90 mmol), y la mitad restante después del burbujeo y la emisión de sonidos se terminó. El color de la solución se

000612

hizo más claro. La solución se mezcló con 4 mL de agua, formando una suspensión, y el PPT blanco se removió por centrifugado. El material orgánico se extrajo en acetato de etilo, y la fase orgánica se secó sobre Na_2SO_4, se filtró, y evaporó hasta secarse. Un aceite amarillo se obtuvo y se usó en la siguiente etapa sin purificación adicional. LC-MS, MS *m/z* 308 (M^+ +H).

Etapa 2:

A la solución amarilla de ácido 2-(3-(N-terc-Butilsulfamoil)fenilamino)-3,3-dimetilbutanoico (0.065 g, 0.189 mmol etapa 1, ejemplo 210) y (2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-N-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropil)pirrolidin-2-carboxamida (0.101 g, 0.189 mmol, etapa 5, ejemplo 22) en CH_2Cl_2 a 0°C se le agregó HATU (0.144 g, 0.378 mmol) seguido por diisopropiletil amina (0.061 g, 0.473 mmol). Una solución color amarillo claro se formó después de la adición de la base. La mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con acetato de etilo (25 ml) y se lavó con agua (pH~6) y salmuera. El material orgánico se secó sobre sulfato de sodio, se filtró, se concentró, y se purificó por HPLC preparativa de fase inversa para dar dos productos separados con MS m/z idénticos como se observa

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por LCMS. El Compuesto 210A (0.021 g, 13.5% de rendimiento) fue el primero de los dos isómeros a eluir por HPLC preparativa de fase inversa. El Compuesto 210B (0.020 g, 13.3% de rendimiento) fue el segundo de los dos isómeros a eluir por HPLC preparativa de fase inversa.

Compuesto 210A: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.04 - 1.14 (m, 11 H) 1.19 - 1.31 (m, 2 H) 1.38 - 1.48 (m, 9 H) 1.50 - 1.60 (m, 1 H)) 1.86 (m, 1 H) 2.15 - 2.24 (m, 2 H) 2.47 (m, 1 H) 2.94 (m, 1 H) 3.92 - 4.04 (m, 4 H) 4.11 (s, 1 H) 4.18 (m, 1 H) 4.46 (m, 1 H) 5.06 - 5.15 (m, 1 H) 5.29 (m, 1 H) 5.67 - 5.77 (m, 2 H) 6.54 (m, 1 H) 6.75 (ddd, *J*=19.83, 7.62, 2.01 Hz, 1 H) 6.89 (m, 1 H) 7.31 (s, 1 H) 7.49 (s, 1 H) 7.59 - 7.68 (m, 2 H) 8.04 (t, *J*=8.44 Hz, 1 H); LC-MS, MS *m/z* 824 (M^+ +H).

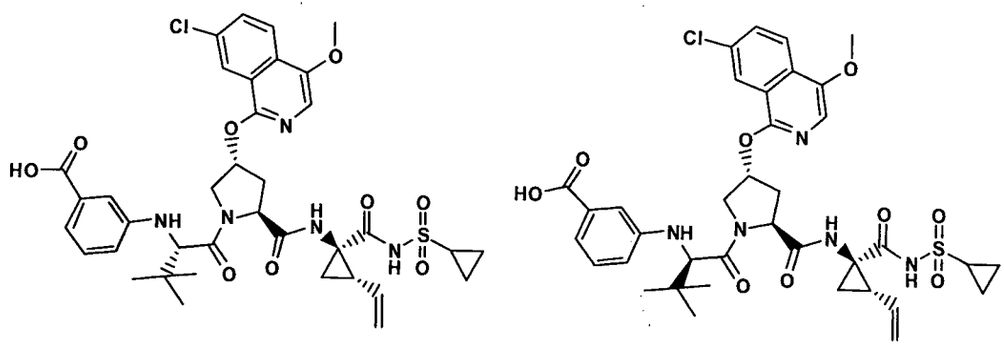
Compuesto 210B: LC-MS, MS *m/z* 824 (M^+ +H).

Isómeros del compuesto 211:

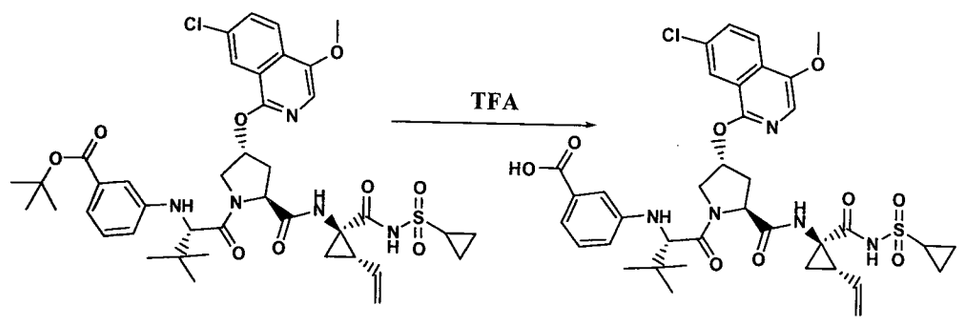
N-(3-carboxifenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

N-(3-carboxifenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

Ejemplo 211: Preparación de Compuestos 211A y 211B



Compuestos 211A y 211B



El 3-((S)-1-((2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-2-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropilcarbamoil)pirrolidin-1-il)-3,3-dimetil-1-oxobutan-2-ilamino)benzoato de terc-butilo (20 mg, 0.024 mmol, compuesto 210A) se disolvió en CH_2Cl_2 (2 ml) a 25°C. El TFA (0.019 ml, 0.243 mmol) se agregó gota a gota. La mezcla se agitó durante la noche. El TFA se removió y el residuo se purificó por HPLC preparativa. El Compuesto 211A se obtuvo como un polvo blanco (0.005g, 26.8% de rendimiento). ^1H RMN (400 MHz, CD_3OD)

δ ppm 1.04 - 1.14 (m, 11 H) 1.19 - 1.30 (m, 2 H) 1.38 - 1.46 (m, 1 H) 1.86 (dd, *J*=8.18, 5.41 Hz, 1 H) 2.21 (ddd, *J*=13.91, 9.76, 3.78 Hz, 2 H) 2.48 (dd, *J*=13.72, 6.92 Hz, 1 H) 2.95 (ddd, *J*=12.84, 8.06, 4.78 Hz, 1 H) 3.94 - 4.02 (m, 5 H) 4.15 (d, *J*=12.09 Hz, 1 H) 4.46 - 4.56 (m, 1 H) 5.10 (dd, *J*=10.32, 1.51 Hz, 1 H) 5.28 (dd, *J*=17.25, 1.39 Hz, 1 H) 5.68 - 5.78 (m, 2 H) 6.48 - 6.56 (m, 1 H) 6.63 (dd, *J*=7.81, 2.01 Hz, 1 H) 6.84 (d, *J*=7.81 Hz, 1 H) 7.17 - 7.28 (m, 1 H) 7.42 - 7.49 (m, 1 H) 7.62 (td, *J*=8.56, 2.01 Hz, 2 H) 7.97 - 8.05 (m, 1 H); LC-MS, MS *m/z* 768 (M^+ +H).

Compuesto 211B se hizo del compuesto 210B por el mismo procedimiento como se usó por la preparación del compuesto 211A. LC-MS, MS *m/z* 768 (M^+ +H).

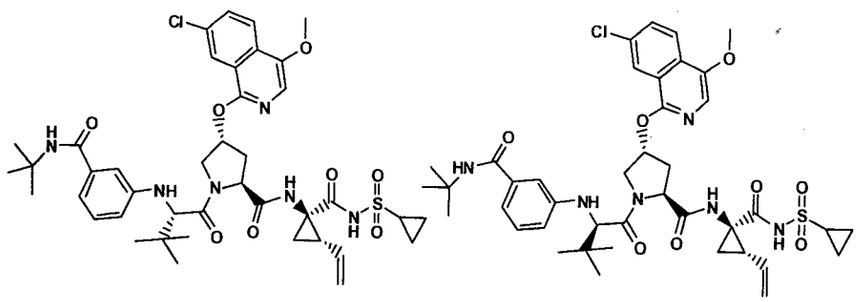
Isómeros del compuesto 212:

N-(3-(terc-Butilcarbamoil)fenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

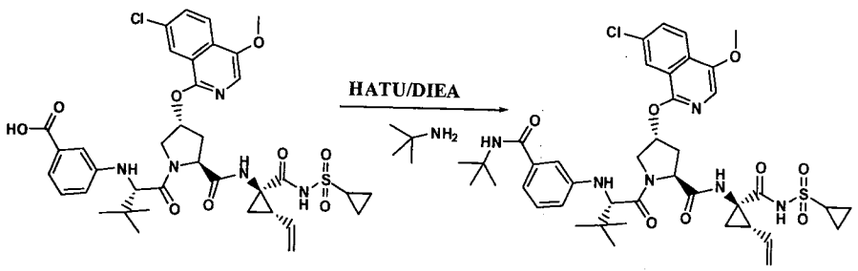
N-(3-(terc-Butilcarbamoil)fenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

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Ejemplo 212: Preparación de Compuestos 212A y 212B



Compuestos 212A y 212B



A la solución de ácido 3-((S)-1-((2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-2-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropilcarbamoil)pirrolidin-1-il)-3,3-dimetil-1-oxobutan-2-ilamino)benzoico (60 mg, 0.078 mmol, compuesto 211A) y 2-metilpropan-2-amina (11.42 mg, 0.156 mmol) en cloruro de metileno a 0°C se le agregó HATU (59.4 mg, 0.156 mmol) seguido por diisopropiletil amina (25.2 mg, 0.195 mmol). Una solución color amarillo claro se formó después de la adición de la base. La mezcla se agitó a temperatura ambiente durante dos horas. La mezcla de reacción se diluyó con acetato de etilo (25 ml), se lavó con agua (pH~6) y salmuera. El material orgánico se secó

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sobre sulfato de sodio, se filtró y se concentró. Un aceite amarillo se obtuvo. La purificación por HPLC preparativa dio el Compuesto 212A como un polvo blanco (0.036g, 56% de rendimiento). ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.04 - 1.14 (m, 11 H) 1.23 - 1.34 (m, 11 H) 1.41 (ddd, *J*=14.73, 5.29, 5.16 Hz, 1 H) 1.86 (dd, *J*=8.18, 5.41 Hz, 1 H) 2.16 - 2.25 (m, 2 H) 2.48 (dd, *J*=13.72, 6.92 Hz, 1 H) 2.95 (ddd, *J*=12.84, 8.06, 4.78 Hz, 1 H) 3.97 - 4.00 (m, 3 H) 4.02 - 4.11 (m, 2 H) 4.26 (d, *J*=12.34 Hz, 1 H) 4.46 (dd, *J*=10.20, 6.92 Hz, 1 H) 5.10 (dd, *J*=10.20, 1.64 Hz, 1 H) 5.23 - 5.31 (m, 1 H) 5.68 - 5.78 (m, 2 H) 6.51 - 6.60 (m, 2 H) 6.69 - 6.78 (m, 1 H) 7.09 (d, *J*=2.01 Hz, 1 H) 7.50 - 7.55 (m, 1 H) 7.63 - 7.73 (m, 2 H) 8.07 (d, *J*=9.06 Hz, 1 H); LC-MS, MS *m/z* 823 (M^+ +H).

Compuesto 212B se hizo del compuesto 211B por el mismo procedimiento usado para la preparación del compuesto 212A. LC-MS, MS *m/z* 768 (M^+ +H).

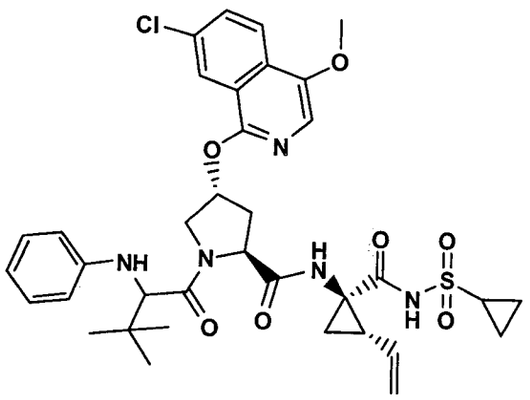
Isómeros del compuesto 213:

3-metil-N-fenil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

3-metil-N-fenil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-

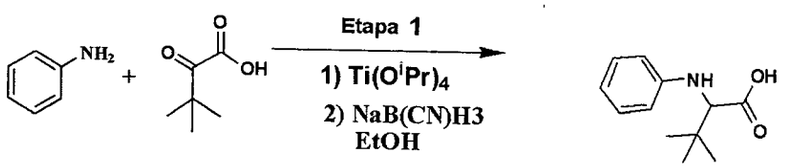
((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

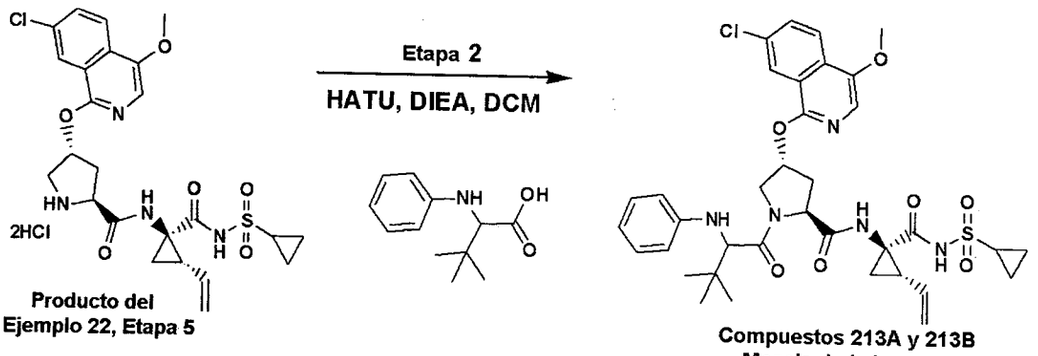
Ejemplo 213: Preparación de Compuestos 213A y 213B



Compuestos 213A y 213B

Esquema de reacción 1





Etapa 1:

A una mezcla de anilina (180 mg, 1.94 mmol) y ácido 3,3-dimetil-2-oxobutanoico (500 mg, 3.84 mmol) en un RBF 100 mL a TA se le agregó tetraisopropoxititanio (2 ml) por medio de una pipeta. El color de la mezcla pronto cambió a un color canario característico. La solución se calentó a 75°C durante alrededor de 15 minutos y el color sigue siendo el mismo. La solución se diluyó con etanol absoluto (8 ml) a TA, seguido por la adición de 1.5X de cianotrihidroborato de sodio (245 mg, 3.90 mmol), y la mitad restante después del burbujeo y la emisión de sonidos se terminó. El color de la solución se hizo más claro. La solución se mezcló con 4 mL de agua, formando una suspensión, y el PPT blanco se removió por centrifugado. El material orgánico se extrajo en acetato de etilo, y la fase orgánica se secó sobre Na_2SO_4, se filtró, y evaporó hasta secarse. Un aceite amarillo se obtuvo y se usó en la siguiente etapa sin purificación adicional. LC-MS, MS *m/z* 208 (M^+ +H).

Etapa 2:

A la solución amarilla de ácido 2-fenilamino-3,3-dimetilbutanoico (0.039 g, 0.189 mmol etapa 1, ejemplo 213) y (2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-N-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-

000620

vinilciclopropil)pirrolidin-2-carboxamida (0.101 g, 0.189 mmol, etapa 5, ejemplo 22) en CH_2Cl_2 a 0°C se le agregó HATU (0.144 g, 0.378 mmol) seguido por diisopropiletil amina (0.061 g, 0.473 mmol). Una solución color amarillo claro se formó después de la adición de la base. La mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con acetato de etilo (25 ml), se lavó con agua (pH~6) y salmuera. El material orgánico se secó sobre sulfato de sodio, se filtró, se concentró, y el residuo se purificó por HPLC preparativa de fase inversa para dar dos productos separados con MS m/z idénticos como se observa por LCMS. El Compuesto 213A (0.0032 g, 2.3% de rendimiento) fue el primero de los dos isómeros a eluir por HPLC preparativa de fase inversa. El Compuesto 213B (0.0035 g, 2.3% de rendimiento) fue el segundo de los dos isómeros a eluir por HPLC preparativa de fase inversa.

Compuesto 213A: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.01 - 1.10 (m, 2 H) 1.11 - 1.21 (m, 9 H) 1.21 - 1.32 (m, 2 H) 1.35 - 1.46 (m, 1 H) 1.87 (dd, *J*=8.18, 5.41 Hz, 1 H) 2.16 - 2.26 (m, 2 H) 2.49 (dd, *J*=13.85, 6.80 Hz, 1 H) 2.95 (ddd, *J*=12.84, 8.06, 4.78 Hz, 1 H) 3.94 - 4.02 (m, 4 H) 4.04 - 4.10 (m, 2 H) 4.46 (dd, *J*=10.70, 6.92 Hz, 1 H) 5.11 (dd, *J*=10.32, 1.51 Hz, 1

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H) 5.29 (dd, *J*=17.12, 1.26 Hz, 1 H) 5.67 - 5.78 (m, 2 H) 6.23 (t, *J*=7.30 Hz, 1 H) 6.58 - 6.63 (m, 2 H) 6.65 - 6.70 (m, 1 H) 7.49 - 7.56 (m, 1 H) 7.67 - 7.76 (m, 2 H) 8.11 (d, *J*=8.81 Hz, 1 H); LC-MS, MS *m/z* 724 (M^+ +H).

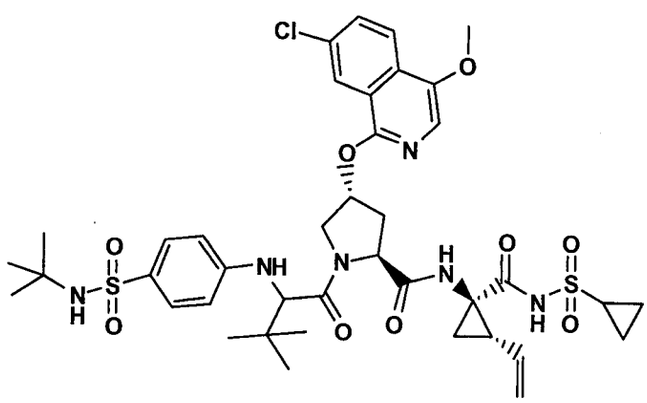
Compuesto 213B: LC-MS, MS *m/z* 724 (M^+ +H).

Isómeros del compuesto 214:

N-(4-(terc-Butilsulfamoil)fenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

N-(4-(terc-Butilsulfamoil)fenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

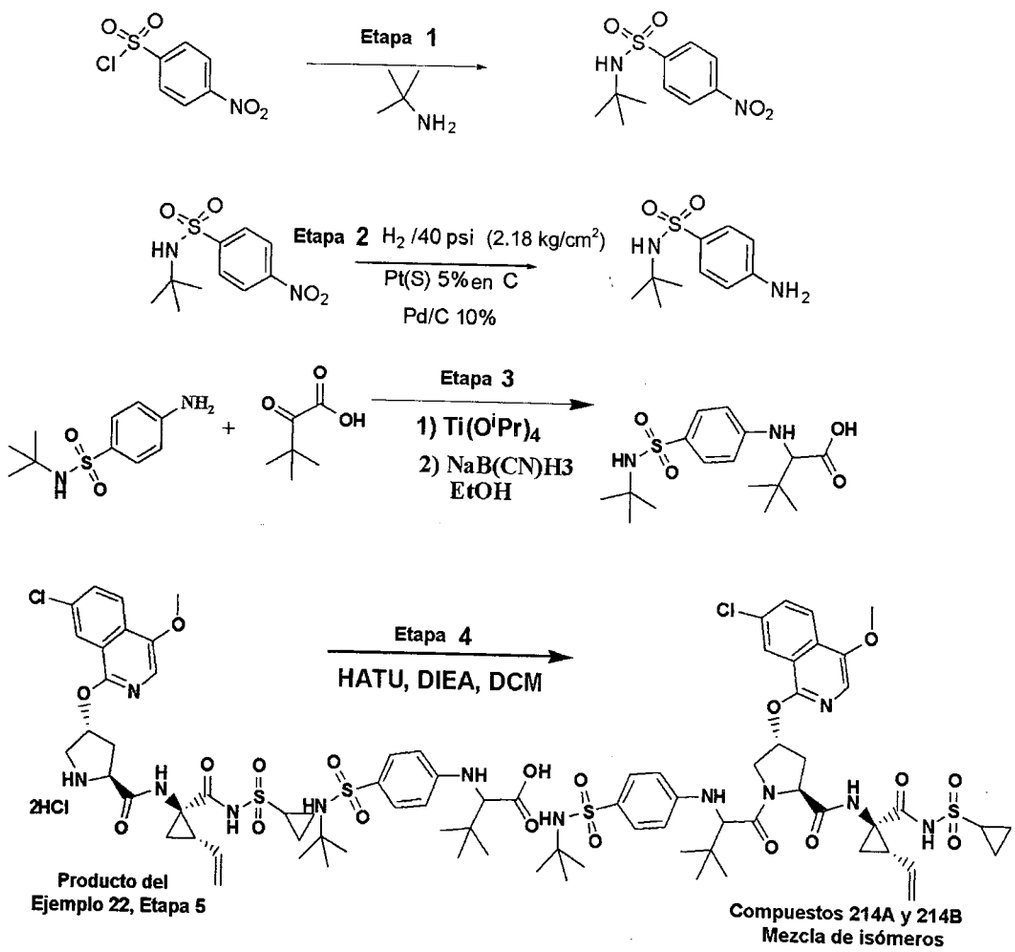
Ejemplo 214: Preparación de Compuestos 214A y 214B



Compuestos 214A y 214B

000622

Esquema de reacción 1



Etapa 1:

A cloruro de 4-nitrobencen-1-sulfonilo (500 mg, 2.256 mmol) en CH_2Cl_2 (20 ml) a 0-25°C se le agregó 2-metilpropan-2-amina (825 mg, 11.28 mmol). La mezcla se agitó durante el fin de semana. Una suspensión color café claro se formó. LC-MS, MS *m/z* 208 (M^+ +H). Se muestra que la reacción se completó. Se diluyó la mezcla de reacción con acetato de etilo (20 ml), se lavó con agua, salmuera. La capa orgánica

se secó y se concentró hasta secarse. El residuo se usó en la siguiente etapa sin purificación adicional.

Etapa 2:

La N-terc-Butil-4-nitrobencensulfonamida (500 mg, 1.936 mmol) de la etapa 1 se disolvió en metanol (30 ml). Pd-C se agregó bajo nitrógeno. El matraz se presurizó con gas de hidrógeno a 2.812 kg/cm^2 (40 PSI) y se agitó en un aparato de Parr durante la noche. El Pd-C se filtró por completo, se evaporó el solvente hasta secarse. El residuo se usó directamente en la siguiente etapa sin purificación adicional. LC-MS, MS *m/z* 229 (M^+ +H).

Etapa 3

A una mezcla de 4-amino-N-terc-Butilbencensulfonamida (180 mg, 0.788 mmol, de la etapa 2) y ácido 3,3-dimetil-2-oxobutanoico (308 mg, 2.4 mmol) en un RBF 100 mL a TA se le agregó tetraisopropoxititanio (2 ml), por medio de una pipeta. El color de la mezcla pronto cambió a un color canario característico. La solución se calentó a 75°C durante alrededor de 15 minutos y el color sigue siendo el mismo. La solución se diluyó con etanol absoluto (8 ml) a TA, seguido por la adición de 1.5X de cianotrihidroborato de sodio (245 mg, 3.90 mmol), y la mitad restante después que el burbujeo y la emisión de sonidos se terminó. El color de la

solución se hizo más claro. La solución se mezcló con 4 mL de agua, formando una suspensión, y el PPT blanco se removió por centrifugado. El material orgánico se extrajo en acetato de etilo, y la fase orgánica se secó sobre Na_2SO_4, se filtró, y evaporó hasta secarse. Un aceite amarillo se obtuvo y se usó directamente en la siguiente etapa sin purificación adicional. LC-MS, MS *m/z* 343 (M^+ +H).

Etapa 4:

A la solución amarilla de ácido 2-(4-(N-terc-Butilsulfamoil)fenilamino)-3,3-dimetilbutanoico (0.066 g, 0.189 mmol etapa 1, ejemplo 214) y (2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-N-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropil)pirrolidin-2-carboxamida (0.101 g, 0.189 mmol, etapa 5, ejemplo 22) en CH_2Cl_2 a 0°C se le agregó HATU (0.144 g, 0.378 mmol) seguido por diisopropiletil amina (0.061 g, 0.473 mmol). Una solución color amarillo claro se formó después de la adición de la base. La mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con acetato de etilo (25 ml) y se lavó con agua (pH~6) y salmuera. El material orgánico se secó sobre sulfato de sodio, se filtró, se concentró, y el residuo se purificó por HPLC preparativa de fase inversa para dar dos productos separados con MS m/z idénticos como se observa por LCMS. El Compuesto 214A (0.021 g, 13.0% de rendimiento) fue el

primero de los dos isómeros a eluir por HPLC preparativa de fase inversa. El Compuesto 214B (0.0022 g, 13.5.0% de rendimiento) fue el segundo de los dos isómeros a eluir por HPLC preparativa de fase inversa.

Compuesto 214A: ^{1}H RMN (500 MHz, CD_3OD) δ ppm 0.98 - 1.06 (m, 9 H) 1.08 - 1.16 (m, 12 H) 1.27 - 1.36 (m, 2 H) 1.46 (dd, *J*=9.46, 5.49 Hz, 1 H) 1.91 (dd, *J*=7.93, 5.49 Hz, 1 H) 2.24 - 2.33 (m, 2 H) 2.60 (d, *J*=6.10 Hz, 1 H) 2.96 - 3.01 (m, 1 H) 4.03 (s, 3 H) 4.09 - 4.13 (m, 2 H) 4.47 (d, *J*=11.90 Hz, 1 H) 4.63 (dd, *J*=10.22, 7.17 Hz, 1 H) 5.15 (d, *J*=10.38 Hz, 1 H) 5.30 - 5.35 (m, 1 H) 5.74 - 5.80 (m, 2 H) 6.52 (d, *J*=8.85 Hz, 2 H) 7.16 (d, *J*=8.85 Hz, 2 H) 7.60 (s, 1 H) 7.71 (dd, *J*=8.85, 2.14 Hz, 1 H) 7.98 (d, *J*=1.83 Hz, 1 H) 8.14 (d, *J*=8.85 Hz, 1 H); LC-MS, MS *m/z* 859 (M^+ +H).

Compuesto 214B: LC-MS, MS *m/z* 859 (M^+ +H).

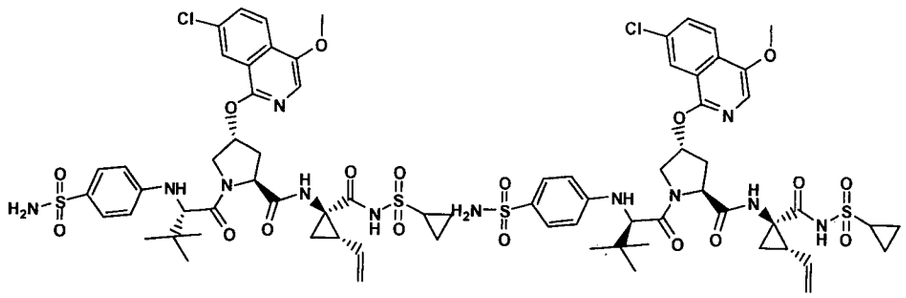
Isómeros del compuesto 215:

3-metil-N-(4-sulfamoilfenil)-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

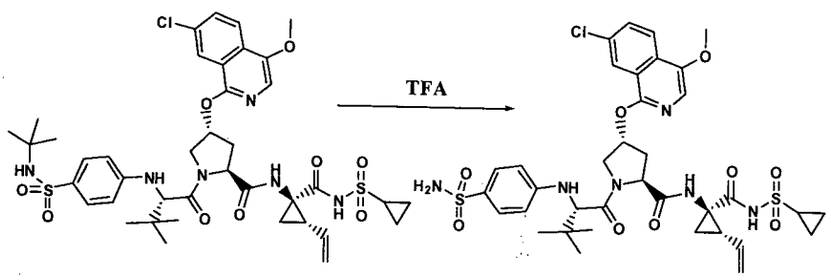
3-metil-N-(4-sulfamoilfenil)-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

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Ejemplo 215: Preparación de Compuestos 215A y 215B



Compuestos 215A y 215B



(2S,4R)-1-((S)-2-(3-(N-terc-Butilsulfamoil)fenilamino)-3,3-dimetilbutanoil)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-N-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropil)pirrolidin-2-carboxamida (20 mg, 0.024 mmol, compuesto 214A) se disolvió en TFA (2 ml) a 25 °C. La mezcla se agitó durante la noche. El TFA se removió y el residuo se purificó por HPLC preparativa. El Compuesto 215A se obtuvo así como un polvo blanco (0.013g, 69.5% de rendimiento). ^{1}H RMN (400 MHz, CD_3OD) δ 1.01 - 1.13 (m, 11 H) 1.27 - 1.37 (m, 2 H) 1.40 - 1.44 (m, 1 H) 1.87 (dd, *J*=8.18, 5.41 Hz, 1 H) 2.20 - 2.28 (m, 2 H) 2.57 (dd, *J*=13.72, 7.18 Hz, 1H) 2.92 - 2.98 (m, 1 H) 3.98 - 4.06 (m, 4 H) 4.09 (s, 1 H) 4.37 (d, *J*=12.09

000627

Hz, 1 H) 4.58 (dd, *J*=10.07, 7.05 Hz, 1 H) 5.11 (dd, *J*=10.32, 1.51 Hz, 1 H) 5.32 (m, 1 H) 5.69 - 5.78 (m, 2 H) 6.48 - 6.53 (m, 2 H) 7.19 - 7.26 (m, 2 H) 7.53 - 7.56 (s, 41H) 7.65 (dd, *J*=8.94, 2.14 Hz, 1 H) 7.90 (d, *J*=2.01 Hz, 1 H) 8.07 (d, *J*=8.81 Hz, 1 H); LC-MS, MS *m/z* 803 (M^+ +H).

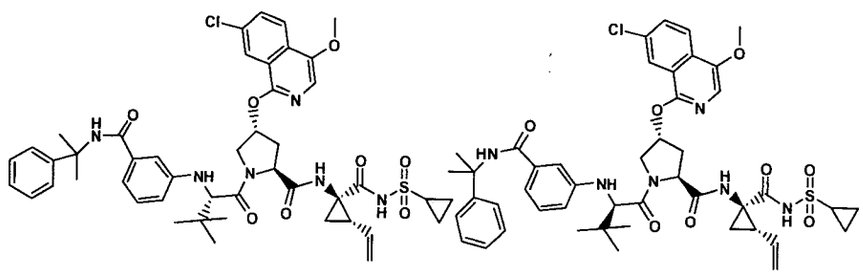
Compuesto 215B se hizo del compuesto 214B por el mismo procedimiento como se usó por la preparación del compuesto 215A. LC-MS, MS *m/z* 803 (M^+ +H).

Isómeros del compuesto 216:

3-metil-N-(3-((1-metil-1-feniletil)carbamoil)fenil)-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

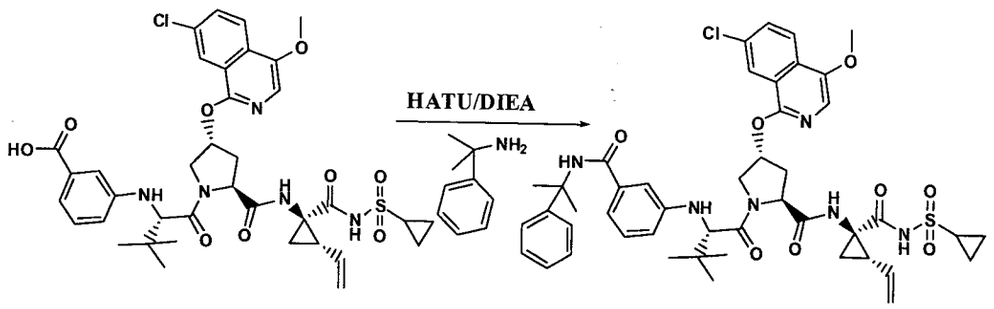
3-metil-N-(3-((1-metil-1-feniletil)carbamoil)fenil)-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

Ejemplo 216: Preparación de Compuestos 216A y 216B



Compuestos 216A y 216B

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A la solución de ácido 3-((S)-1-((2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-2-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropilcarbamoil)pirrolidin-1-il)-3,3-dimetil-1-oxobutan-2-ilamino)benzoico (60 mg, 0.078 mmol, compuesto 211A) y 2-fenilpropan-2-amina (21.12 mg, 0.156 mmol) en cloruro de metileno a 0°C se le agregó HATU (59.4 mg, 0.156 mmol) seguido por diisopropiletil amina (25.2 mg, 0.195 mmol). Una solución color amarillo claro se formó después de la adición de la base. La mezcla se agitó a temperatura ambiente durante dos horas. La mezcla de reacción se diluyó con acetato de etilo (25 ml) y se lavó con agua (pH~6) y salmuera. El material orgánico se secó sobre sulfato de sodio, se filtró y se concentró a un aceite amarillo. La purificación por preparativa dio el Compuesto 216A como un polvo blanco (0.056g, 81% de rendimiento). ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.03 - 1.13 (m, 11 H) 1.19 - 1.30 (m, 2 H) 1.41 (dd, J=9.44, 5.41 Hz, 1 H) 1.63 (d,

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J=5.79 Hz, 6 H) 1.85 (dd, *J*=8.06, 5.54 Hz, 1 H) 2.16 - 2.25 (m, 2 H) 2.49 (dd, *J*=13.72, 6.92 Hz, 1 H) 2.91 - 2.98 (m, 1 H) 3.99 (s, 3 H) 4.06 (dd, *J*=12.09, 3.53 Hz, 1 H) 4.10 (s, 1 H) 4.30 (d, *J*=12.09 Hz, 1 H) 4.46 (dd, *J*=10.07, 7.05 Hz, 1 H) 5.10 (dd, *J*=10.45, 1.64 Hz, 1 H) 5.25-5.29 (dd, J=17.12, *J*=1.51 Hz, 1H) 5.68 - 5.79 (m, 2 H) 6.52 - 6.59 (m, 2H) 6.82 (dd, *J*=6.42, 1.89 Hz, 1 H) 7.10 - 7.13 (m, 2 H) 7.17 - 7.23 (m, 2 H) 7.29 - 7.34 (m, 2 H) 7.54 (s, 1 H) 7.67 (dd, *J*=8.94, 2.14 Hz, 1 H) 7.74 (d, *J*=2.01 Hz, 1 H) 8.09 (d, *J*=8.81 Hz, 1 H); LC-MS, MS *m/z* 886 (M^+ +H).

Compuesto 216B se hizo del compuesto 211B por el mismo procedimiento como se usó por la preparación del compuesto 216A. LC-MS, MS *m/z* 886 (M^+ +H).

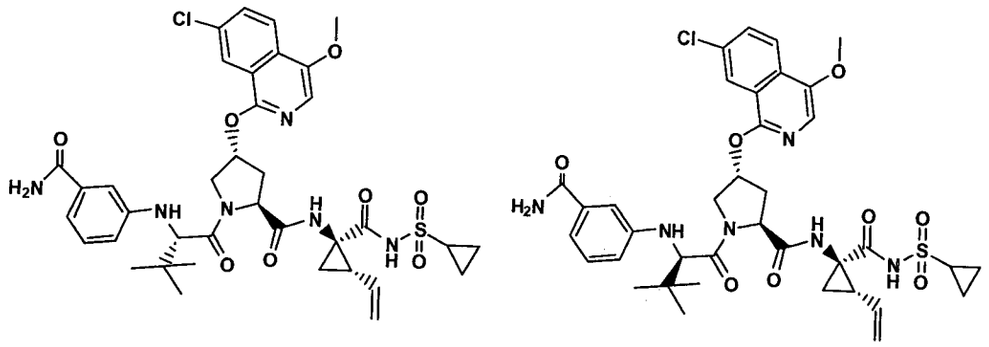
Isómeros del compuesto 217:

N-(3-carbamoilfenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

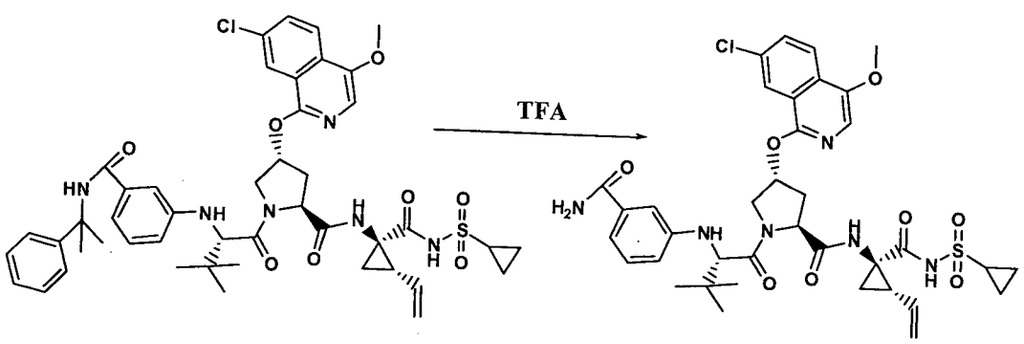
N-(3-carbamoilfenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

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Ejemplo 217: Preparación de Compuestos 217A y 217B



Compuestos 217A y 217B



(2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-N-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropil)-1-((S)-3,3-dimetil-2-(3-(2-fenilpropan-2-ilcarbamoil)fenilamino)butanoil)pirrolidin-2-carboxamida (50 mg, 0.056 mmol compuesto 216A) se disolvió en 1 ml de ácido 2,2,2-trifluoroacético a 25°C. La solución resultante se agitó durante la noche. El TFA se removió y el residuo se purificó por HPLC preparativa para dar el Compuesto 217A como un polvo blanco (0.023g, 46% de

rendimiento). ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.03 - 1.12 (m, 11 H) 1.19 - 1.30 (m, 2 H) 1.42 (dd, *J*=9.44, 5.41 Hz, 1 H) 1.87 (dd, *J*=8.06, 5.54 Hz, 1 H) 2.16 - 2.26 (m, 2 H) 2.49 (dd, *J*=13.72, 6.92 Hz, 1 H) 2.92 - 2.99 (m, 1 H) 3.96 - 4.05 (m, 5 H) 4.20 (t, *J*=11.83 Hz, 1 H) 4.51 (dd, *J*=10.58, 7.05 Hz, 1 H) 5.11 (dd, *J*=10.32, 1.76 Hz, 1 H) 5.29 (dd, *J*=17.25, 1.39 Hz, 1 H) 5.69 - 5.79 (m, 2 H) 6.56 - 6.66 (m, 2 H) 6.76 (d, *J*=7.55 Hz, 1 H) 7.11 (d, *J*=1.76 Hz, 1 H) 7.47 - 7.52 (s, 1 H) 7.66 (dd, *J*=8.81, 2.27 Hz, 1 H) 7.74 (d, *J*=1.76 Hz, 1 H) 8.07 (d, *J*=8.81 Hz, 1 H); LC-MS, MS *m/z* 767 (M^+ +H).

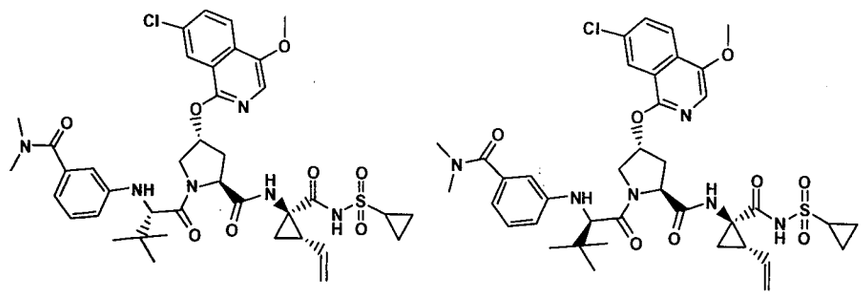
Compuesto 217B se hizo del compuesto 216B por el mismo procedimiento como se usó por la preparación del compuesto 217A. LC-MS, MS *m/z* 767 (M^+ +H).

Isómeros del compuesto 218:

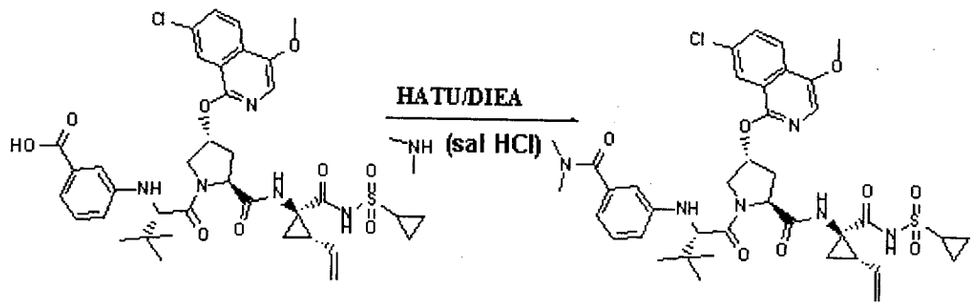
N-(3-(dimetilcarbamoil)fenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

N-(3-(dimetilcarbamoil)fenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

Ejemplo 218: Preparación de Compuestos 218A y 218B



Compuestos 218A y 218B



A la solución de ácido 3-((S)-1-((2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-2-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropilcarbamoil)pirrolidin-1-il)-3,3-dimetil-1-oxobutan-2-ilamino)benzoico (60 mg, 0.078 mmol, compuesto 211A) y dimetilaminaclorohidrato de (12.6 mg, 0.156 mmol) en cloruro de metileno a 0°C se le agregó HATU (59.4 mg, 0.156 mmol) seguido por diisopropiletil amina (25.2 mg, 0.195 mmol). Una solución color amarillo claro se formó después de la adición de la base. La mezcla se agitó a temperatura ambiente durante dos horas. La mezcla de reacción se diluyó con acetato de etilo (25 ml) y se lavó con agua (pH~6) y salmuera. El material orgánico se secó sobre

sulfato de sodio, se filtró y se concentró a un aceite amarillo. La purificación por HPLC preparativa proporcionó el Compuesto 218A como un polvo blanco (0.035g, 58% de rendimiento). ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.03 - 1.13 (m, 11 H) 1.16 - 1.28 (m, 2 H) 1.38 - 1.45 (m, 1 H) 1.86 (dd, *J*=8.18, 5.41 Hz, 1 H) 2.18 - 2.27 (m, 2 H) 2.51 (dd, *J*=13.72, 6.92 Hz, 1 H) 2.77 - 2.87 (m, 3 H) 2.91 - 3.00 (m, 4 H) 3.96 - 4.07 (m, 5 H) 4.23 (d, *J*=12.34 Hz, 1 H) 4.48 (dd, *J*=10.32, 7.05 Hz, 1 H) 5.11 (dd, *J*=10.32, 1.51 Hz, 1 H) 5.28 (dd, *J*=17.12, 1.51 Hz, 1 H) 5.69 - 5.79 (m, 2 H) 6.30 - 6.36 (m, 1 H) 6.47 - 6.54 (m, 2 H) 6.76 (d, *J*=1.26 Hz, 1 H) 7.52 - 7.56 (m, 1 H) 7.68 (dd, *J*=8.94, 2.14 Hz, 1 H) 7.81 (d, *J*=2.01 Hz, 1 H) 8.04 - 8.11 (m, 1 H); LC-MS, MS *m/z* 795 (M^+ +H).

Compuesto 218B se hizo del compuesto 211B por el mismo procedimiento como se usó por la preparación del compuesto 218A. LC-MS, MS *m/z* 795 (M^+ +H).

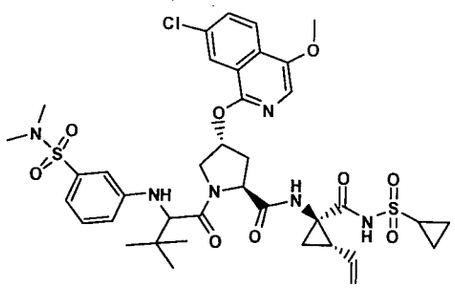
Isómeros del compuesto 219:

N-(3-(dimetilsulfamoil)fenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

N-(3-(dimetilsulfamoil)fenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

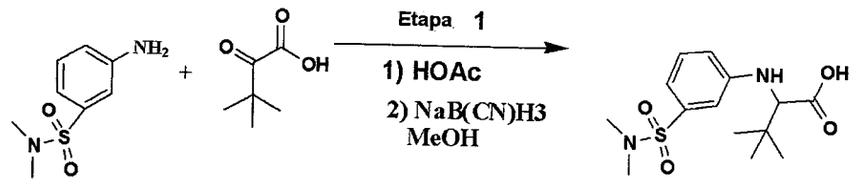
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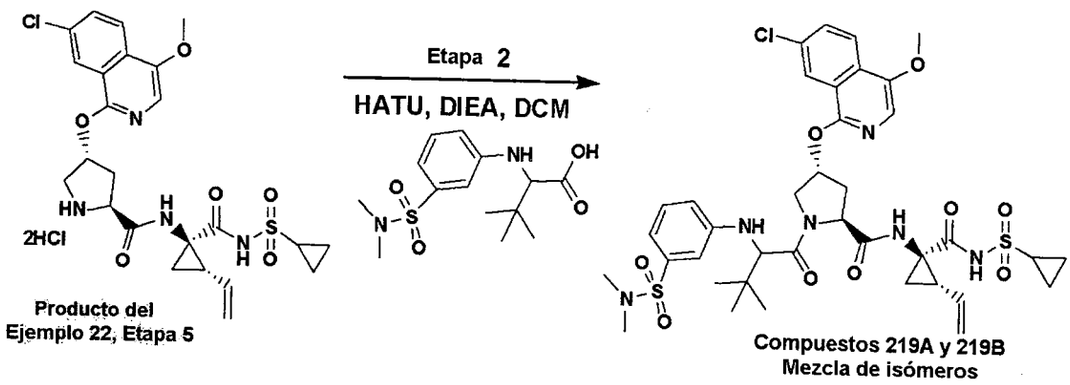
Ejemplo 219: Preparación de Compuestos 219A y 219B



Compuestos 219A y 219B

Esquema de reacción 1





Etapa 1:

A una mezcla de 3-amino-N,N-dimetilbencensulfonamida (203 mg, 1.014 mmol) y ácido 3,3-dimetil-2-oxobutanoico (264 mg, 2.027 mmol)) en un RBF 100 mL a TA se le agregó ácido acético (2 ml,) por medio de una pipeta. El color de la mezcla pronto cambió a un color canario característico. La solución se

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calentó a 75°C durante alrededor de 120 minutos y el color sigue siendo el mismo. La solución se diluyó con metanol (2 ml) a TA, seguido por la adición de 1.5X de cianotrihidroborato de sodio (245 mg, 3.90 mmol), y la mitad restante después que el burbujeo y la emisión de sonidos se terminó. El color de la solución se hizo más claro. Se agregó 30 ml de agua a la mezcla, luego se extrajo esto con 10 ml de acetato de etilo (ajuste de pH a 4). Luego el material orgánico se lavó por bicarbonato de sodio a pH = 8. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo aceitoso se secó bajo alto vacío. Un aceite amarillo se obtuvo y se usó directamente en la siguiente etapa sin purificación adicional. LC-MS, MS *m/z* 315 (M^+ +H).

Etapa 2:

A la solución amarilla de ácido 2-(3-(N,N-dimetilsulfamoil)fenilamino)-3,3-dimetilbutanoico (59.4 mg, 0.189 mmol, etapa 1, ejemplo 219) y (2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-N-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropil)pirrolidin-2-carboxamida (0.150 g, 0.28 mmol, etapa 5, ejemplo 22) en CH_2Cl_2 a 0°C se le agregó HATU (0.144 g, 0.378 mmol) seguido por diisopropiletil amina (0.061 g, 0.473 mmol). Una solución color amarillo claro se formó después de la adición de la base. La mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con acetato de etilo (25 ml) y se

lavó con agua (pH~6) y salmuera. El material orgánico se secó sobre sulfato de sodio, se filtró, se concentró, y el residuo se purificó por HPLC preparativa de fase inversa para dar dos productos separados con MS m/z idénticos como se observa por LCMS. El Compuesto 219A (0.062 g, 39.5% de rendimiento) fue el primero de los dos isómeros a eluir por HPLC preparativa de fase inversa. El Compuesto 219B (0.038 g, 24.2% de rendimiento) fue el segundo de los dos isómeros a eluir por HPLC preparativa de fase inversa.

Compuesto 219A: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.02 - 1.12 (m, 9 H) 1.17 - 1.20 (m, 2 H) 1.22 - 1.29 (m, 2 H) 1.32 - 1.44 (m, 1 H) 1.87 (dt, *J*=8.25, 5.57 Hz, 1 H) 2.16 - 2.28 (m, 2 H) 2.46 - 2.57 (m, 7 H) 2.90 - 2.98 (m, 1 H) 3.96 - 4.00 (s, 3 H) 4.03 - 4.10 (m, 2 H) 4.30 (t, *J*=11.96 Hz, 1 H) 4.47 - 4.58 (m, 1 H) 5.10 (dd, *J*=10.32, 1.76 Hz, 1 H) 5.29 (ddd, *J*=17.12, 7.93, 1.39 Hz, 1 H) 5.68 - 5.79 (m, 2 H) 6.55 - 6.67 (m, 3 H) 7.02 (s, 1 H) 7.50 - 7.55 (m, 1 H) 7.63 - 7.69 (m, 1 H) 7.81 (d, *J*=2.01 Hz, 1 H) 8.02 - 8.09 (m, 1 H); LC-MS, MS *m/z* 831 (M^+ +H).

Compuesto 219B: LC-MS, MS *m/z* 831 (M^+ +H).

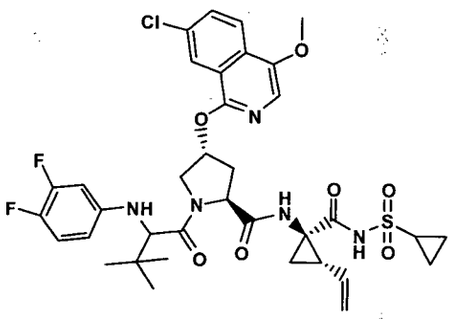
Isómeros del compuesto 220:

N-(3,4-difluorofenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

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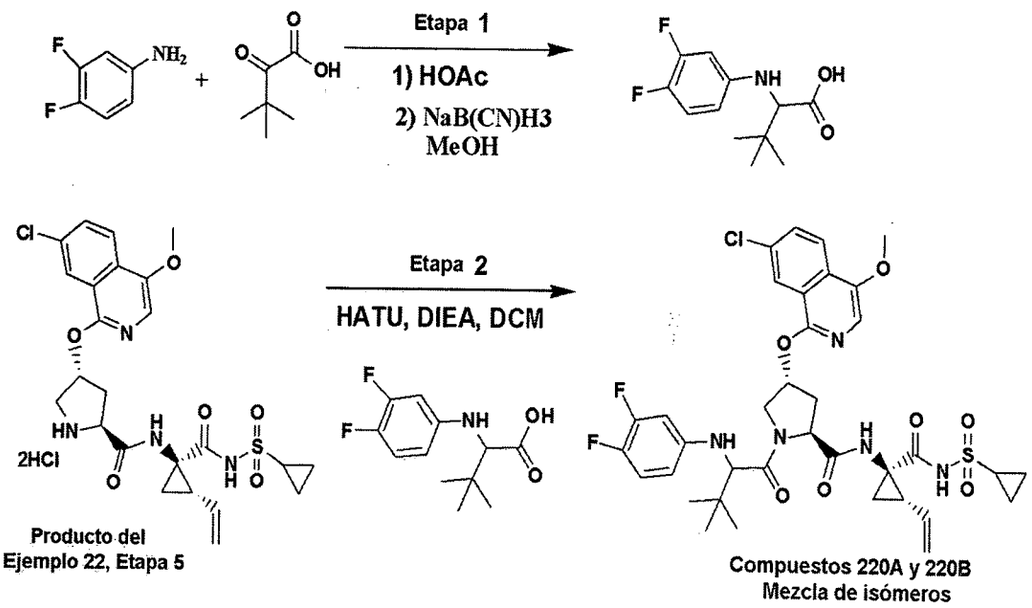
N-(3,4-difluorofenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

Ejemplo 220: Preparación de Compuestos 220A y 220B



Compuestos 220A y 220B

Esquema de reacción 1



Etapa 1:

A una mezcla de 3,4-difluoroanilina (180 mg, 1.394 mmol) y ácido 3,3-dimetil-2-oxobutanoico (500 mg, 3.84 mmol) en un RBF 25 ml a TA se le agregó 2 ml de ácido acético. La solución se calentó a 75°C durante alrededor de 120 minutos. La solución se diluyó con metanol (2 ml) a TA, seguido por la adición de 1.5X de cianotrihidroborato de sodio (245 mg, 3.90 mmol), y la mitad restante después del burbujeo y la emisión de sonidos se terminó. El color de la solución se hizo más claro. Se agregó 30 ml de agua a la mezcla, luego se extrajo esto con 10 ml de acetato de etilo (ajuste de pH a 4). El material orgánico se lavó con bicarbonato de sodio a PH = 8. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo aceitoso resultante se secó bajo alto vacío. Un aceite amarillo se obtuvo así y se usó directamente en la siguiente etapa sin purificación adicional. LC-MS, MS *m/z* 244 (M^+ +H).

Etapa 2:

A la solución amarilla de ácido 2-(3,4-difluorofenilamino)-3,3-dimetilbutanoico (0.046 g, 0.189 mmol, etapa 1, ejemplo 208) y (2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-N-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropil)pirrolidin-2-carboxamida (0.101 g, 0.189 mmol, etapa 5, ejemplo 22) en

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CH_2Cl_2 a 0°C se le agregó HATU (0.144 g, 0.378 mmol) seguido por diisopropiletil amina (0.061 g, 0.473 mmol). Una solución color amarillo claro se formó después de la adición de la base. La mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con acetato de etilo (25 ml) y se lavó con agua (pH~6) y salmuera. El material orgánico se secó sobre sulfato de sodio, se filtró, se concentró, y el residuo se purificó por HPLC preparativa de fase inversa para dar dos productos separados con MS m/z idénticos como se observa por LCMS. El Compuesto 220A (0.033 g, 23.0% de rendimiento) fue el primero de los dos isómeros a eluir por HPLC preparativa de fase inversa. El Compuesto 220B (0.026 g, 19% de rendimiento) fue el segundo de los dos isómeros a eluir por HPLC preparativa de fase inversa.

Compuesto 220A: ^{1}H RMN (500 MHz, CD_3OD) δ ppm 1.07 - 1.16 (m, 11 H) 1.23 - 1.31 (m, 2 H) 1.41 - 1.49 (m, 1 H) 1.90 (dd, *J*=8.24, 5.49 Hz, 1 H) 2.21 - 2.29 (m, 2 H) 2.55 (dd, *J*=13.58, 6.56 Hz, 2 H) 2.92 - 3.00 (m, 1 H) 3.88 - 3.95 (s, 1 H) 3.97 - 4.04 (m, 4 H) 4.27 (d, *J*=12.21 Hz, 1 H) 4.57 (dd, *J*=10.53, 7.17 Hz, 1 H) 5.14 (d, *J*=10.38 Hz, 1 H) 5.32 (d, *J*=17.40 Hz, 1 H) 5.73 - 5.81 (m, 2 H) 6.15 (d, *J*=8.85 Hz, 1 H) 6.26 - 6.34 (m, 1 H) 6.44 (ddd, *J*=13.12, 6.71, 2.75 Hz, 1 H) 7.55 (s, 1 H) 7.66 - 7.73 (m, 1 H) 7.80 (d, *J*=2.14 Hz, 1 H) 8.07 - 8.14 (m, 1 H); LC-MS, MS *m/z* 760 (M^+ +H).

Compuesto 220B: LC-MS, MS *m/z* 760 (M^+ +H).

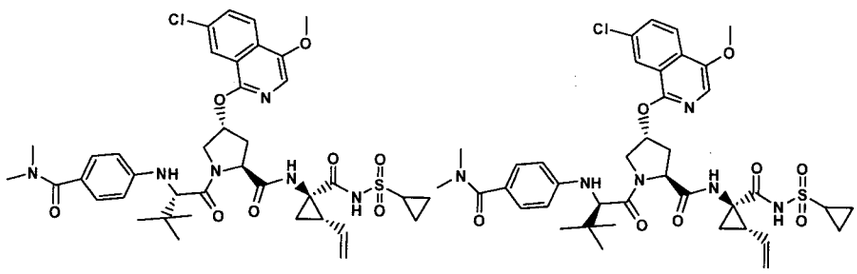
000640

Isómeros del compuesto 221:

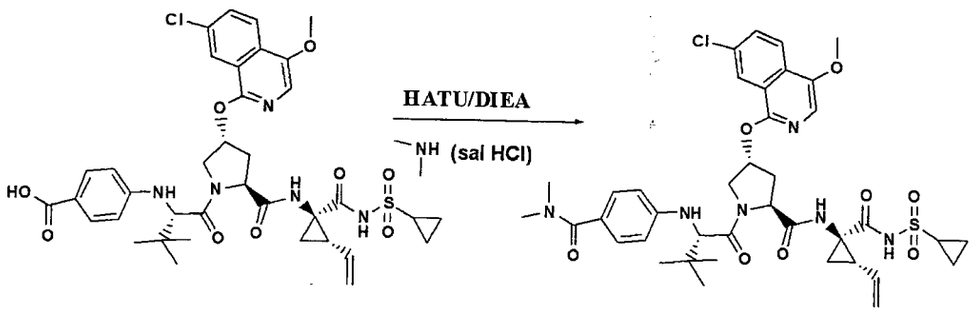
N-(4-(dimetilcarbamoil)fenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

N-(4-(dimetilcarbamoil)fenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

Ejemplo 221: Preparación de Compuestos 221A y 221B



Compuestos 221A y 221B



A la solución de ácido 4-((S)-1-((2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-2-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropilcarbamoil)pirrolidin-1-il)-3,3-dimetil-1-

oxobutan-2-ilamino)benzoico (20 mg, 0.026 mmol, compuesto 209A) y dimetilaminaclorohidrato (4.2mg, 0.052 mmol) en cloruro de metileno a 0°C se le agregó HATU (20 mg, 0.052 mmol) seguido por diisopropiletil amina (8.4 mg, 0.065 mmol). Una solución color amarillo claro se formó después de la adición de la base. La mezcla se agitó a temperatura ambiente durante dos horas. La mezcla de reacción se diluyó con acetato de etilo (25 ml) y se lavó con agua (pH~6) y salmuera. El material orgánico se secó sobre sulfato de sodio, se filtró y se concentró a un aceite amarillo. La purificación por HPLC preparativa proporcionó el Compuesto 221A como un polvo blanco (0.04g, 19% de rendimiento). ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.02 - 1.13 (m, 11 H) 1.20 - 1.33 (m, 2 H) 1.41 (dd, *J*=9.44, 5.41 Hz, 1 H) 1.86 (dd, *J*=8.06, 5.54 Hz, 1 H) 2.18 - 2.30 (m, 2 H) 2.57 (dd, *J*=13.72, 7.18 Hz, 1H) 2.77 - 2.89 (s, 3 H) 2.89 - 3.00 (m, 4H) 3.99 - 4.09 (m, 5 H) 4.48 (d, *J*=12.84 Hz, 1 H) 4.55 (dd, *J*=10.58, 7.05 Hz, 1 H) 5.11 (dd, *J*=10.32, 1.51 Hz, 1 H) 5.28 (dd, *J*=17.12, 1.26 Hz, 1 H) 5.68 - 5.80 (m, 2 H) 6.41 (d, *J*=8.81 Hz, 2 H) 6.66 (d, *J*=8.81 Hz, 2 H) 7.61 (s, 1 H) 7.69 (dd, *J*=8.94, 2.14 Hz, 1 H) 7.92 (d, *J*=2.01 Hz, 1 H) 8.12 (d, *J*=9.07 Hz, 1 H); LC-MS, MS *m/z* 795 (M^+ +H).

Compuesto 221B se hizo del compuesto 209B por el mismo procedimiento como se usó por la preparación del compuesto 221A. LC-MS, MS *m/z* 795 (M^+ +H).

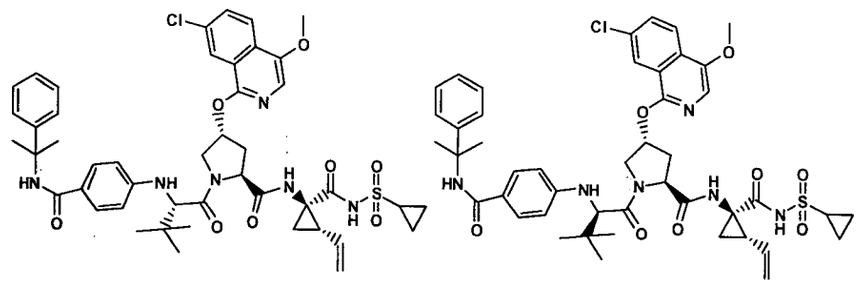
000642

Isómeros del compuesto 222:

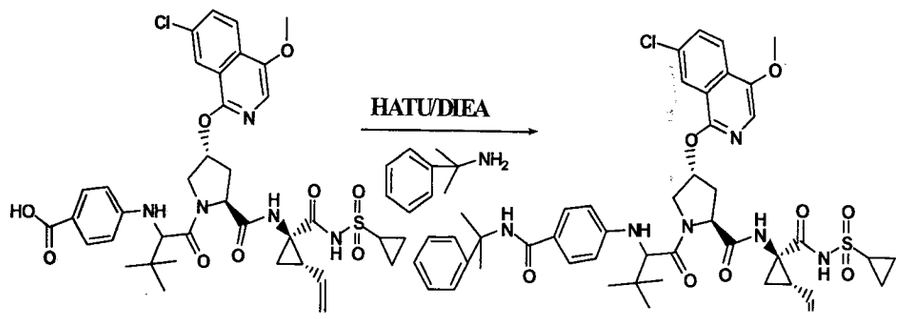
3-metil-N-(4-((1-metil-1-feniletil)carbamoil)fenil)-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

3-metil-N-(4-((1-metil-1-feniletil)carbamoil)fenil)-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

Ejemplo 222: Preparación de Compuestos 222A y 222B



Compuestos 222A y 222B



Compuestos 222A y 222B
Mezcla de isómeros

000643

A la solución de ácido 4-((S)-1-((2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-2-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropilcarbamoil)pirrolidin-1-il)-3,3-dimetil-1-oxobutan-2-ilamino)benzoico (60 mg, 0.078 mmol, compuesto 209A) y 2-fenilpropano-2-amina (10.56 mg, 0.078 mmol) en cloruro de metileno a 0°C se le agregó HATU (60 mg, 0.156 mmol) seguido por diisopropiletil amina (25 mg, 0.21 mmol). Una solución color amarillo claro se formó después de la adición de la base. La mezcla se agitó a temperatura ambiente durante dos horas. La mezcla de reacción se diluyó con acetato de etilo (25 ml) y se lavó con agua (pH~6) y salmuera. El material orgánico se secó sobre sulfato de sodio, se filtró y se concentró a un aceite amarillo. La purificación por HPLC preparativa dio dos productos separados con MS m/z idénticos como se observa por LCMS.

Compuesto 222A: Polvo blanco (0.01g, 14.6% de rendimiento). ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.03 - 1.12 (m, 11 H) 1.20 - 1.26 (m, 2 H) 1.41 (dd, *J*=9.44, 5.41 Hz, 1 H) 1.70 (d, *J*=3.02 Hz, 6 H) 1.87 (dd, *J*=8.18, 5.41 Hz, 1 H) 2.18 - 2.27 (m, 2 H) 2.54 (dd, *J*=13.72, 6.92 Hz, 1 H) 2.92 - 2.98 (m, 1 H) 3.95 - 4.06 (m, 4 H) 4.11 (s, 1 H) 4.38 (d, *J*=12.09 Hz, 1 H) 4.55 (dd, *J*=10.07, 7.05 Hz, 1 H) 5.11 (dd, *J*=10.45, 1.64 Hz, 1 H) 5.26 -5.30 (dd, *J*=17.12, *J*=1.26 Hz,

000644

1 H)) 5.69 - 5.80 (m, 2 H) 6.49 (d, *J*=8.81 Hz, 2 H) 7.12 - 7.17 (m, 1 H) 7.22 - 7.28 (m, 3 H) 7.33 - 7.40 (m, 2 H) 7.54 (s, 1 H) 7.60 (dd, *J*=8.94, 2.14 Hz, 1 H) 7.83 (d, *J*=2.27 Hz, 1 H) 8.04 (d, *J*=9.06 Hz, 1 H); LC-MS, MS *m/z* 886 (M^+ +H).

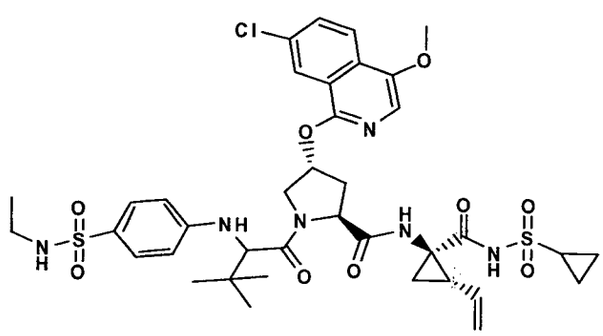
Compuesto 222B: LC-MS, MS *m/z* 886 (M^+ +H).

Isómeros del compuesto 223:

N-(4-(etilsulfamoil)fenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

N-(4-(etilsulfamoil)fenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

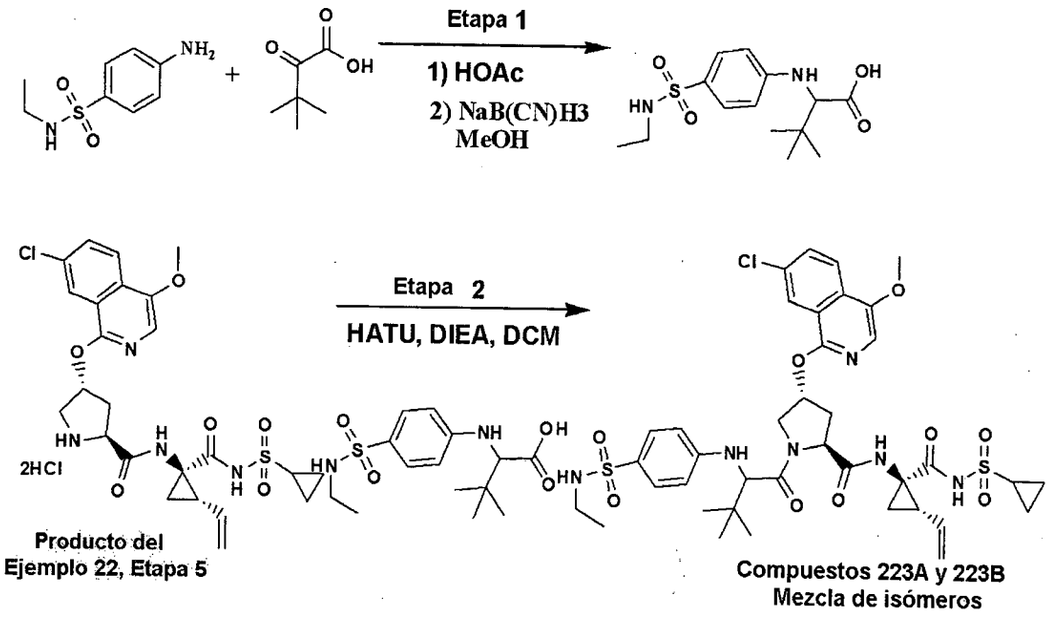
Ejemplo 223: Preparación de Compuestos 223A y 223B



Compuestos 223A y 223B

000645

Esquema de reacción 1



Etapa 1

A una mezcla de 4-amino-N-etilbencensulfonamida (203 mg, 1.014 mmol) y ácido 3,3-dimetil-2-oxobutanoico (264 mg, 2.027 mmol) en un RBF 25 ml a TA se le agregó ácido acético (2 ml) por medio de una pipeta. El color de la mezcla pronto cambió a un color canario característico. La solución se calentó a 75°C durante alrededor de 120 minutos y el color sigue siendo el mismo. La solución se diluyó con metanol (2 ml) a TA, seguido por la adición de 1.5X de cianotrihidroborato de sodio (245 mg, 3.90 mmol), y la mitad restante después del burbujeo y la emisión de sonidos se terminó. El color de la solución se hizo más claro. Se agregó 30 ml de agua a la

000646

mezcla, luego se extrajo esto con 10 ml de acetato de etilo (ajuste de pH a 4). El material orgánico se lavó con bicarbonato de sodio a pH = 8. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró a un residuo aceitoso el cual se secó bajo alto vacío. El aceite amarillo así obtenido se usó directamente en la siguiente etapa sin purificación adicional. LC-MS, MS *m/z* 315 (M^+ +H).

Etapa 2:

A la solución amarilla de ácido 2-(4-(N-etilsulfamoil)fenilamino)-3,3-dimetilbutanoico (0.059 g, 0.189 mmol etapa 1, ejemplo 223) y (2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-N-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropil)pirrolidin-2-carboxamida (0.101 g, 0.189 mmol, etapa 5, ejemplo 22) en CH_2Cl_2 a 0°C se le agregó HATU (0.144 g, 0.378 mmol) seguido por diisopropiletil amina (0.061 g, 0.473 mmol). Una solución color amarillo claro se formó después de la adición de la base. La mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con acetato de etilo (25 ml) y se lavó con agua (pH~6) y salmuera. El material orgánico se secó sobre sulfato de sodio, se filtró, se concentró, y el residuo se purificó por HPLC preparativa de fase inversa para dar dos productos separados con MS m/z idénticos como se observa por

008647

LCMS. El Compuesto 223A (0.033 g, 21.0% de rendimiento) fue el primero de los dos isómeros a eluir por HPLC preparativa de fase inversa. El Compuesto 223B (0.024 g, 15.3.0% de rendimiento) fue el segundo de los dos isómeros a eluir por HPLC preparativa de fase inversa.

Compuesto 223A: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 0.92 (t, *J*=7.30 Hz, 3 H) 1.02 - 1.11 (m, 11 H) 1.19 - 1.29 (m, 2 H) 1.42 (dd, *J*=9.44, 5.41 Hz, 1 H) 1.87 (dd, *J*=8.18, 5.41 Hz, 1 H) 2.20 - 2.29 (m, 2 H) 2.54 - 2.64 (m, 3 H) 2.95 (ddd, *J*=12.84, 8.06, 4.78 Hz, 1 H) 3.96 - 4.01 (s, 3 H) 4.01 - 4.09 (m, 2 H) 4.45 (d, *J*=12.09 Hz, 1 H) 4.59 (dd, *J*=10.07, 7.05 Hz, 1 H) 5.11 (dd, *J*=10.32, 1.76 Hz, 1 H) 5.29 (dd, *J*=17.25, 1.39 Hz, 1 H) 5.68 - 5.78 (m, 2 H) 6.45 - 6.50 (m, 2 H) 7.04 - 7.09 (m, 2 H) 7.55 (s, 1 H) 7.65 (dd, *J*=8.81, 2.27 Hz, 1 H) 7.90 (d, *J*=1.76 Hz, 1 H) 8.08 (d, *J*=9.06 Hz, 1 H); LC-MS, MS *m/z* 831 (M^+ +H).

Compuesto 223B: LC-MS, MS *m/z* 831 (M^+ +H).

Isómeros del compuesto 224:

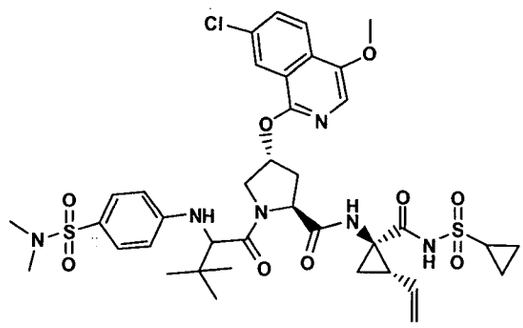
N-(4-(dimetilsulfamoil)fenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

N-(4-(dimetilsulfamoil)fenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-

000645

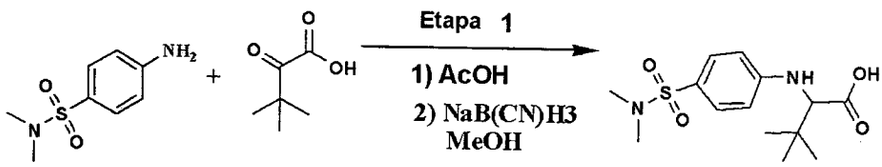
((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

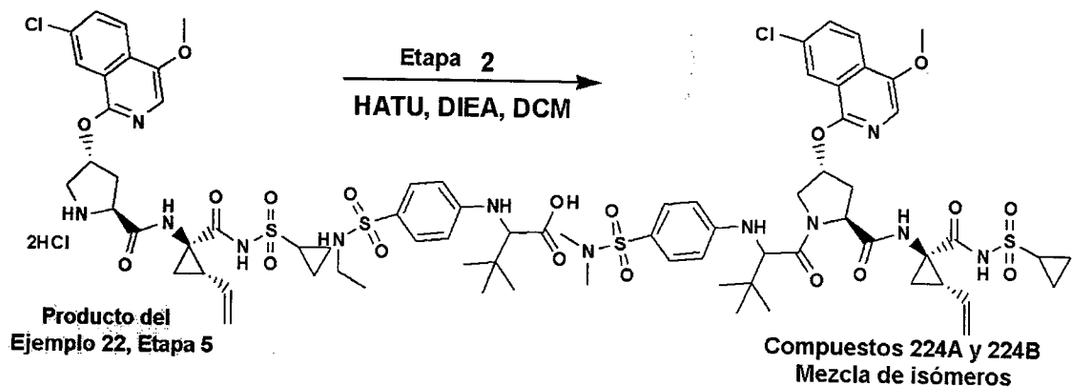
Ejemplo 224: Preparación de Compuestos 224A y 224B



Compuestos 224A y 224B

Esquema de reacción 1





Etapa 1

A una mezcla de 4-amino-N-etilbencensulfonamida (203 mg, 1.014 mmol) y ácido 3,3-dimetil-2-oxobutanoico (264 mg, 2.027

000649

mmol) en un RBF 100 mL a TA se le agregó 2 ml de ácido acético. La solución se calentó a 75°C durante alrededor de 120 minutos. La solución se diluyó con metanol (2 ml) a TA, seguido por la adición de 1.5X de cianotrihidroborato de sodio (245 mg, 3.90 mmol), y la mitad restante después del burbujeo y la emisión de sonidos se terminó. El color de la solución se hizo más claro. Se agregó 30 ml de agua a la mezcla, luego se extrajo esto con 10 ml de acetato de etilo (ajuste de pH a 4). El material orgánico se lavó con bicarbonato de sodio a pH=8. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró a un aceite amarillo el cual se secó bajo alto vacío. Este material se usó directamente en la siguiente etapa sin purificación adicional. LC-MS, MS *m/z* 315 (M^+ +H).

Etapa 2:

A la solución amarilla de ácido 2-(4-(N,N-dimetilsulfamoil)fenilamino)-3,3-dimetilbutanoico (0.059 g, 0.189 mmol etapa 1, ejemplo 224) y (2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-N-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropil)pirrolidin-2-carboxamida (0.101 g, 0.189 mmol, etapa 5, ejemplo 22) en CH_2Cl_2 a 0°C se le agregó HATU (0.144 g, 0.378 mmol) seguido por diisopropiletil amina (0.061 g, 0.473 mmol). Una solución color amarillo claro se formó después de la adición de la

000659

base. La mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con acetato de etilo (25 ml) y se lavó con agua (pH~6) y salmuera. El material orgánico se secó sobre sulfato de sodio, se filtró, se concentró, y el residuo se purificó por HPLC preparativa de fase inversa para dar dos productos separados con MS m/z idénticos como se observa por LCMS. El Compuesto 224A (0.020 g, 13.0% de rendimiento) fue el primero de los dos isómeros a eluir por HPLC preparativa de fase inversa. El Compuesto 224B (0.014 g, 9.0% de rendimiento) fue el segundo de los dos isómeros a eluir por HPLC preparativa de fase inversa.

Compuesto 224A: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.03 - 1.12 (m, 11 H) 1.22 - 1.26 (m, 2 H) 1.42 (dd, *J*=9.32, 5.54 Hz, 1 H) 1.88 (dd, *J*=8.18, 5.41 Hz, 1 H) 2.20 - 2.31 (m, 2 H) 2.35 - 2.40 (m, 6 H) 2.53 - 2.64 (m, 1 H) 2.91 - 3.00 (m, 1 H) 3.95 - 4.00 (s, 3 H) 4.03 - 4.09 (m, 2 H) 4.51 (d, *J*=12.09 Hz, 1 H) 4.57 - 4.67 (m, 1 H) 5.11 (dd, *J*=10.32, 1.51 Hz, 1 H) 5.29 (dd, *J*=17.12, 1.26 Hz, 1 H) 5.68 - 5.79 (m, 2 H) 6.47 (d, *J*=9.06 Hz, 2 H) 6.93 (d, *J*=8.81 Hz, 2 H) 7.53 - 7.57 (s, 1 H) 7.63 - 7.69 (m, 1 H) 7.91 (d, *J*=2.01 Hz, 1 H) 8.03 - 8.12 (m, 1 H); LC-MS, MS *m/z* 831 (M^+ +H).

Compuesto 224B: LC-MS, MS *m/z* 831 (M^+ +H).

Isómeros del compuesto 226:

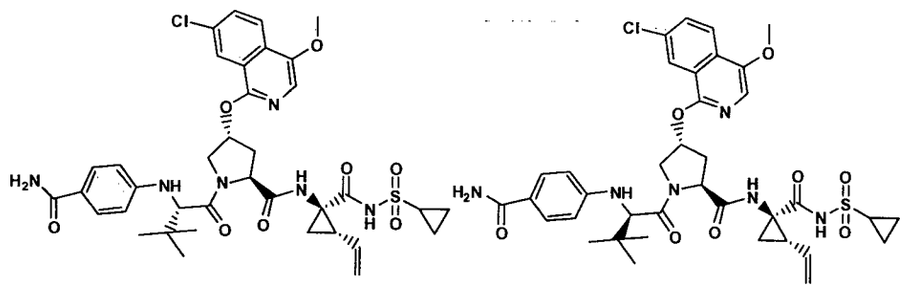
N-(4-carbamoilfenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-

000651

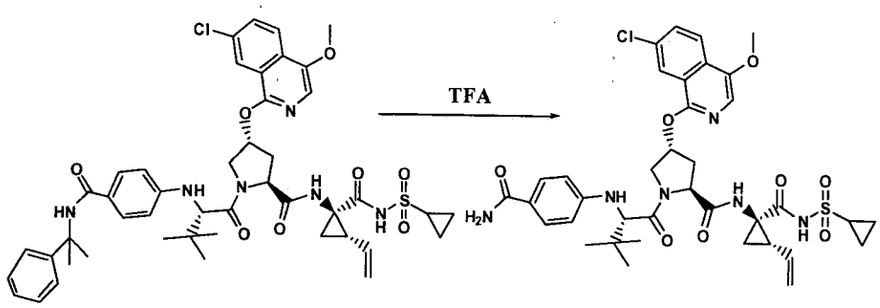
((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

N-(4-carbamoilfenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

Ejemplo 226: Preparación de Compuestos 226A y 226B



Compuestos 226A y 226B



La (2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-N-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropil)-1-((S)-3,3-dimetil-2-(4-(2-fenilpropan-2-ilcarbamoil)fenilamino)butanoil)pirrolidin-2-carboxamida (8 mg, 0.009 mmol, compuesto 222A) se disolvió en 1 ml de ácido 2,2,2-

000652

trifluoroacético a 25°C. La mezcla resultante se agitó durante la noche. El TFA se removió y el residuo se purificó por HPLC preparativa para proporcionar el Compuesto 226A como un polvo blanco (0.005g, 81% de rendimiento). ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.04 - 1.12 (m, 11 H) 1.23 - 1.33 (m, 2H) 1.42 (dd, *J*=9.57, 5.29 Hz, 1 H) 1.87 (dd, *J*=8.18, 5.41 Hz, 1 H) 2.19 - 2.27 (m, 2 H) 2.54 (dd, *J*=13.72, 7.43 Hz, 1 H) 2.92 - 2.98 (m, 1 H) 3.98 - 4.05 (m, 4 H) 4.12 (s, 1 H) 4.33 (d, *J*=12.59 Hz, 1 H) 4.55 (dd, *J*=10.32, 7.05 Hz, 1 H) 5.11 (dd, *J*=10.32, 1.76 Hz, 1 H) 5.27 (m, 2 H) 5.72 - 5.79 (m, 2 H) 6.45 - 6.49 (m, 2 H) 7.22 - 7.25 (2, 4 H) 7.52 (s, 1 H) 7.62 (dd, *J*=8.94, 2.14 Hz, 1 H) 7.79 (d, *J*=2.01 Hz, 1 H) 8.05 (d, *J*=8.81 Hz, 1 H); LC-MS, MS *m/z* 767 (M^+ +H).

Compuesto 226B se hizo del compuesto 222B por el mismo procedimiento como se usó por la preparación del compuesto 226A. LC-MS, MS *m/z* 767(M^+ +H).

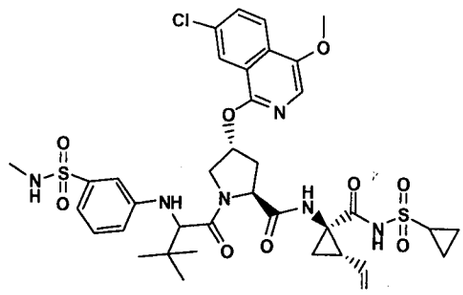
Isómeros del compuesto 227:

3-metil-N-(3-(metilsulfamoil)fenil)-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

3-metil-N-(3-(metilsulfamoil)fenil)-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

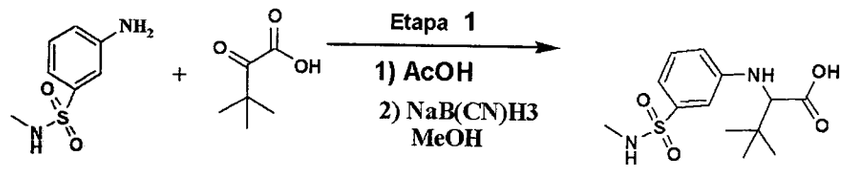
000653

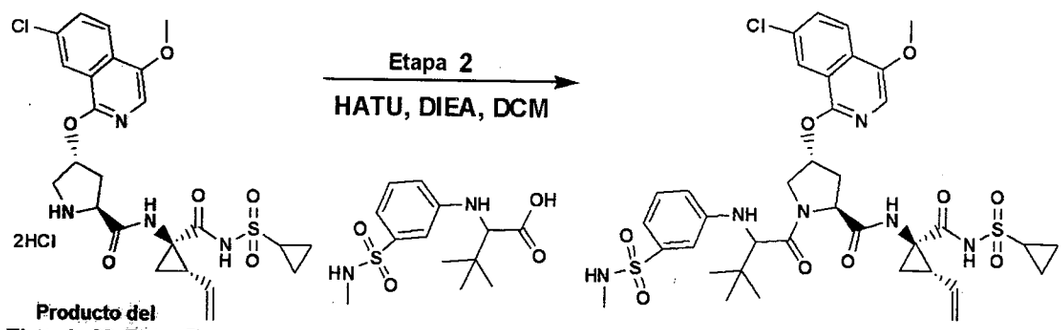
Ejemplo 227: Preparación de Compuestos 227A y 227B



Compuestos 227A y 227B

Esquema de reacción 1





Etapa 1

A una mezcla de 3-amino-N-metilbencensulfonamida (203 mg, 1.09 mmol) y ácido 3,3-dimetil-2-oxobutanoico (264 mg, 2.027 mmol) en un RBF 25 ml a TA se le agregó 2 ml de ácido acético. La solución se calentó a 75°C durante alrededor de 120 minutos. La solución se diluyó con metanol (2 ml) a TA, seguido por la

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adición de 1.5X de cianotrihidroborato de sodio (245 mg, 3.90 mmol), y la mitad restante después del burbujeo y la emisión de sonidos se terminó. El color de la solución se hizo más claro. Se agregó 30 ml de agua a la mezcla, luego se extrajo esto con 10 ml de acetato de etilo (ajuste de pH a 4). El material orgánico se lavó con bicarbonato de sodio a pH=8. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró a un aceite amarillo el cual se secó bajo alto vacío. Este material se usó directamente en la siguiente etapa sin purificación adicional. LC-MS, MS *m/z* 301 (M^+ +H).

Etapa 2:

A la solución amarilla de ácido 2-(3-(N,-metilsulfamoil)fenilamino)-3,3-dimetilbutanoico (0.034 g, 0.114 mmol etapa 1, ejemplo 227) y (2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-N-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropil)pirrolidin-2-carboxamida (0.101 g, 0.189 mmol, etapa 5, ejemplo 22) en CH_2Cl_2 a 0°C se le agregó HATU (0.087 g, 0.228 mmol) seguido por diisopropiletil amina (0.061 g, 0.473 mmol). Una solución color amarillo claro se formó después de la adición de la base. La mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con acetato de etilo (25 ml) y se lavó con agua (pH~6) y salmuera. El material orgánico se secó sobre sulfato de sodio, se filtró, se

concentró, y el residuo se purificó por HPLC preparativa de fase inversa para dar dos productos separados con MS m/z idénticos como se observa por LCMS. El Compuesto 227A (0.013 g, 14.0% de rendimiento) fue el primero de los dos isómeros a eluir por HPLC preparativa de fase inversa. El Compuesto 227B (0.009 g, 9.0% de rendimiento) fue el segundo de los dos isómeros a eluir por HPLC preparativa de fase inversa.

Compuesto 227A: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.04 - 1.12 (m, 11 H) 1.17 - 1.27 (m, 2 H) 1.42 (dd, *J*=9.44, 5.41 Hz, 1 H) 1.87 (dd, *J*=8.18, 5.41 Hz, 1 H) 2.18 - 2.27 (m, 2 H) 2.38 (s, 3 H) 2.52 (dd, *J*=13.47, 6.92 Hz, 1 H) 2.95 (ddd, *J*=12.78, 8.12, 4.78 Hz, 1 H) 3.97 - 4.01 (s, 3 H) 4.03 - 4.11 (m, 2 H) 4.30 (d, *J*=12.09 Hz, 1 H) 4.52 (dd, *J*=10.07, 7.05 Hz, 1 H) 5.11 (dd, *J*=10.32, 1.51 Hz, 1 H) 5.28 (dd, *J*=17.25, 1.38 Hz, 1 H) 5.69 - 5.79 (m, 2 H) 6.53 - 6.63 (m, 2 H) 6.77 (d, *J*=7.55 Hz, 1 H) 7.08 (t, *J*=1.89 Hz, 1 H) 7.53 - 7.57 (m, 1 H) 7.65 - 7.69 (m, 1 H) 7.84 (d, *J*=1.76 Hz, 1 H) 8.08 (d, *J*=8.81 Hz, 1 H); LC-MS, MS *m/z* 817 (M^+ +H).

Compuesto 227B: LC-MS, MS *m/z* 817 (M^+ +H).

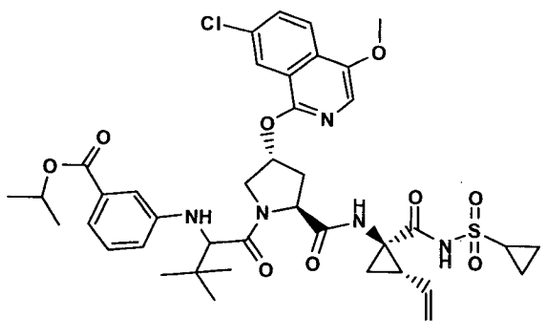
Isómeros del compuesto 231:

N-(3-(isopropoxicarbonil)fenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

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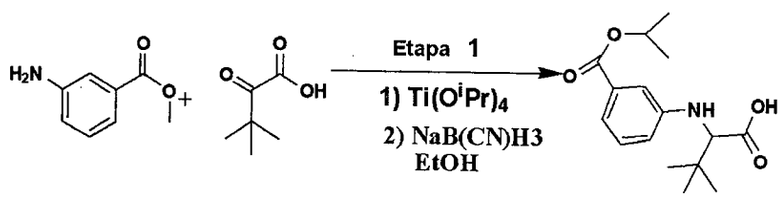
N-(3-(isopropoxicarbonil)fenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

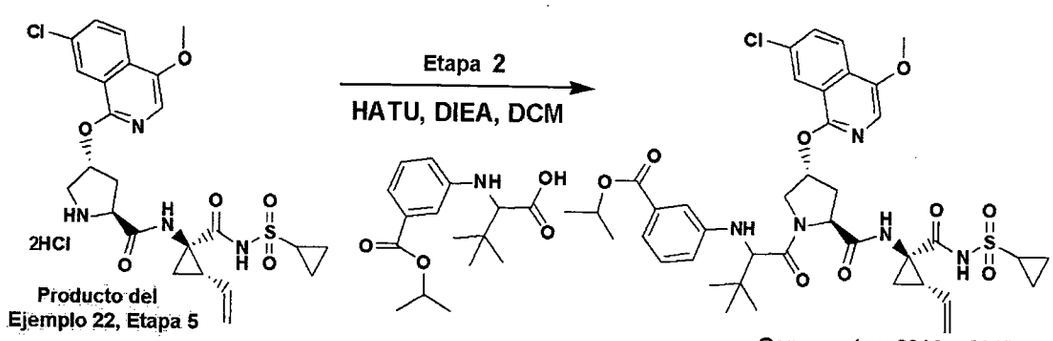
Ejemplo 231: Preparación de Compuestos 231A y 231B



Compuestos 231A y 231B

Esquema de reacción 1





000657

Etapa 1:

A una mezcla de 3-benzoato de metilo (230 mg, 1.52 mmol) y ácido 3,3-dimetil-2-oxobutanoico (198 mg, 1.52 mmol) en un RBF 100 mL a TA se le agregó tetraisopropoxititanio (2 ml) por medio de una pipeta. El color de la mezcla pronto cambió a un color canario característico. La solución se calentó a 75°C durante alrededor de 15 minutos y el color sigue siendo el mismo. La solución se diluyó con etanol absoluto (8 ml) a TA, seguido por la adición de 1.5X de cianotrihidroborato de sodio (245 mg, 3.90 mmol), y la mitad restante después del burbujeo y la emisión de sonidos se terminó. El color de la solución se hizo más claro. La solución se mezcló con 4 mL de agua, formando una suspensión, el PPT blanco se removió por centrifugado. El material orgánico se extrajo en acetato de etilo, y la fase orgánica se secó sobre Na_2SO_4, se filtró, y evaporó a una espuma blanca. Este material se usó directamente en la siguiente etapa sin purificación adicional. LC-MS, MS *m/z* 294 (M^+ +H).

Etapa 2:

A la solución amarilla de ácido 2-(3-(isopropoxicarbonil)fenilamino)-3,3-dimetilbutanoico (0.055 g, 0.189 mmol, etapa 1, ejemplo 231) y (2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-N-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropil)pirrolidin-

000658

2-carboxamida (0.101 g, 0.189 mmol, etapa 5, ejemplo 22) en CH_2Cl_2 a 0°C se le agregó HATU (0.144 g, 0.378 mmol) seguido por diisopropiletil amina (0.061 g, 0.473 mmol). Una solución color amarillo claro se formó después de la adición de base. La mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con acetato de etilo (25 ml) y se lavó con agua (pH~6) y salmuera. El material orgánico se secó sobre sulfato de sodio, se filtró, se concentró, y el residuo se purificó por HPLC preparativa de fase inversa para dar dos productos separados con MS m/z idénticos como se observa por LCMS. El Compuesto 231A (0.0235 g, 15.3.0% de rendimiento) fue el primero de los dos isómeros a eluir por HPLC preparativa de fase inversa. El Compuesto 231B (0.0175 g, 11.6% de rendimiento) fue el segundo de los dos isómeros a eluir por HPLC preparativa de fase inversa.

Compuesto 231A: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 1.04 - 1.14 (m, 11 H) 1.19 - 1.29 (m, 6 H) 1.29 - 1.38 (m, 2 H) 1.38 - 1.43 (m, 1 H) 1.81 - 1.89 (m, 1 H) 2.16 - 2.25 (m, 2 H) 2.47 (dd, *J*=13.60, 7.05 Hz, 1 H) 2.95 (ddd, *J*=12.78, 8.12, 4.78 Hz, 1 H) 3.96 - 4.02 (m, 4 H) 4.02 - 4.08 (m, 1 H) 4.14 - 4.24 (m, 1 H) 4.42 - 4.53 (m, 1 H) 4.93 - 5.03 (m, *J*=6.24, 6.24, 6.24, 6.24, 6.24 Hz, 1 H) 5.06 - 5.16 (m, 1 H) 5.20 - 5.32 (m, 1 H) 5.68 - 5.78 (m, 2 H) 6.54 (t, *J*=7.81 Hz, 1 H) 6.60 - 6.69 (m, 1 H) 6.87 (d, *J*=7.55 Hz, 1 H) 7.20 - 7.26 (m, 1 H) 7.45 - 7.52 (m, 1 H) 7.58 - 7.68 (m, 2 H) 7.97 - 8.06 (m, 1 H); LC-MS, MS *m/z* 810 (M^+ +H).

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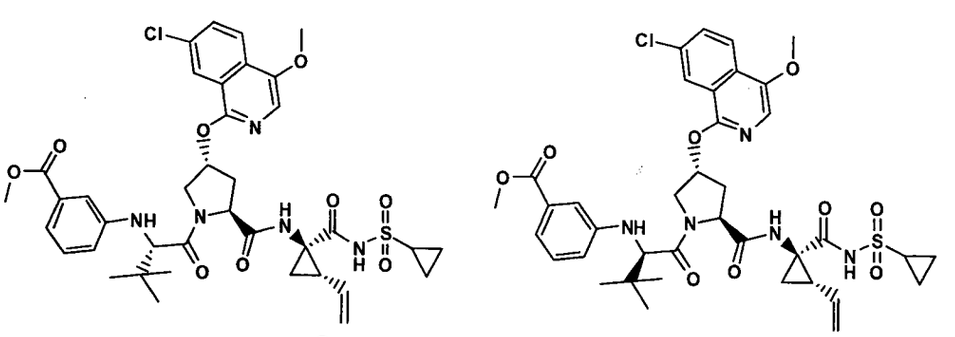
Compuesto 231B: LC-MS, MS *m/z* 810 (M^+ +H).

Isómeros del compuesto 232:

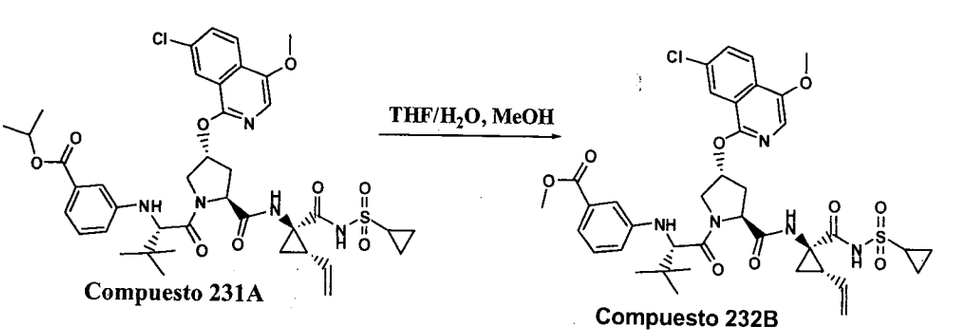
N-(3-(metoxicarbonil)fenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida y

N-(3-(metoxicarbonil)fenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida

Ejemplo 232: Preparación de Compuestos 232A y 232B



Compuestos 232A y 232B



Compuesto 231A

Compuesto 232B

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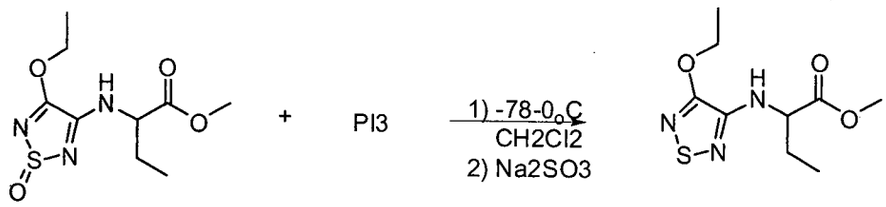
El 3-((S)-1-((2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-2-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropilcarbamoil)pirrolidin-1-il)-3,3-dimetil-1-oxobutan-2-ilamino)benzoato de isopropilo (20 mg, 0.025 mmol, compuesto 231A) se disolvió en THF (0.200 ml) y MeOH (0.2 ml) a 25°C. Hidróxido de litio acuoso 1.0M (0.049 ml, 0.049 mmol) se agregó gota a gota, y la mezcla se agitó durante 4 horas. La mezcla de reacción se diluyó con acetato de etilo (25 ml) y se lavó con agua (pH~4) y salmuera. El material orgánico se secó sobre sulfato de sodio, se filtró, se concentró, y el residuo se purificó por HPLC preparativa de fase inversa para dar Compuesto 232A (0.005 g, 25.6%). ^{1}H RMN (400 MHz, CD_3OD) δ ppm 0.89 - 1.02 (m, 2 H) 1.04 - 1.12 (m, 11 H) 1.29 - 1.36 (m, 2 H) 1.42 (dd, *J*=9.44, 5.41 Hz, 1 H) 1.87 (dd, *J*=8.06, 5.54 Hz, 1 H) 2.16 - 2.25 (m, 2 H) 2.46 (d, *J*=6.55 Hz, 1 H) 2.91 - 2.99 (m, 1 H) 3.63 - 3.71 (m, 3 H) 3.93 - 4.03 (m, 4 H) 4.08 (m, 1 H) 4.21 (s, 1 H) 4.51 (dd, *J*=10.32, 7.05 Hz, 1 H) 5.06 - 5.16 (m, 1 H) 5.28 (d, *J*=17.37 Hz, 1H) 5.70 - 5.79 (m, 2 H) 6.58 (t, *J*=7.81 Hz, 1 H) 6.69 (dd, *J*=8.06, 1.51 Hz, 1 H) 6.80 (d, *J*=7.55 Hz, 1 H) 7.18 (s, 1 H) 7.50 (s, 1 H) 7.61 - 7.69 (m, 2 H) 8.04 - 8.11 (m, 1 H); LC-MS, MS *m/z* 782 (M^+ +H).

Compuesto 232B se hizo del compuesto 231B por el mismo método como se describió por la preparación del compuesto 232A. LC-MS, MS *m/z* 782 (M^+ +H).

096672

en EtOH (5 ml) a 25°C se le agregó 2-aminobutanoato de metilo (0.070 g, 0.600 mmol) seguido por DIEA (0.210 ml, 1.200 mmol). La mezcla se agitó durante la noche a temperatura ambiente. El solvente se removió, y el material se secó bajo alto vacío. Este material se usó directamente en la siguiente etapa sin purificación adicional.

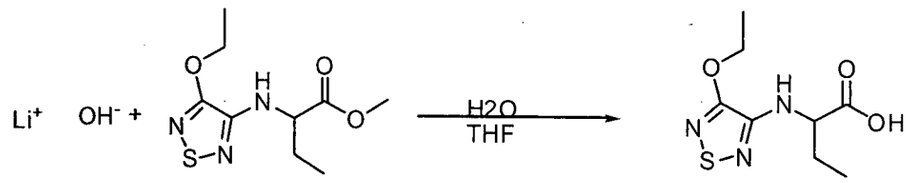
Etapa 2



Etapa 2:

A una solución amarilla del producto del ejemplo 233, etapa 1 (0.157 g, 0.6 mmol) en CH_2Cl_2 (8 ml) a -78°C se le agregó triyodofosfina (0.247 g, 0.600 mmol). Una suspensión anaranjada se obtuvo. La mezcla se permitió calentar hasta 0°C durante 2 h. Una solución café oscura se formó. La mezcla de reacción se diluyó con acetato de etilo (15ml) y se lavó con bisulfito de sodio (2 g en 10 ml de agua), H_2O, y NaCl saturado. El material orgánico se secó sobre Na_2SO_4, se filtró y se concentró. El producto sin refinar se purificó por columna en gel de sílice (elución con 5-15% acetato de etilo en hexanos). Un aceite incoloro se obtuvo así.

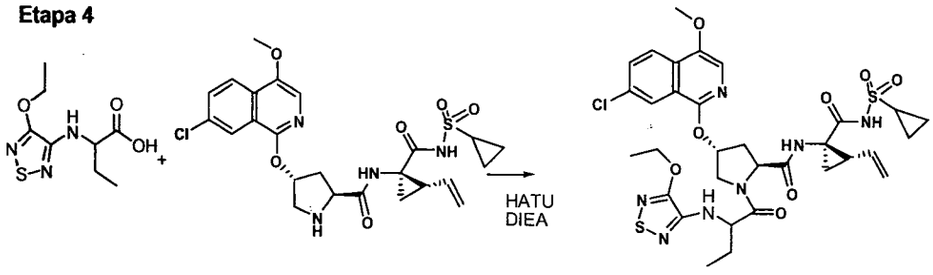
Etapa 3



Etapa 3:

A la solución de 2-(4-etoxi-1,2,5-tiadiazol-3-ilamino)butanoato de metilo (57 mg, 0.232 mmol) en 4 ml de THF a TA se le agregó hidróxido de litio (6.68 mg, 0.279 mmol) y agua (0.6 ml). La mezcla se agitó durante 2 h. La mezcla se ajustó hasta pH 4 y se extrajo con acetato de etilo (10 ml x 2). Las capas orgánicas se combinaron y se lavaron con agua (1 x 10 mL). El material orgánico se secó sobre Na_2SO_4, se filtró y se concentró para proporcionar un sólido blanco.

Etapa 4



Compuesto 233A y Compuesto 232B

Etapa 4:

A la solución amarilla de ácido 2-(4-etoxi-1,2,5-tiadiazol-3-ilamino)butanoico (23.34 mg, 0.101 mmol) y (2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-N-((1R,2S)-1-

(ciclopropilsulfonilcarbamoil)-2-vinilciclopropil)pirrolidin-2-carboxamida (54 mg, 0.101 mmol) a 0°C se le agregó HATU (77 mg, 0.202 mmol) seguido por diisopropiletil amina (32.6 mg, 0.252 mmol). Una solución amarilla se formó. La mezcla se agitó durante la noche a temperatura ambiente. La mezcla de reacción se diluyó con acetato de etilo (15 ml) y se lavó con H_2O (pH = 6) y salmuera. El material orgánico se secó sobre Na_2SO_4, se filtró y se concentró. El material sin refinar se purificó por HPLC preparativa para dar dos productos separados con MS m/z idénticos como se observa por LCMS. El Compuesto 233A (0.046 g, 5.3% de rendimiento) fue el primero de los dos isómeros a eluir por HPLC preparativa de fase inversa. El Compuesto 233B (0.085 g, 10% de rendimiento fue el segundo de los dos isómeros a eluir por HPLC preparativa de fase inversa.

Compuesto 233A: LC-MS, MS *m/z* 748 (M^+ +H).

Compuesto 233B: LC-MS, MS *m/z* 748 (M^+ +H).

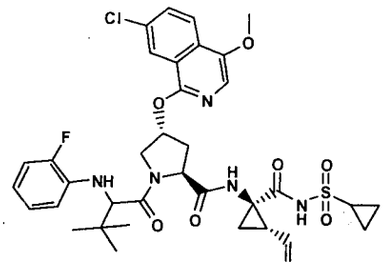
Isómeros del compuesto 234:

N-(2-fluorofenil)-3-metil-D-valil-(4R)-4-[(7-cloro-4-metoxi-1-isoquinolinil)oxi]-N-((1R,2S)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-L-prolinamida y

N-(2-fluorofenil)-3-metil-L-valil-(4R)-4-[(7-cloro-4-metoxi-1-isoquinolinil)oxi]-N-((1R,2S)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-L-prolinamida

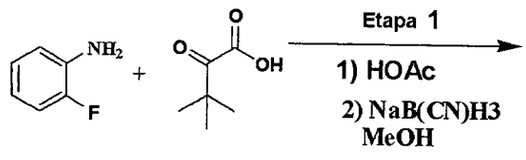
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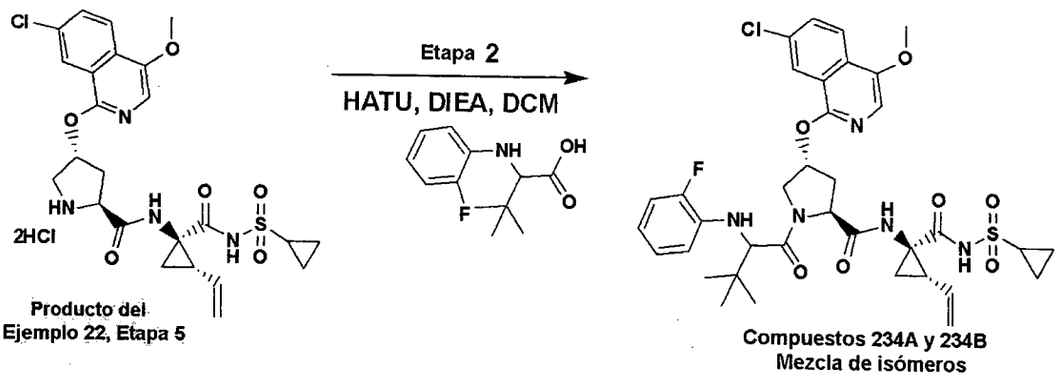
Ejemplo 234: Preparación de Compuestos 234A y 234B



Compuestos 234A y

Esquema de reacción 1





Etapa 1:

A una mezcla de 2-fluoroanilina (203 mg, 1.827 mmol) y ácido 3,3-dimetil-2-oxobutanoico (476 mg, 3.65 mmol) en un RBF 100 mL a TA se le agregó ácido acético (2 ml) por medio de una pipeta. El color de la mezcla pronto cambió a un color canario característico. La

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solución se calentó a 75°C durante alrededor de 120 minutos y el color sigue siendo el mismo. La solución se diluyó con metanol (2 ml) a TA, seguido por la adición de 0.5X de cianotrihidroborato de sodio (230 mg, 3.65 mmol)), y la mitad restante después del burbujeo y la emisión de sonidos se terminó. El color de la solución se hizo más claro. Se agregó 30 ml de agua a la mezcla, luego se extrajo esto con 10 ml de acetato de etilo (ajuste de pH a 4). Luego el material orgánico se lavó con bicarbonato de sodio a pH = 8. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró a un aceite amarillo. El material se purificó por HPLC preparativa y se llevó a cabo en la siguiente etapa. LC-MS, MS *m/z* 226 (M^+ +H).

Etapa 2:

A la solución amarilla de ácido 2-(2-fluorofenilamino)-3,3-dimetilbutanoico (63.2 mg, 0.280 mmol, etapa 1, ejemplo 234) y (2S,4R)-4-(7-cloro-4-metoxiisoquinolin-1-iloxi)-N-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropil)pirrolidin-2-carboxamida (0.150 g, 0.28 mmol, etapa 5, ejemplo 22) en CH_2Cl_2 a 0°C se le agregó HATU (0.213 g, 0.561 mmol) seguido por diisopropiletil amina (0.091 g, 0.701 mmol). Una

- 000677

solución color amarillo claro se formó después de la adición de la base. La mezcla se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con acetato de etilo (25 ml) y se lavó con agua (pH~6) y salmuera. El material orgánico se secó sobre sulfato de sodio, se filtró, se concentró, y el residuo se purificó por HPLC preparativa de fase inversa para dar dos productos separados con MS m/z idénticos como se observa por LCMS. El Compuesto 234A (0.050 g, 24% de rendimiento) fue el primero de los dos isómeros a eluir por HPLC preparativa de fase inversa. El Compuesto 234B (0.038 g, 18.2% de rendimiento) fue el segundo de los dos isómeros a eluir por HPLC preparativa de fase inversa.

Compuesto 234A: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 0.99 - 1.08 (m, 2 H) 1.09 - 1.17 (m, 9 H) 1.20 - 1.29 (m, 2 H) 1.40 (dd, *J*=9.44, 5.41 Hz, 1 H) 1.86 (dd, *J*=8.06, 5.54 Hz, 1 H) 2.17 - 2.27 (m, 2 H) 2.52 (dd, *J*=13.72, 6.92 Hz, 1 H) 2.94 (ddd, *J*=12.78, 8.12, 4.78 Hz, 1 H) 3.97 - 4.04 (m, 5 H) 4.27 (d, *J*=12.09 Hz, 1 H) 4.50 (dd, *J*=10.45, 6.92 Hz, 1 H) 5.11 (dd, *J*=10.32, 1.51 Hz, 1 H) 5.28 (dd, *J*=17.12, 1.51 Hz, 1 H) 5.67 - 5.77 (m, 2 H) 6.08 - 6.14 (m, 1 H) 6.14 - 6.20 (m, 1 H) 6.40 - 6.47 (m, 1 H) 6.58 (ddd, *J*=11.96, 8.06, 1.39 Hz, 1 H) 7.56 (s, 1 H) 7.69 (dd, *J*=8.81, 2.01 Hz, 1 H) 7.77 (d,

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J=2.01 Hz, 1 H) 8.10 (d, *J*=8.81 Hz, 1 H); LC-MS, MS *m/z* 742 (M^+ +H).

Compuesto 234B: LC-MS, MS *m/z* 742 (M^+ +H).

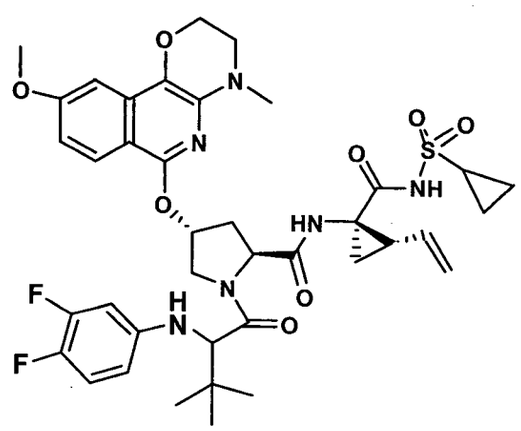
Isómeros del compuesto 235:

N-(3,4-difluorofenil)-3-metil-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((9-metoxi-4-metil-3,4-dihidro-2H-[1,4]oxazino[3,2-c]isoquinolin-6-il)oxi)-L-prolinamida

y

N-(3,4-difluorofenil)-3-metil-D-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((9-metoxi-4-metil-3,4-dihidro-2H-[1,4]oxazino[3,2-c]isoquinolin-6-il)oxi)-L-prolinamida

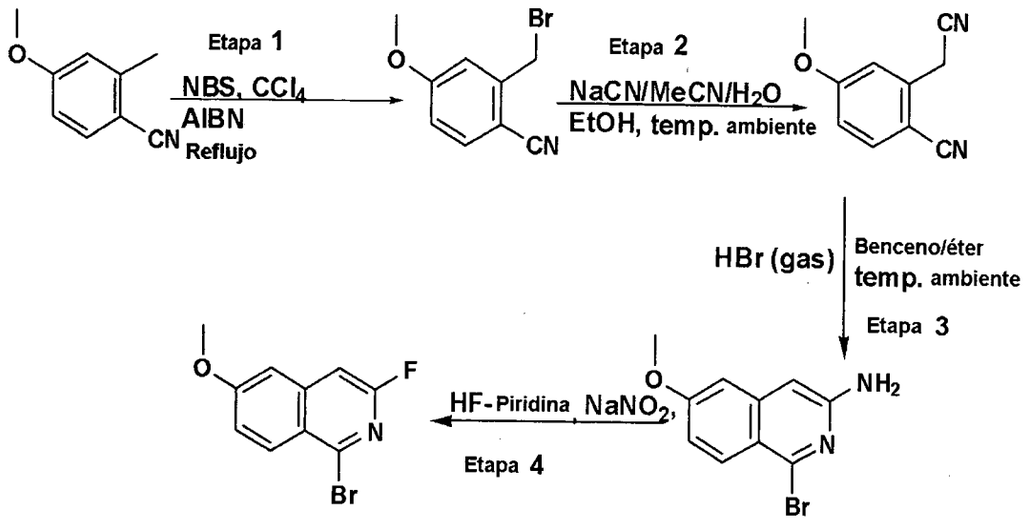
Ejemplo 235: Preparación de Compuestos 235A y 235B



Compuestos 235A y 235B
Mezcla de Isómeros

001679

Esquema de reacción 1



Etapa 1

El 4-metoxi-2-metilbenzonitrilo (50 g, 340 mmol) y NBS (62g, 350 mmoles) se suspendieron en CCl_4 (500 ml) y AIBN (5g, 10% en peso) se agregó. La mezcla se calentó a reflujo durante la noche. Se filtró completamente el precipitado y se removió el solvente. El aceite café se purificó por cromatografía columna por desorción súbita (2-5% acetona: hexanos). Cristales blancos (36 g) se obtuvieron.

Etapa 2

2-(Bromometil)-4-metoxibenzonitrilo (36 g, ejemplo 235, etapa 1) se suspendió en 200 ml de etanol, 200 ml de acetonitrilo se agregó seguido por KCN (8.3 g) y 150 ml

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de agua. La mezcla se agitó y la solución incolora se tornó amarilla. La reacción se completó después de 4 horas de agitación. Los materiales volátiles se removieron bajo vacío, y el sólido residual se volvió a disolver en acetato de etilo (200 ml) y se lavó con agua (100 ml) y salmuera (100ml). Los orgánicos se secaron luego sobre sulfato de sodio. El acetato de etilo se removió y el residuo se recristalizó de acetato de etilo y dicloruro metano para proporcionar 17g de 2-(cianometil)-4-metoxibenzonitrilo.

Etapa 3

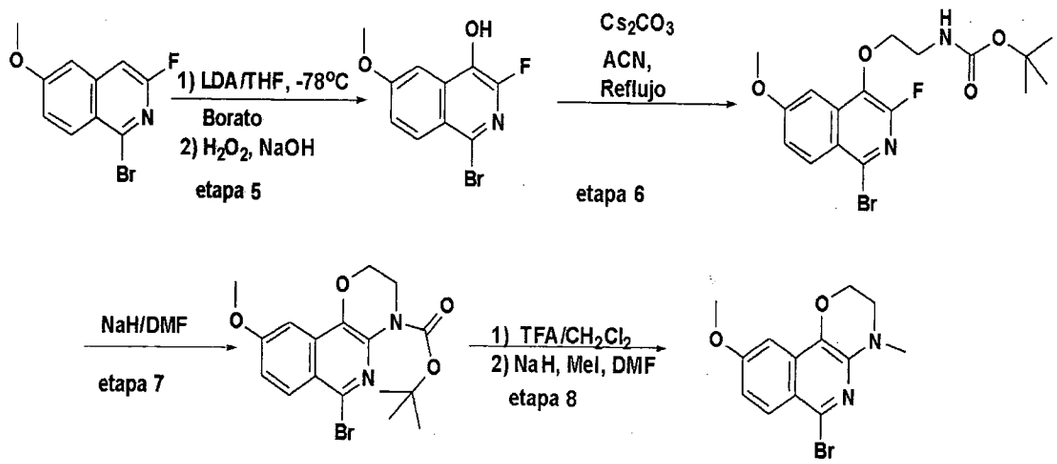
Véase J. Med. Chem., 1970, Vol. 13, No. 4, pp 613 para la preparación de 1-bromo-6-metoxiisoquinolin-3-amina.

Etapa 4

La 1-bromo-6-metoxiisoquinolin-3-amina (1.5 g, ejemplo 235, etapa 3) se disolvió en HF-Py (12.5 ml) a -10°C, y $NaNO_2$ (600 mg) se agregó. Un sólido amarillo se observó que se forma. La mezcla de reacción se suspendió en una gran cantidad de agua, se ajusta PH a 5, se extrajo con acetato de etilo (3 X 30 ml), se lavó con agua y salmuera, luego se secó sobre sulfato de sodio. El sólido amarillo claro (1.2 g) se obtuvo después de la purificación en columna por desorción súbita.

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Esquema de reacción 2



Etapa 5

La 1-bromo-3-fluoro-6-metoxiisoquinolina (322 mg, 1.26 mmol, ejemplo 235, etapa 4) se disolvió en THF (7 ml) a -78°C, LDA (1.5 M, 2.52 ml) se agregó gota a gota, se agitó durante 30 min, luego borato de isopropilo (477 mg, 585 ul) se agregó. 30 minutos más tarde, la reacción se apagó por NH_4Cl saturado y HCl 1 N, se extrajo con acetato de etilo (3X30 ml). Se removió el solvente hasta sequedad. El residuo se disolvió en CH_2Cl_2 (8 ml), NaOH (1 N, 4 ml) se agregó seguido por H_2O_2 (1.2 ml, 50%). Evolución de gas se observó. Se agitó durante 30 min. Se forma una pasta amarilla. La mezcla se tomó en 50 ml de acetato de etilo, la capa orgánica se lavó con solución de bisulfito de sodio, y salmuera, luego se secó sobre sulfato de sodio. Se purificó por gel de sílice (eluido

- 000682

con 5-10% acetato de etilo: hexano). Se obtuvieron 200 mg de sólido amarillo.

Etapa 6

El 1-bromo-3-fluoro-6-metoxiisoquinolin-4-ol (160 mg, ejemplo 235, etapa 5) se disolvió en acetonitrilo (10 ml) a TA, Cs_2CO_3 (215 mg) y 2-bromoetilcarbamato de terc-butilo (60 ul) se agregaron. La mezcla resultante se llevó a reflujo durante 2 horas. El solvente se removió y el residuo se tomó en 30 ml de acetato de etilo, se lavó con agua y salmuera, se secó sobre sulfato de sodio. El residuo se purificó por columna instantánea con 5% acetona: hexanos. El sólido blanco (169 mg) se obtuvo.

Etapa 7

El 2-(1-bromo-3-fluoro-6-metoxiisoquinolin-4-iloxi)etilcarbamato de terc-butilo (169 mg, ejemplo 235, etapa 6) se disolvió en 10 ml de DMF a 0°C, 24 mg de hidruro de sodio (95%) se agregó, se agitó durante la noche. La mezcla de reacción se diluyó con 50 ml de agua, se extrajo con acetato de etilo (3X20 ml). El material orgánico se combinó y se lavó con agua (2 X 10 ml), salmuera (20 ml), se secó sobre sulfato de sodio. El solvente se removió y el residuo se purificó por columna

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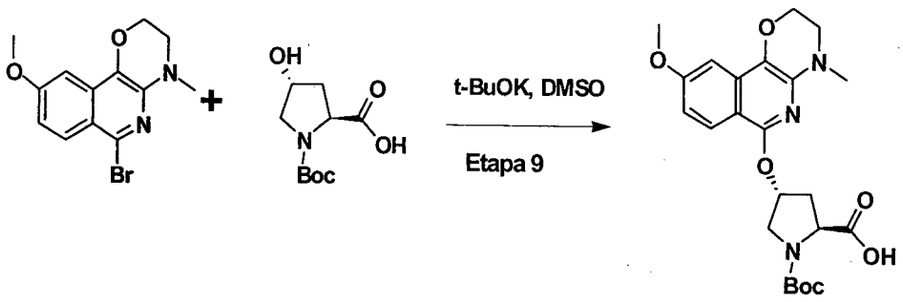
instantánea con 2.5-10% acetona: hexanos. El sólido blanco (100 mg) se obtuvo.

Etapa 8

El 6-bromo-9-metoxi-2H-[1,4]oxazino[3,2-c]isoquinolina-4(3H)-carboxilato de terc-butilo (20 mg, ejemplo 235, etapa 7) se disolvió en 5 ml de CH2Cl2 a 0°C, 2 ml de TFA se agregó, se agitó durante 2 horas. La mezcla de reacción se secó bajo vacío, el residuo se volvió a disolver en acetato de etilo y se lavó con agua (PH~5), salmuera, se secó sobre sulfato de sodio. El solvente se removió hasta secarse y el sólido obtenido se disolvió en DMF (5 ml) a temperatura ambiente, se trató con NaH (10 mg), seguido por MeI (10 ul). Se agitó durante 60 min. La mezcla de reacción se diluyó con 50 ml de agua, se extrajo con acetato de etilo (3X20 ml). El material orgánico se combinó y se lavó con agua (2X10 ml), salmuera (20 ml), se secó sobre sulfato de sodio. El solvente se removió y el residuo se purificó por columna instantánea con 5-15% acetona: hexanos. Se obtuvo un sólido blanco (10 mg). RMN 1H RMN (400 MHz, CLOROFORMO-D) δ ppm 2.89 (s, 3 H) 3.16 - 3.21 (m, 2 H) 4.40 - 4.44 (m, 2 H) 7.05 (dd, *J*=9.32, 2.52 Hz, 1 H) 7.20 (d, *J*=2.52 Hz, 1 H) 8.04 (d, *J*=9.32 Hz, 1 H).

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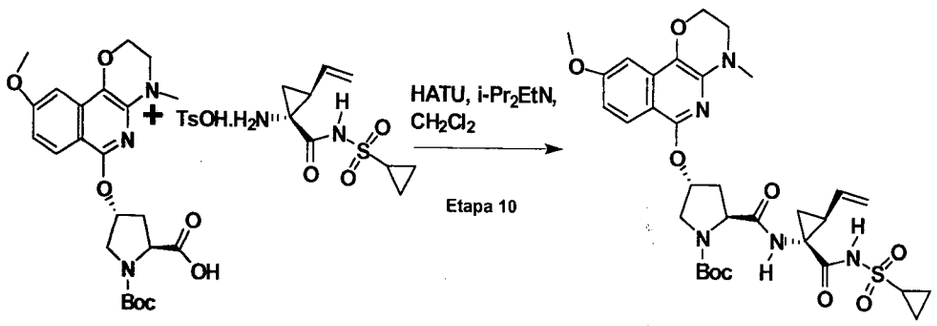
Esquema de reacción 3



Etapa 9

Una solución de 6-bromo-9-metoxi-4-metil-3,4-dihidro-2H-[1,4]oxazino[3,2-c]isoquinolina (62 mg, 0.2 mmol, ejemplo 235, etapa 8), Boc-L-Hyp-OH (50.8 mg, 0.22 mmol), t-BuOK (82 mg, 0.60 mmol) en DMSO (2 mL) se agitó durante 3 h. La reacción se apagó con agua (5 mL) a 0°C y se neutralizó con HCl 1 N a un pH 5, se extrajo con EtOAc (40 mL), se lavó con salmuera (10 mL) y agua (15 mLx2), se secó sobre $MgSO_4$, se concentró para dar un producto sin refinar (90 mg) como un sólido, el cual se usó en la siguiente etapa sin purificación adicional.

Esquema de reacción 4

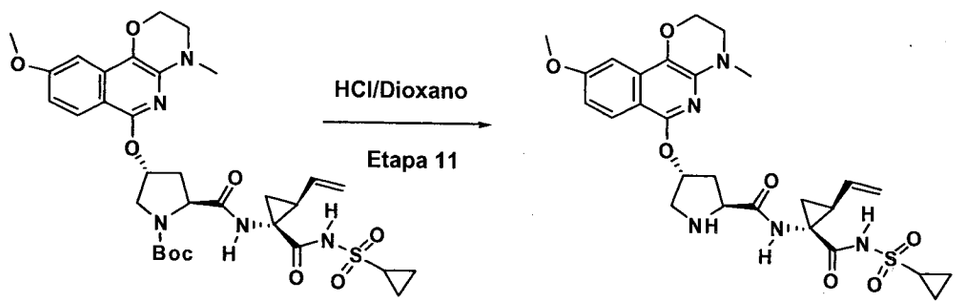


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Etapa 10

A una solución de ácido (2S,4R)-1-(terc-Butoxicarbonil)-4-(9-metoxi-4-metil-3,4-dihidro-2H-[1,4]oxazino[3,2-c]isoquinolin-6-iloxi)pirrolidin-2-carboxílico (90 mg, ejemplo 235, etapa 9), (1R,2S)-1-amino-N-(ciclopropilsulfonil)-2-vinilciclopropanocarboxamida sal TsOH (90 mg), i-Pr_2EtN (0.5 mL) en CH_2Cl_2 (5 mL) se le agregó HATU (112 mg). La mezcla resultante se agitó durante 16 h. Después de la concentración, el residuo se extrajo con EtOAc (30 mL), se lavó con HCl 1 N (10 mL x 3), agua (10 mL x 2), y salmuera (10 ml x 2), se secó sobre $MgSO_4$, se concentró, se purificó por HPLC preparativa. Se obtuvieron 113 mg de un sólido.

Esquema de reacción 5



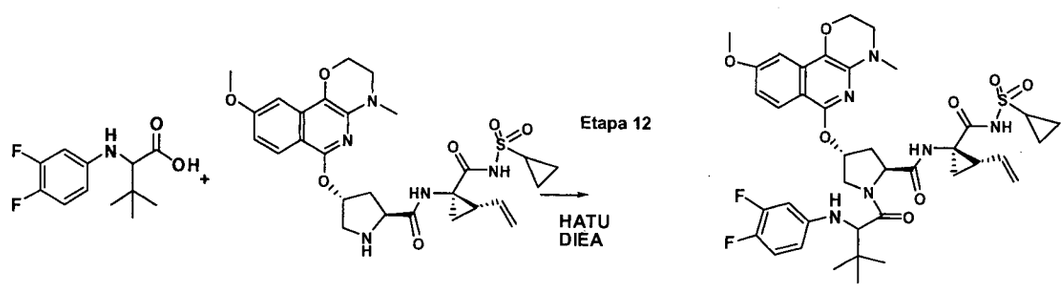
Etapa 11

El 2-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropilcarbamoil)-4-(9-metoxi-4-metil-3,4-dihidro-2H-[1,4]oxazino[3,2-c]isoquinolin-6-iloxi)pirrolidin-1-carboxilato de (2S,4R)-terc-Butilo (50 mg, ejemplo 235, etapa 10) se disolvió en 2 ml de HCl 4N en dioxano, se agitó

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durante 2 horas. El solvente se removió hasta secarse, el sólido café resultante se usó como es.

Esquema de reacción 6



Etapa 12

A la solución amarilla de ácido 2-(3,4-difluorofenilamino)-3,3-dimetilbutanoico (0.043 g, 0.175 mmol, del ejemplo 220, etapa 1) y (2S,4R)-N-((1R,2S)-1-(ciclopropilsulfonilcarbamoil)-2-vinilciclopropil)-4-(9-metoxi-4-metil-3,4-dihidro-2H-[1,4]oxazino[3,2-c]isoquinolin-6-iloxi)pirrolidin-2-carboxamida (20 mg, ejemplo 235, etapa 11) a 0°C se le agregó HATU (0.133 g, 0.350 mmol) seguido por diisopropiletil amina (0.057 g, 0.437 mmol). La solución café se formó después de la adición de base. La mezcla se agitó a temperatura ambiente.

La mezcla de reacción se diluyó con acetato de etilo. Se lavó con agua y salmuera. Se secó sobre sulfato de sodio. Se purificó por HPLC preparativa para dar dos productos separados con MS m/z idénticos como se observa por LCMS. El Compuesto 235A (0.0008 g, 3.0% de rendimiento) fue el primero de los dos isómeros a eluir por HPLC preparativa de fase

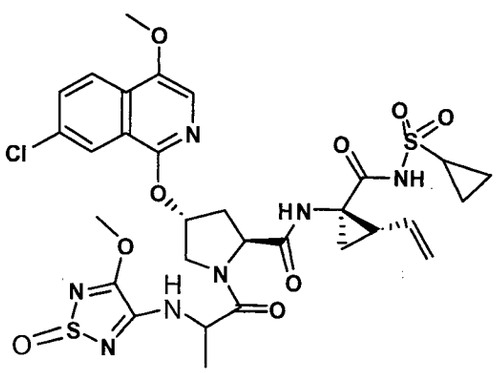
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inversa. El Compuesto 235B (0.003 g, 11.0% de rendimiento) fue el segundo de los dos isómeros a eluir por HPLC preparativa de fase inversa. Compuesto 235A: LC-MS, MS *m/z* 798 (M^+ +H).

1H RMN (400 MHz, MeOD) δ ppm 1.01 - 1.10 (m, 11 H) 1.41 (m, 2 H) 1.86 (dd, *J*=8.18, 5.41 Hz, 1 H) 2.13 - 2.24 (m, 2 H) 2.50 (d, *J*=6.80 Hz, 1 H) 2.90 - 3.01 (m, 1 H) 3.02 - 3.09 (m, 3 H) 3.42 (d, *J*=2.52 Hz, 2 H) 3.91 - 4.01 (m, 5 H) 4.22 - 4.32 (m, 1 H) 4.42 - 4.48 (m, 1 H) 4.50 - 4.59 (m, 2 H) 5.11 (dd, *J*=10.32, 1.76 Hz, 1 H) 5.28 (dd, *J*=17.25, 1.39 Hz, 1 H) 5.67 - 5.78 (m, 2 H) 6.19 - 6.24 (m, 1 H) 6.35 - 6.40 (m, 1 H) 6.49 - 6.56 (m, 1 H) 6.87 (dd, *J*=9.07, 2.27 Hz, 1 H) 7.13 - 7.17 (m, 1 H) 7.60 (d, *J*=2.27 Hz, 1 H) Compuesto 235: LC-MS, MS *m/z* 798 (M^+ +H).

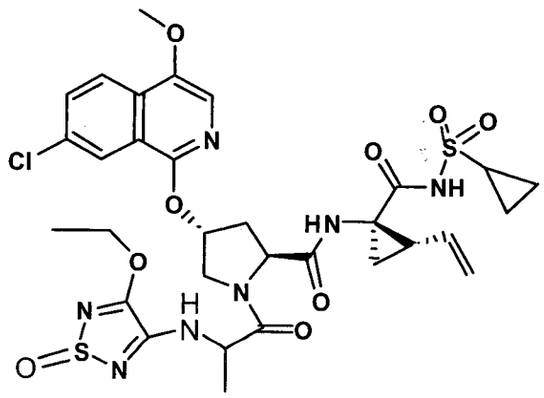
Los Compuestos 236, 237, 238, 239, 240, 241, 242, 243 se prepararon usando los métodos descritos en la presente.

Ejemplo 236: Compuesto 236.

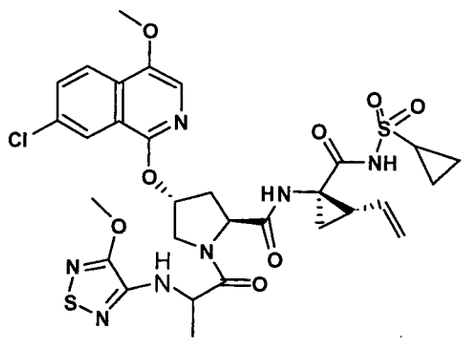


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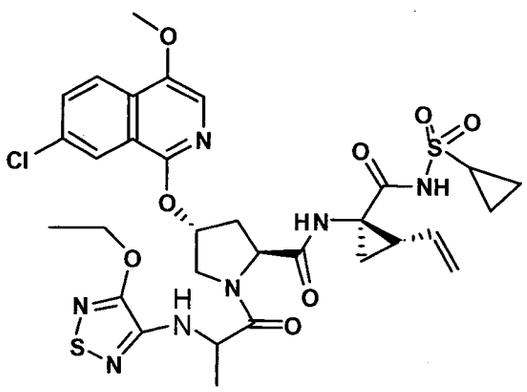
Ejemplo 237: Compuesto 237.



Ejemplo 238: Compuesto 238.

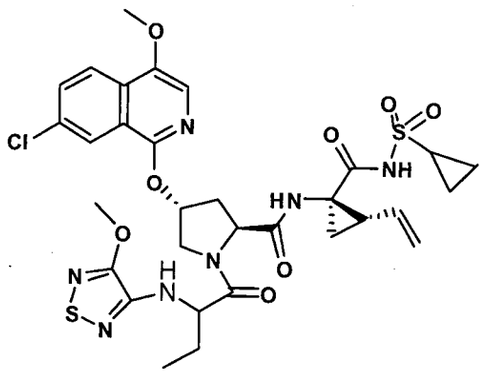


Ejemplo 239: Compuesto 239.

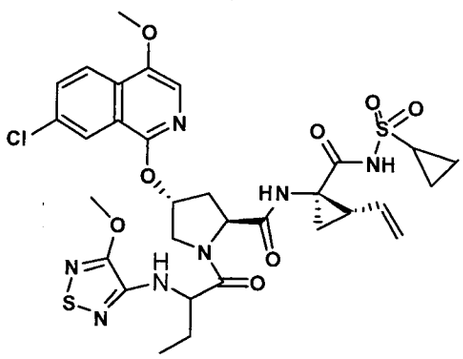


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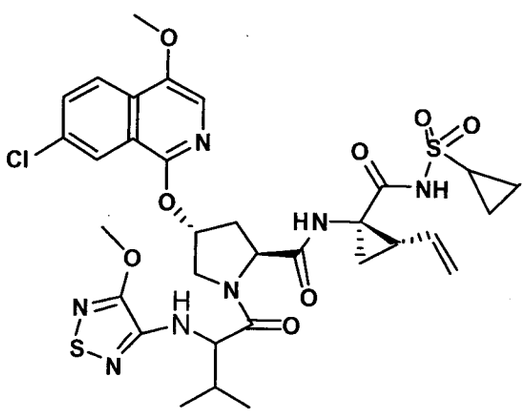
Ejemplo 240: Compuesto 240.



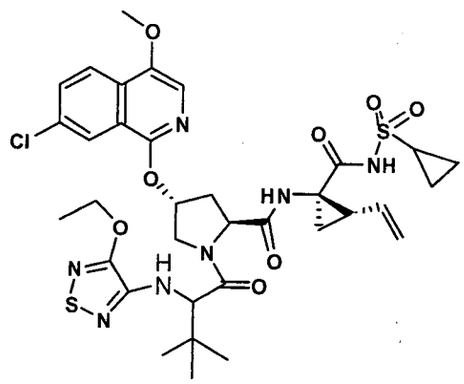
Ejemplo 241: Compuesto 241.



Ejemplo 242: Compuesto 242.

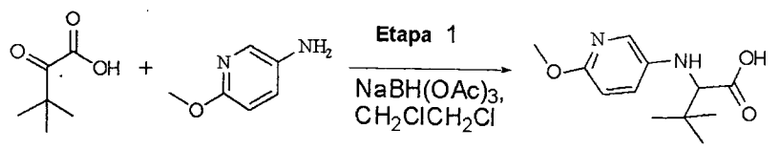


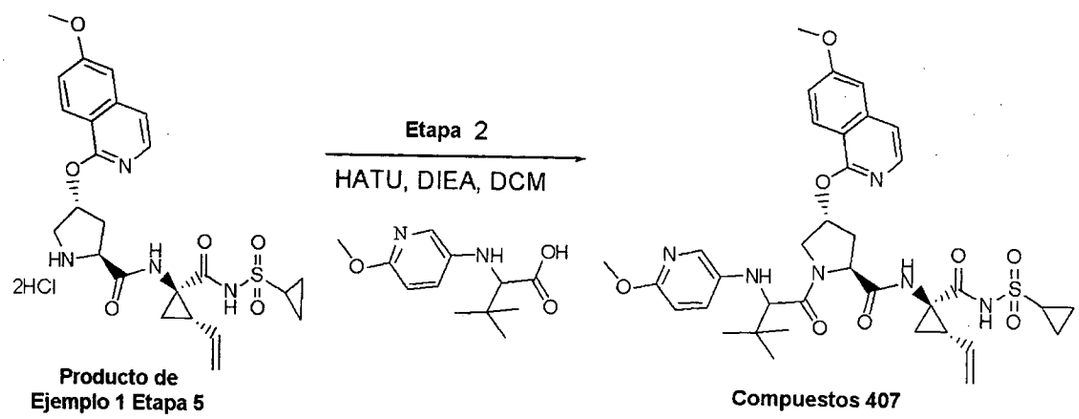
Ejemplo 243: Compuesto 243.



Ejemplo 407: Preparación de Compuestos 407

Esquema de reacción 1





Etapa 1:

Una mezcla de 6-metoxipiridin-3-amina (372 mg, 3

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mmol), ácido 3,3-dimetil-2-oxobutanoico (781 mg, 6.00 mmol), y triacetoxihidroborato de sodio (1907 mg, 9.00 mmol) en CH_2ClCH_2Cl (5 ml) se agitó durante 24 h. La reacción se apagó con NH_4Cl saturado (20 mL), se diluyó con EtOAc (50 mL), se lavó con salmuera (20 ml), se secó sobre $MgSO_4$, se filtró, se concentró. La concentración dio 0.71 g (99%) de un producto sin refinar deseado el cual se usó en la siguiente etapa sin purificación adicional. ^1H RMN (400 MHz, CCl_3D) δ ppm 1.09 (s, 9H), 3.63 (s, 1H), 3.85 (s, 3 H), 6.63 (d, J=8.81 Hz, 1 H), 7.07 (dd, J=8.81, 3.02 Hz, 1 H), 7.63 (d, J=3.02 Hz, 1 H); LC-MS, MS *m/z* 239 (M^+ +H).

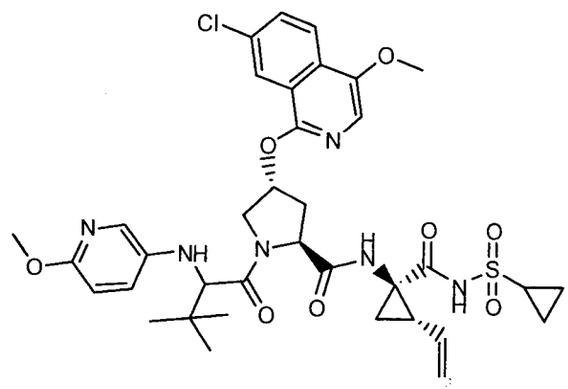
Etapa 2:

A una mezcla del producto de la Etapa 5, Ejemplo 1 (150 mg, 0.3 mmol), se le agregó el producto de la Etapa 1, Ejemplo 407 (71 mg, 0.3 mmol), y base Hunig (0.524 ml, 3 mmol) en CH_2Cl_2 (5 ml) se agregó HATU (171 mg, 0.45 mmol). Después de agitar durante 16 h y la concentración, purificación del residuo por HPLC preparativa de fase inversa dio dos productos con *m/z* idéntico por LCMS. El Compuesto 407A fue el primero de los dos isómeros a eluir por HPLC preparativa de fase inversa y se obtuvo como un sólido (37 mg, 18% de rendimiento). El Compuesto 407B fue el segundo de los dos isómeros a eluir por HPLC preparativa de fase inversa

000692

y se obtuvo como un sólido (31 mg, 14% de rendimiento). El Compuesto 407: LC-MS, MS *m/z* 721 (M^+ +H). El Compuesto 407B: LC-MS, MS *m/z* 721 (M^+ +H).

Ejemplo 408: Preparación de Compuestos 408A y 408B

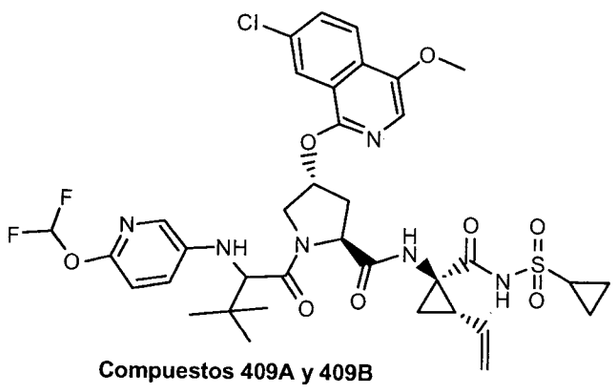


Compuestos 408A y 408B

Los Compuestos 408 se prepararon por el mismo procedimiento como el que se describió por la preparación del compuesto 407, excepto que el producto de la Etapa 5 del Esquema de reacción 2 en el Ejemplo 22 (182 mg, 0.299 mmol) se usó en la síntesis del Compuesto 408. El Compuesto 408A fue el primero de los dos isómeros a eluir por HPLC preparativa de fase inversa y se obtuvo como un sólido (66 mg, 29% de rendimiento). El Compuesto 408B fue el segundo de los dos isómeros a eluir por HPLC preparativa de fase inversa y se obtuvo como un sólido (46 mg, 20% de rendimiento). Compuesto 408A: LC-MS, MS *m/z* 755 (M^+ +H). Compuesto 408B: LC-MS, MS *m/z* 755 (M^+ +H).

000693

Ejemplo 409: Preparación de Compuestos 409A y 409B



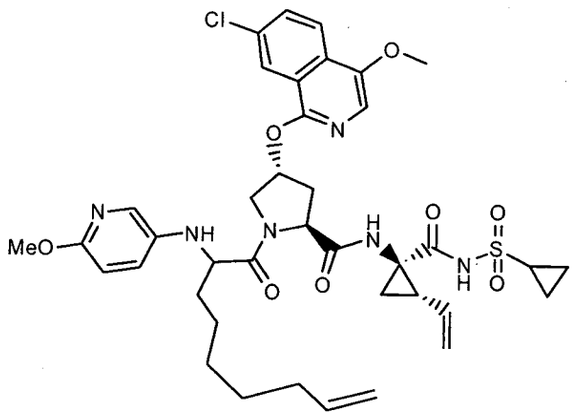
Compuestos 409A y 409B

Los Compuestos 409 se prepararon por el mismo procedimiento como el que se describió por la preparación del compuesto 407, excepto que 6-(difluorometoxi)piridin-3-amina se usó en la Etapa 1 y el producto de la Etapa 5 del Esquema de reacción 2 en el Ejemplo 22 (182 mg, 0.299 mmol) se usó en la Etapa 2. El Compuesto 409A fue el primero de los dos isómeros a eluir por HPLC preparativa de fase inversa y se obtuvo como un sólido (45 mg, 33% de rendimiento). El Compuesto 409B fue el segundo de los dos isómeros a eluir por HPLC preparativa de fase inversa y se obtuvo como un sólido (50 mg, 37% de rendimiento). Compuesto 409A: LC-MS, MS *m/z* 791 (M^+ +H). Compuesto 409B: LC-MS, MS *m/z* 791 (M^+ +H).

Los Compuestos 410 y 411 se prepararon de conformidad con los métodos descritos en la presente.

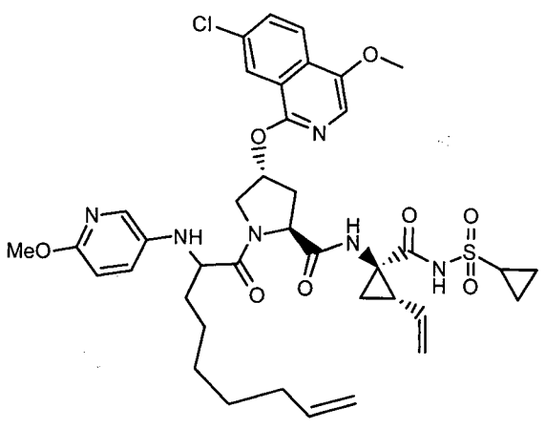
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Ejemplo 410: Preparación de Compuestos 410



Compuesto 410

Ejemplo 411: Preparación de Compuestos 411

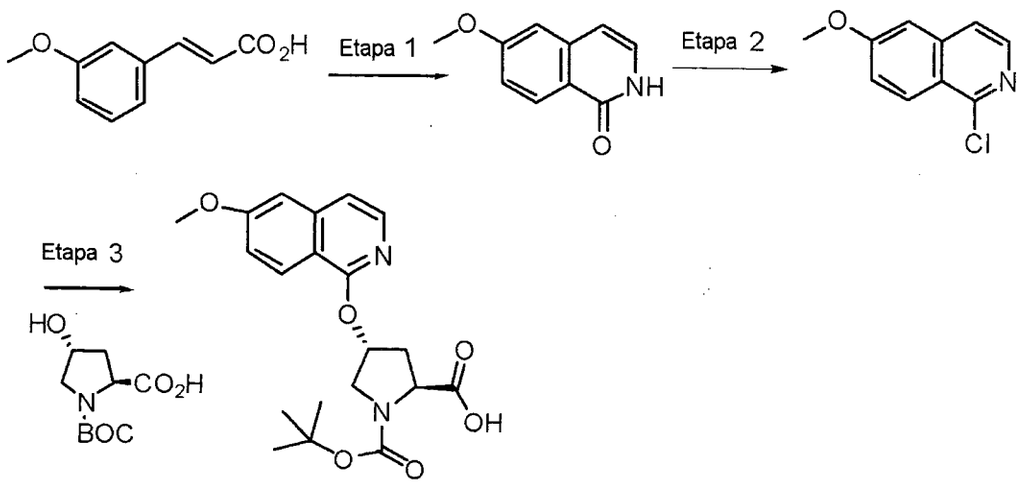


Compuesto 411

Ejemplo 412 Preparación de Intermediarios

Ejemplo de preparaciones de intermediarios de isoquinolina P2 por incorporación en los compuestos de la fórmula 1

Método A



Etapa 1:

A una solución de ácido 3-metoxicinámico (11.04 g, 62 mmol) y trietilamina (12.52 g, 124 mmol) en acetona (80 mL) se agregó cloroformiato de etilo (aproximadamente 1.5 equivalentes) gota a gota a 0°C. Después de la agitación a esta temperatura durante 1 h, NaN_3 acuoso (6.40 g, 100 mmol en 35 mL H_2O; deberán tomarse precauciones apropiadas cuando se usa azida de sodio) se agregó gota a gota y la mezcla de reacción se agitó durante 16 h a la temperatura ambiente. Agua (100 mL) se agregó a la mezcla y el material volátil se removió *in vacuo*. La mezcla espesa resultante se extrajo con tolueno (3X50 mL) y las capas orgánicas combinadas se secaron sobre $MgSO_4$. Esta solución seca se agregó gota a gota a una solución caliente de difenilmetano (50 mL) y tributilamina (30 mL) a 190°C. El tolueno se destiló completamente como se agregó. Después de que terminó la adición, la temperatura de

000696

reacción se elevó a 210°C durante 2 h. Después del enfriamiento, el producto precipitado se colectó por filtración, se lavó con hexano (2X50 mL), y se secó hasta producir el producto deseado como un sólido blanco (5.53 g, 51%) (Nicolas Briet *at el*, Tetrahedron, 2002, 5761-5766). MS *m/z* 176 (M^++H).

Un procedimiento alternativo al anterior emplea azida de difenilfosforilo por la conversión del ácido carboxílico a la acilazida correspondiente. En un procedimiento de un recipiente luego el ácido se convierte a la quinolona correspondiente. El proceso se describe abajo por la preparación de 4-metil-*2H*-isoquinolin-1-ona del ácido 3-fenil-but-2-enoico:

Una solución de ácido 3-fenil-but-2-enoico (16.2 g), azida de difenilfosforilo (27.5 g), y trietilamina (10.1 g) en benceno (100 mL) se agitó durante 1 h. Después de la filtración a través de un tapón de gel de sílice lavando con benceno y concentración, el residuo se disolvió en difenilmetano (80 mL) y se puso a reflujo durante 3 h. Después del enfriamiento a ta, los sólidos se colectaron a través de un tapón lavado con benceno y se secó para dar 10 g (63%) de la 4-metil-*2H*-isoquinolin-1-ona deseada como un sólido. ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.30 (s, 3 H), 7.00 (s, 1 H), 7.54 (m, 1 H), 7.77 (m, 2 H), 8.33 (d, *J*=7.34 Hz, 1 H).

000697

Etapa 2:

La 6-metoxi-*2H*-isoquinolin-1-ona (5.0 g, 28.4 mmol) en $POCl_3$ (10 mL) se calentó a reflujo suave durante 3 h el evaporado *in vacuo* (Nicolas Briet *at el*, **Tetrahedron**, 2002, 5761-5766). El residuo se vació en agua congelada (20 mL) y se neutralizó a un pH 10 con NaOH 10 M. Se extrajo con $CHCl_3$. La capa orgánica se lavó con salmuera, se secó sobre $MgSO_4$, se filtró, evaporó. El residuo se purificó por cromatografía instantánea (1:1 hexano-EtOAc) para proporcionar 4.41 g (80%) del producto deseado como un sólido blanco.

^1H RMN (CD_3OD) δ 3.98 (s, 3H), 7.34-7.38 (m, 2 H), 7.69 (d, *J*=5.5 Hz, 1H), 8.10 (d, *J*=6.0 Hz, 1H), 8.23 (d, *J*=9.5 Hz, 1H). MS *m/z* 194 (M^++H).

Etapa 3:

A una solución de N-BOC-3-(*R*)-hidroxi-L-prolina (892 mg, 3.89 mmol) en DMSO (40 mL) a la temperatura ambiente se le agregó terc-butóxido de potasio (1.34 g, 12.0 mmol) en una porción. La suspensión formada se agitó a esta temperatura durante 30 min antes de enfriarse a 10°C. La 1-cloro-6-metoxi-isoquinolina (ejemplo 11, Etapa 2) (785 mg, 4.05 mmol) se agregó como sólido en una porción y la mezcla final se agitó a la temperatura

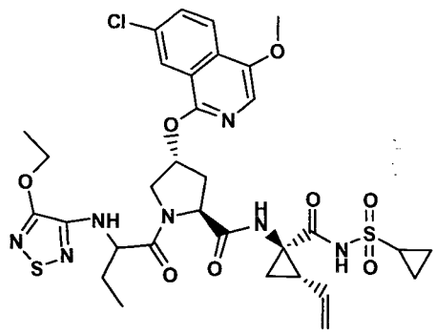
000671

Isómeros del compuesto 233:

(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-1-((2S)-2-((4-etoxi-1,2,5-tiadiazol-3-il)amino)butanoil)-L-prolinamida y

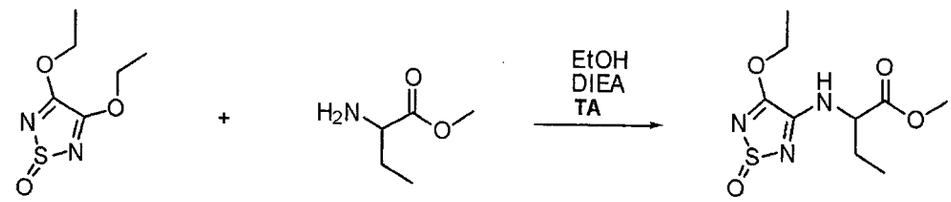
(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-1-((2R)-2-((4-etoxi-1,2,5-tiadiazol-3-il)amino)butanoil)-L-prolinamida

Ejemplo 233: Preparación de Compuestos 233A y 233B



Compuestos 233A y 233B

Etapa 1



Reactivo 1 **sal HCl**

Etapa 1:

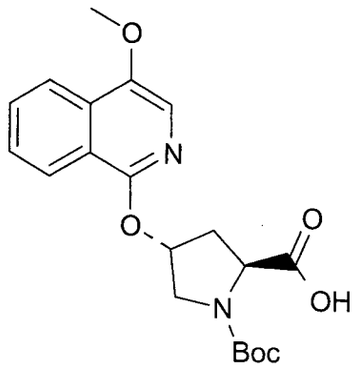
A una solución de Reactante 1 (0.114 g, 0.6 mmol)

006698

ambiente durante 12 h. Se apagó con ácido cítrico al 5% enfriado (ac), se extrajo con EtOAC (100 mL). La fase acuosa se extrajo con EtOAC nuevamente. Las capas orgánicas combinadas se lavaron con ácido cítrico al 5% (ac) y salmuera respectivamente, se secó sobre $MgSO_4$, se filtró. El filtrado se evaporó *in vacuo* hasta secarse hasta producir 1.49 g (99%) del producto deseado como una espuma blanca opaca. Este material se usó en la siguiente etapa de reacción como está sin purificación adicional.

^1H RMN (CD_3OD) δ 1.42, 1.44 (rotámeros, 9H), 2.38-2.43 (m, 1H), 2.66-2.72 (m, 1H), 3.80-3.87 (m, 2H), 3.92 (s, 3H), 4.44-4.52 (m, 1H), 5.73 (a, 1H), 7.16-7.18 (m, 2H), 7.24-7.25 (m, 1H), 7.87-7.88 (m, 1H), 8.07 (d, *J*=8.5 Hz, 1H). MS *m/z* 389 (M^++H).

Los siguientes intermediarios se prepararon como se describe en la presente y se pueden incorporar en los compuestos de la fórmula 1

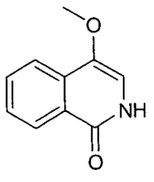


000699

Etapa 1:

Modificaciones: 15 g ácido 3-metoxi-3-fenil-acrílico se usaron, 250 mg de producto se obtuvieron (2% de rendimiento).

Producto:

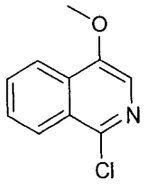


^{1}H RMN (400 MHz, CD_3COCD_3) δ ppm 3.85 (s, 3 H), 6.96 (s, 1 H), 7.54 (m, 1 H), 7.71 (m, 1 H), 7.86 (d, *J*=8.07 Hz, 1 H), 8.31 (d, *J*=8.07 Hz, 1 H).

Etapa 2:

Modificaciones: 200 mg 4-metoxi-2H-isoquinolin-1-ona se usaron, 150 mg de producto se obtuvieron (68% de rendimiento).

Producto:

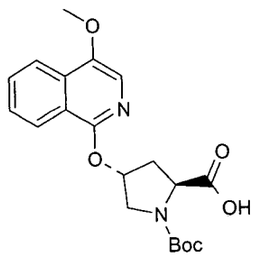


^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 4.05 (s, 2 H), 7.71 (m, 1 H), 7.72 (m, 2 H), 7.80 (s, 1 H), 8.23 (dd, *J*=18.71, 7.70 Hz, 2 H).

Etapa 3:

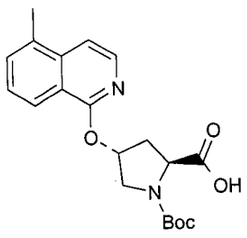
Modificaciones: 122 mg 1-cloro-4-metoxi-isoquinolina se usaron, 218 mg de producto se obtuvieron (89% de rendimiento).

Producto:



EM: $(M+Na)^+$ 411.

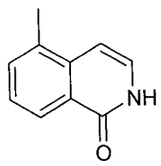
Los siguientes intermediarios se prepararon como se describe en la presente y se pueden incorporar en los compuestos de la fórmula 1



Etapa 1:

Modificaciones: 20 g ácido 2-metilcinámico se usaron, 14.3 g de producto se obtuvieron (72% de rendimiento).

Producto:



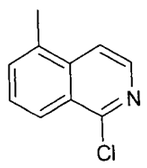
000701

Datos: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.54 (s, 1 H), 6.69 (d, *J*=7.3 Hz, 1 H), 7.23 (d, *J*=7.3 Hz, 1 H), 7.39 (t, *J*=7.8 Hz, 1 H), 7.50 (d, *J*=7.1 Hz, 1 H), 8.30 (d, *J*=8.1 Hz, 1 H), 11.62 (s, 1 H); EM: $(M+H)^+$ 160.

Etapa 2:

Modificaciones: 14.4 g 5-metil-2H-isoquinolin-1-ona se usaron, 10.6 g de producto se obtuvieron (66% de rendimiento).

Producto:

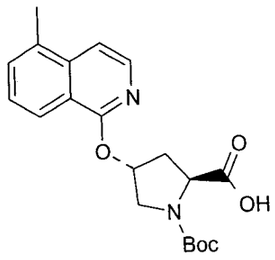


Datos: ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 2.67 (s, 3 H), 7.55 (m, 2 H), 7.70 (dd, *J*=5.9, 1.0 Hz, 1 H), 8.19 (m, 1 H), 8.28 (d, *J*=5.9 Hz, 1 H); EM: $(M+H)^+$ 178.

Etapa 3:

Modificaciones: 533 mg 1-cloro-5-metil-isoquinolina se usaron, 1116 mg de producto se obtuvieron (100% de rendimiento).

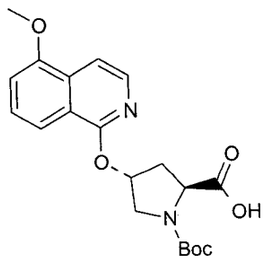
Producto:



000762

Datos: EM: $(M+H)^+$ 373.

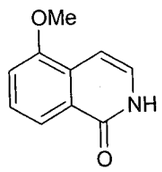
Los siguientes intermediarios se prepararon como se describe en la presente y se pueden incorporar en los compuestos de la fórmula 1



Etapa 1:

Modificaciones: 10 g ácido 2-metoxicinámico se usaron, 5.3 g de producto se obtuvieron (53% de rendimiento).

Producto:



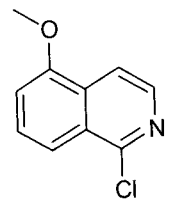
Datos: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 3.95 (s, 3 H), 6.94 (d, *J*=7.3 Hz, 1 H), 7.08 (d, *J*=8.1 Hz, 1 H), 7.14 (d, *J*=7.3 Hz, 1 H), 7.43 (t, *J*=8.1 Hz, 1 H), 7.99 (d, *J*=8.1 Hz, 1 H), 10.92 (s, 1 H); EM: $(M+H)^+$ 176.

Etapa 2:

Modificaciones: 5.3 g 5-metoxi-*2H*-isoquinolin-1-ona se usaron, 5.38 g producto se obtuvieron (92% de rendimiento).

0007-3

Producto:

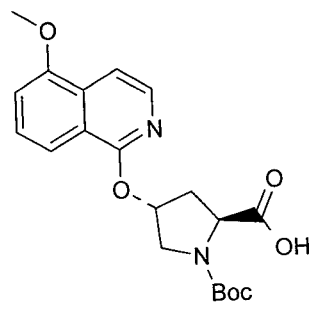


Datos: ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 4.01 (s, 3 H), 7.04 (d, *J*=7.8 Hz, 1 H), 7.57 (t, *J*=8.1 Hz, 1 H), 7.88 (d, *J*=8.6 Hz, 1 H), 7.97 (d, *J*=5.9 Hz, 1 H), 8.25 (d, *J*=5.9 Hz, 1 H); EM: $(M+H)^+$ 194.

Etapa 3:

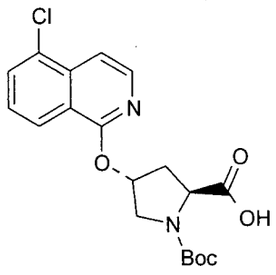
Modificaciones: 581 mg 1-cloro-5-metoxi-isoquinolina se usaron, 1163 mg producto se obtuvieron (100% de rendimiento).

Producto:



Datos: EM: $(M+H)^+$ 389.

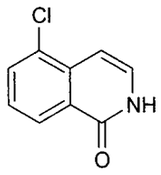
Los siguientes intermediarios se prepararon como se describe en la presente y se pueden incorporar en los compuestos de la fórmula 1



Etapa 1:

Modificaciones: 25 g ácido 2-clorocinámico se usaron, 14.6 g de producto se obtuvieron (59% de rendimiento).

Producto:

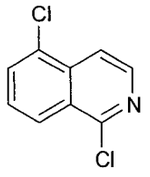


Datos: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 7.22 (d, J=7.3 Hz, 1 H), 7.42 (t, J=7.8 Hz, 1 H), 7.73 (d, J=7.8 Hz, 1 H), 8.34 (d, J=8.1 Hz, 1 H), 10.61 (s, 1H); EM: $(M+H)^+$ 180.

Etapa 2:

Modificaciones: 14.2 g de 5-cloro-2H-isoquinolin-1-ona se usaron, 8.28 g del producto se obtuvieron (53% de rendimiento).

Producto:



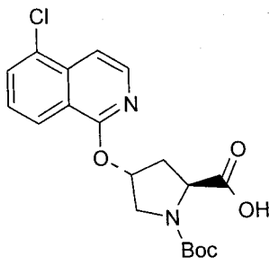
0067.5

Datos: ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 7.60 (dd, J=8.6, 7.6 Hz, 1 H), 7.83 (m, 1 H), 8.00 (d, J=5.9 Hz, 1 H), 8.29 (dt, J=8.9, 1.0 Hz, 1 H), 8.38 (d, J=5.9 Hz, 1 H); EM: $(M+H)^+$ 198.

Etapa 3:

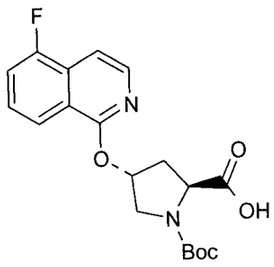
Modificaciones: 594 mg de 1,5-dicloro-isoquinolina se usaron, 1174 mg del producto se obtuvieron (100% de rendimiento).

Producto:



Datos: EM: $(M+H)^+$ 393.

Los siguientes intermediarios se preparan como se describe en la presente y pueden ser incorporados en los compuestos de la fórmula 1

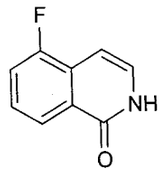


Etapa 1:

Modificaciones: 16.6 g de ácido 2-fluorocinámico se usaron, 8.55 g producto se obtuvieron (51% de rendimiento).

0007.6

Producto:

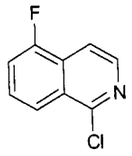


Datos: ^{1}H RMN (400 MHz, CD_3COCD_3) δ ppm 6.62 (d, *J*=7.3 Hz, 1 H), 7.32 (d, *J*=7.3 Hz, 1 H), 7.47 (m, 2 H), 8.09 (m, 1 H).

Etapa 2:

Modificaciones: 8.4 g de 5-fluoro-*2H*-isoquinolin-1-ona usaron, 7.5 g del producto se obtuvieron (80% de rendimiento).

Producto:

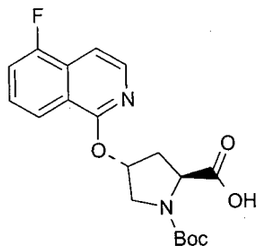


Datos: ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 7.43 (ddd, *J*=9.7, 7.8, 0.9 Hz, 1 H), 7.62 (td, *J*=8.2, 5.4 Hz, 1 H), 7.84 (d, *J*=5.6 Hz, 1 H), 8.14 (d, *J*=8.6 Hz, 1 H), 8.33 (d, *J*=5.9 Hz, 1 H); EM: $(M+H)^+$ 182.

Etapa 3:

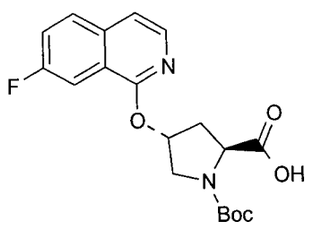
Modificaciones: 203 mg de 1-cloro-5-fluoro-isoquinolina se usaron, 384 mg del producto se obtuvieron (90% de rendimiento).

Producto:



Datos: ^{1}H RMN (400 MHz, CD_3SOCD_3) δ ppm 1.34, 1.36 (2s, 9 H, rotámeros), 2.35 (m, 1 H), 2.61 (m, 1 H), 3.65 (d, *J*=12.23 Hz, 1 H), 3.80 (m, 1 H), 4.35 (m, 1 H), 5.70 (s, 1 H), 7.48 (d, *J*=6.11 Hz, 1 H), 7.63 (m, 2 H), 7.99 (m, 1 H), 8.10 (d, *J*=5.87 Hz, 1 H); EM: $(M+Na)^+$ 399.

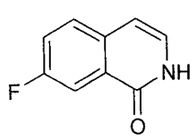
Los siguientes intermediarios se preparan como se describe en la presente y pueden ser incorporados en los compuestos de la fórmula 1



Etapa 1:

Modificaciones: 16.6 g de ácido 4-fluorocinámico se usaron, 8.2 g producto se obtuvieron (49% de rendimiento).

Producto:



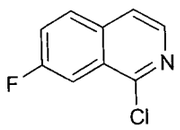
00078

Datos: ^{1}H RMN (400 MHz, CD_3COCD_3) δ ppm 6.57 (d, *J*=7.09 Hz, 1 H), 7.21 (d, *J*=7.09 Hz, 1 H), 7.50 (m, 1 H), 7.72 (dd, *J*=8.68, 5.26 Hz, 1 H), 7.90 (dd, *J*=9.54, 2.93 Hz, 1 H).

Etapa 2:

Modificaciones: 8.15 g de 7-fluoro-2H-isoquinolin-1-ona se usaron, 7.6 g del producto se obtuvieron (84% de rendimiento).

Producto:

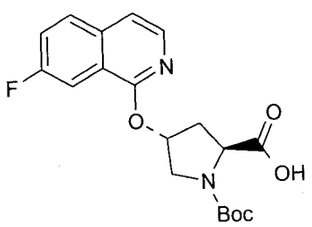


Datos: ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 7.52 (td, *J*=8.6, 2.6 Hz, 1 H), 7.59 (d, *J*=5.6 Hz, 1 H), 7.86 (dd, *J*=9.1, 5.4 Hz, 1 H), 7.95 (dd, *J*=9.5, 2.5 Hz, 1 H), 8.26 (d, *J*=5.6 Hz, 1 H); EM: $(M+H)^+$ 182.

Etapa 3:

Modificaciones: 191 mg de 1-cloro-7-fluoro-isoquinolina se usaron, 350 mg del producto se obtuvieron (93% de rendimiento).

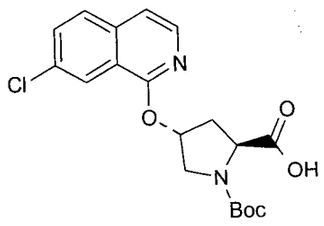
Producto:



000799

Datos: EM: $(M+Na)^+$ 399.

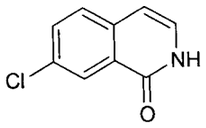
Los siguientes intermediarios se preparan como se describe en la presente y pueden ser incorporados en los compuestos de la fórmula 1



Etapa 1:

Modificaciones: 9.13 g de ácido 4-clorocinámico se usaron, 4 g del producto se obtuvieron (44% de rendimiento).

Producto:

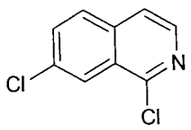


Datos: ^{1}H RMN (400 MHz, CD_3SOCD_3) δ ppm 6.58 (d, *J*=7.1 Hz, 1 H), 7.20 (dd, *J*=7.1, 5.9 Hz, 1 H), 7.72 (m, 2 H), 8.10 (m, 1 H).

Etapa 2:

Modificaciones: 3.5 g de 7-cloro-2*H*-isoquinolin-1-ona se usaron, 2.8 g del producto se obtuvieron (72% de rendimiento).

Producto:



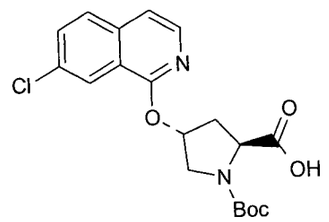
000710

Datos: ^{1}H RMN (500 MHz, $CDCl_3$) δ ppm 7.59 (d, J=5.5 Hz, 1 H), 7.69 (dd, J=8.9, 2.1 Hz, 1 H), 7.80 (d, J=8.6 Hz, 1 H), 8.29 (d, J=5.5 Hz, 1 H), 8.34 (s, 1 H); EM: $(M+H)^+$ 198.

Etapa 3:

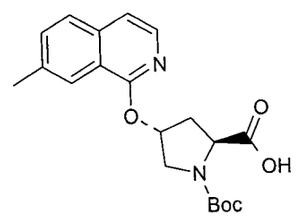
Modificaciones: 208 mg de 1,7-dicloro-isoquinolina se usaron, 350 mg del producto se obtuvieron (89% de rendimiento).

Producto:



Datos: EM: $(M+Na)^+$ 415.

Los siguientes intermediarios se preparan como se describe en la presente y pueden ser incorporados en los compuestos de la fórmula 1

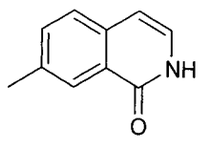


Etapa 1:

Modificaciones: 25 g de ácido 4-metilcinámico se usaron, 15.3 g del producto se obtuvieron (62% de rendimiento).

000711

Producto:

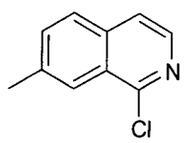


Datos: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 2.50 (s, 3 H), 6.54 (d, *J*=7.1 Hz, 1 H), 7.13 (d, *J*=7.1 Hz, 1 H), 7.49 (m, 2 H), 8.22 (s, 1 H), 11.49 (s, 1 H); EM: $(M+H)^+$ 160.

Etapa 2:

Modificaciones: 15.3 g de 7-metil-2*H*-isoquinolin-1-ona se usaron, 5.15 g del producto se obtuvieron (30% de rendimiento).

Producto:



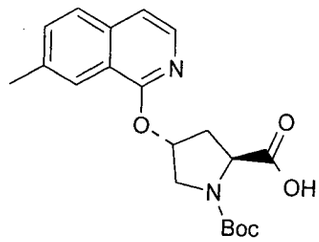
Datos: ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 2.58 (s, 3 H), 7.56 (m, 2 H), 7.73 (d, *J*=8.3 Hz, 1 H), 8.09 (s, 1 H), 8.20 (d, *J*=5.6 Hz, 1 H); EM: $(M+H)^+$ 178.

Etapa 3:

Modificaciones: 205 mg de 1-cloro-7-metil-isoquinolina se usaron, 350 mg de producto se obtuvieron (89 % de rendimiento).

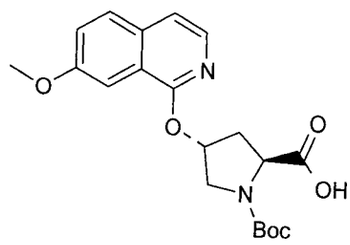
000712

Producto:



Datos: EM: $(M+H)^+$ 373.

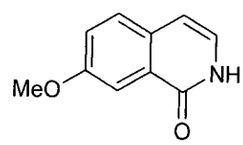
Los siguientes intermediarios se preparan como se describe en la presente y pueden ser incorporados en los compuestos de la fórmula 1



Etapa 1:

Modificaciones: 33 g usando ácido 4-metoxicinámico se usaron, 7 g del producto se obtuvieron (33% de rendimiento).

Producto:



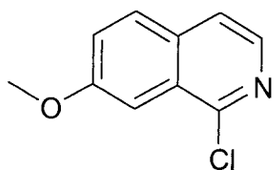
Datos: ^{1}H RMN (500 MHz, CD_3COCD_3) δ ppm 3.90 (s, 3 H), 6.49 (d, J=7.0 Hz, 1 H), 7.10 (d, J=7.3 Hz, 1 H), 7.28 (dd, J=8.6, 2.8 Hz, 1 H), 7.57 (d, J=8.9 Hz, 1 H), 7.71 (d, J=2.8 Hz, 1 H).

000713

Etapa 2:

Modificaciones: 4 g de 7-metoxi-2*H*-isoquinolin-1-ona se usaron, 3 g del producto se obtuvieron (68 % de rendimiento).

Producto:

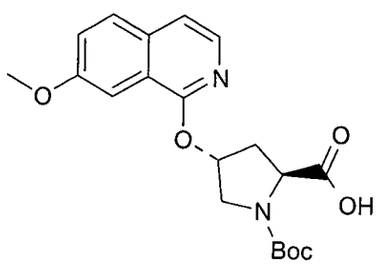


Datos: ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 3.98 (s, 3 H), 7.38 (dd, *J*=8.9, 2.6 Hz, 1 H), 7.52 (m, 2 H), 7.73 (d, *J*=8.8 Hz, 1 H), 8.16 (d, *J*=5.4 Hz, 1 H).

Etapa 3:

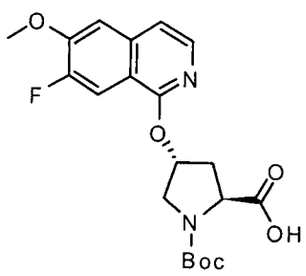
Modificaciones: 533 mg de 1-cloro-7-metoxi-isoquinolina se usaron, 1115 mg del producto se obtuvieron (100% de rendimiento).

Producto:



Los siguientes intermediarios se preparan como se describe en la presente y pueden ser incorporados en los compuestos de la fórmula 1

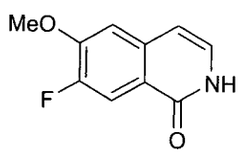
030714



Etapa 1:

Modificaciones: 19.6 g de ácido 4-fluoro-3-metoxicinámico se usaron, 9.5 g del producto se obtuvieron (48% de rendimiento).

Producto:

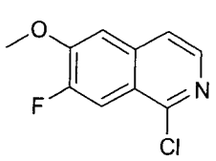


Datos: ^{1}H RMN (400 MHz, CD_3COCD_3) δ ppm 4.00 (s, 1 H), 6.49 (d, *J*=7.34 Hz, 1 H), 7.19 (d, *J*=7.09 Hz, 1 H), 7.29 (d, *J*=8.07 Hz, 1 H), 7.86 (d, *J*=11.74 Hz, 1 H).

Etapa 2:

Modificaciones: 9 g de 7-fluoro-6-metoxi-*2H*-isoquinolin-1-ona se usaron, 7 g del producto se obtuvieron (70% de rendimiento).

Producto:



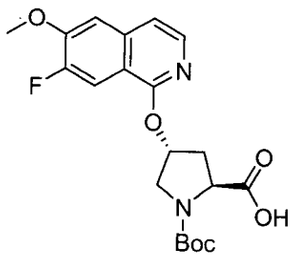
030715

Datos: ^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 4.04 (s, 3 H), 7.17 (d, *J*=8.07 Hz, 1 H), 7.48 (d, *J*=5.62 Hz, 1 H), 7.94 (d, *J*=11.49 Hz, 1 H), 8.20 (d, *J*=5.62 Hz, 1 H).

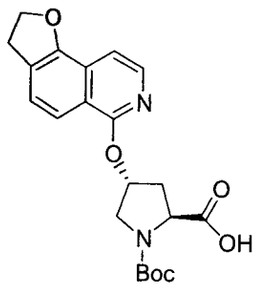
Etapa 3:

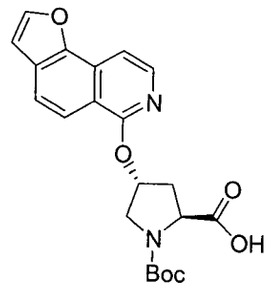
Modificaciones: 222 mg de 1-cloro-7-fluoro-6-metoxi-isoquinolina se usaron, 406 mg del producto deseado se obtuvieron.

Producto Deseado:



Los siguientes intermediarios se preparan como se describe en la presente y pueden ser incorporados en los compuestos de la fórmula 1



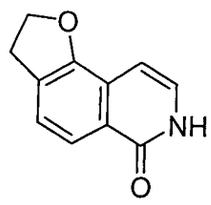


Etapa 1:

Modificaciones: 3.8 g de ácido 3-(2,3-dihidro-benzofuran-7-il)-acrílico se usaron, 2 g del producto se obtuvieron (53% de rendimiento).

000716

Producto:

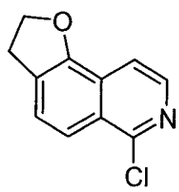


Datos: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 3.37 (t, *J*=9.05 Hz, 1 H), 4.73 (t, *J*=9.05 Hz, 2 H), 6.67 (d, *J*=7.09 Hz, 1 H), 7.10 (d, *J*=7.09 Hz, 1 H), 7.37 (d, *J*=8.07 Hz, 1 H), 7.81 (d, *J*=8.07 Hz, 1 H); EM: $(M+H)^+$ 188.

Etapa 2:

Modificaciones: 1.87 g de 2,3-dihidro-7*H*-furo[2,3-f]isoquinolin-6-ona se usaron, 1.84 g del producto se obtuvieron (90% de rendimiento).

Producto:



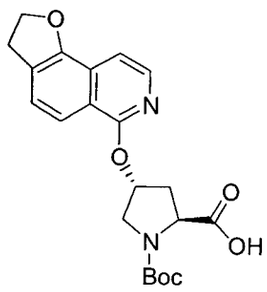
Datos: ^{1}H RMN (400 Hz, $CDCl_3$) δ ppm 3.43 (t, *J*=9.05 Hz, 2 H), 4.82 (t, *J*=9.05 Hz, 2 H), 7.52 (d, *J*=8.56 Hz, 1 H), 7.66 (d, *J*=5.62 Hz, 1 H), 7.84 (d, *J*=8.31 Hz, 1 H), 8.19 (d, *J*=5.62 Hz, 1 H); MS $(M+H)^+$ 206.

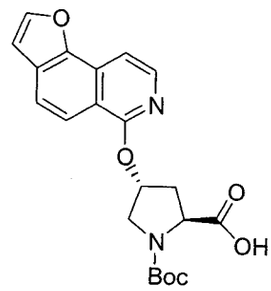
000717

Etapa 3:

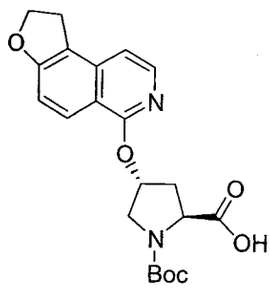
Modificaciones: 206 mg 6-cloro-2,3-dihidro-furo[2,3-f]isoquinolina se usaron, 300 mg de mezcla de productos se obtuvieron.

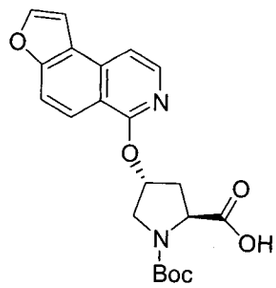
Productos:





Los siguientes intermediarios se preparan como se describe en la presente y pueden ser incorporados en los compuestos de la fórmula 1

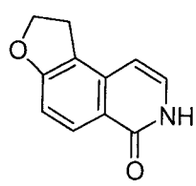




Etapa 1:

Modificaciones: 1.14 g de ácido 3-(2,3-dihidro-benzofuran-4-il)-acrílico se usaron, 600 mg del producto se obtuvieron (52% de rendimiento).

Producto:



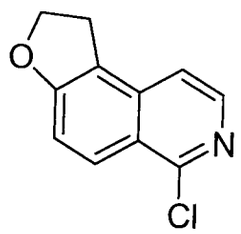
000718

Datos: ^{1}H RMN (400 MHz, CD_3OD) δ ppm 3.35 (t, *J*=8.93 Hz, 2 H), 4.74 (t, *J*=8.93 Hz, 2 H), 6.49 (d, *J*=7.09 Hz, 1 H), 6.95 (d, *J*=8.56 Hz, 1 H), 7.25 (d, *J*=7.09 Hz,, 1 H), 8.13 (d, *J*=8.80 Hz, 1 H); MS $(M+H)^+$ 188.

Etapa 2:

Modificaciones: 560 mg de 1,7-dihidro-2*H*-furo[3,2-f]isoquinolin-6-ona se usaron, 380 mg del producto se obtuvieron (48% de rendimiento).

Producto:



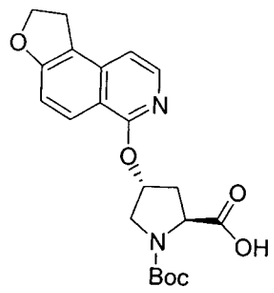
Datos: ^{1}H RMN (400 Hz, $CDCl_3$) δ ppm 3.47 (t, *J*=9.05 Hz, 2 H), 4.84 (t, *J*=9.05 Hz, 2 H), 7.24 (d, *J*=8.56 Hz, 1 H), 7.33 (d, *J*=5.87 Hz, 1 H), 8.20 (m, 2 H); MS $(M+H)^+$ 206.

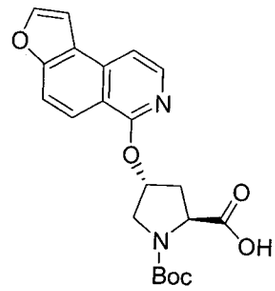
Etapa 3:

Modificaciones: 105 mg de 6-cloro-1,2-dihidro-furo[3,2-f]isoquinolina se usaron, 390 mg de productos de mezcla se obtuvieron.

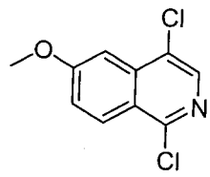
000719

Productos:





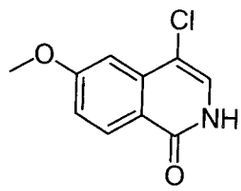
Los siguientes intermediarios se preparan como se describe en la presente y pueden ser incorporados en los compuestos de la fórmula 1



Etapa 1:

Modificaciones: una mezcla de 6-metoxi-2*H*-isoquinolin-1-ona (700 mg) y NCS (532 mg) en MeCN (10 mL) se puso a reflujo durante 3 h. La filtración dió 600 mg (72%) del producto deseado como un sólido.

Producto:



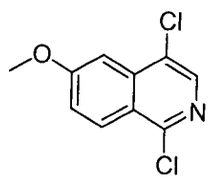
Datos: ^{1}H RMN(400 MHz, CD_3OD) δ ppm 3.96 (s, 1 H), 7.19 (dd, *J*=8.80, 2.45 Hz, 1 H), 7.28 (d, *J*=2.45 Hz, 1 H), 7.34 (s, 1 H), 8.25 (d, *J*=9.05 Hz, 1 H); EM: $(M+H)^+$ 210.

000720

Etapa 2:

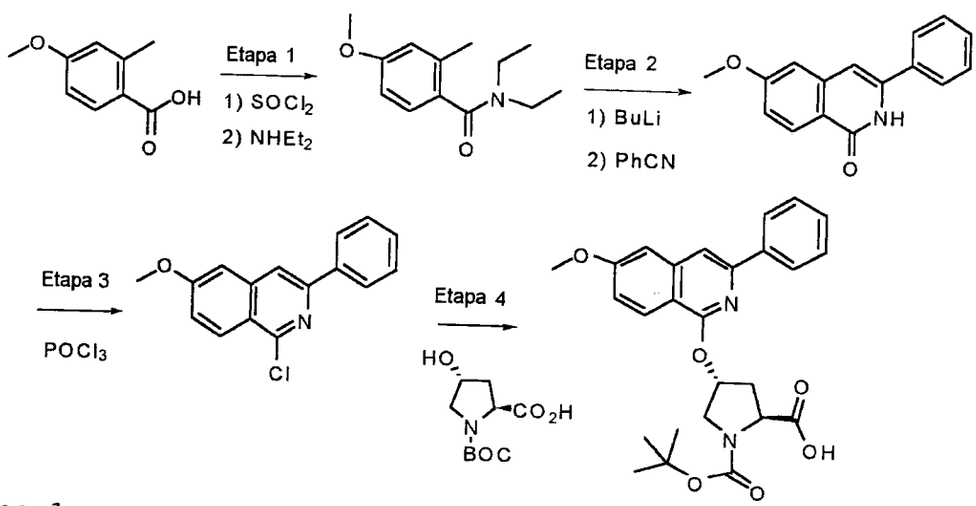
Modificaciones: 500 mg de 4-cloro-6-metoxi-2H-isoquinolin-1-ona se usaron, 400 mg del producto se obtuvieron.

Producto:



Datos: ^{1}H RMN (400 Hz, $CDCl_3$) δ ppm 4.01 (s, 3 H), 7.35 (d, *J*=2.45 Hz, 1 H), 7.41 (d, *J*=2.45 Hz, 1 H), 8.24 (d, *J*=9.29 Hz, 1 H), 8.27 (s, 1 H); EM: $(M+H)^+$ 229.

Método B



Etapa 1:

Una mezcla de ácido 4-metoxi-2-metil-benzoico (5.00 g, 30.1 mmol) y cloruro de tionilo (20.0 g, 0.17 mol) se calentó a reflujo durante 30 min. Se removieron los

006721

materiales volátiles *in vacuo*. Después de bombeo durante la noche, el cloruro del ácido de aceite viscoso se usó como está para la siguiente reacción sin cualquier purificación.

A una solución de cloruro de 4-metoxi-2-metil-benzoilo en CH_2Cl_2 (60 mL) a 0°C se agregó dietilamina gota a gota. La mezcla formada se permitió calentar hasta la temperatura ambiente durante 2 h con agitación. Se remueven los materiales volátiles *in vacuo*. El residuo se trituró con EtOAc (100 mL) y se filtró. El filtrado se lavó con HCl 1M, NaOH 1M y salmuera, se secó sobre $MgSO_4$. La evaporación del solvente proporciona 6.51 g (98%) del producto deseado como un aceite viscoso. MS *m/z* 222 (M^++H).

Etapa 2:

A una solución de N,N-dietil-4-metoxi-2-metil-benzamida (221 mg, 1.0 mmol) en THF (2 mL) a -78°C se agregó n-BuLi (0.84 mL de 2.5 M en hexano, 2.10 mmol) gota a gota. La solución anaranjada formada se mantuvo a esta temperatura durante 30 min adicionales antes de agregar gota a gota benzonitrilo (103 mg, 1.0 mmol). La solución final se permitió calentar hasta temperatura ambiente durante la noche con agitación. Se apagó con 5% de ácido cítrico enfriado. Se filtró, se lavó con agua, se secó. La trituración con 2:1 hexano-EtOAc (5 mL) proporcionó 205 mg (82%) del producto deseado como un sólido blanco.

000722

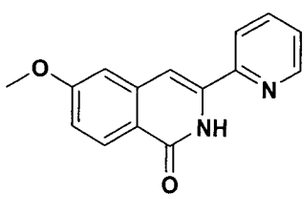
^{1}H RMN (d_6-DMSO) δ 3.89 (s, 3H), 6.84 (s, 1H), 7.05-7.07 (m, 1H), 7.18 (d, *J*=2.5 Hz, 1H), 7.44-7.51 (m, 3H), 7.78 (d, *J*=7.0 Hz, 1H), 8.11 (d, *J*=9.0 Hz, 1H). MS *m/z* 252 (M^++H).

Etapa 3:

Este producto, 1-cloro-6-metoxi-3-fenil-isoquinolina, se preparó por el mismo método como se describe arriba excepto que se usó 6-metoxi-3-fenil-2H-isoquinolin-1-ona.

^{1}H RMN ($CDCl_3$) δ 3.97 (s, 3H), 7.12 (d, *J*=2.5 Hz, 1H), 7.23-7.26 (m, 1H), 7.40-7.42 (m, 1H), 7.46-7.50 (m, 2H), 7.89 (s, 1H), 8.08 (d, *J*=7.0 Hz, 2H), 8.21 (d, *J*=9.0 Hz, 1H). MS *m/z* 270, 271 (M^++H).

Los siguientes intermediarios se preparan como se describe en la presente y pueden ser incorporados en los compuestos de la fórmula 1



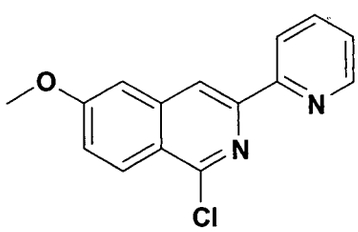
A una solución de N,N-Dietil-4-metoxi-2-metil-benzamida (332 mg, 1.5 mmol) en THF (15 mL) a -78°C, t-BuLi (1.7 M solución en pentano, 1.3 mL, 2.25 mmol) se agregó. La solución roja resultante se agitó a -78°C durante 10 min, luego 2-cianopiridina (156 mg, 1.5 mmol) se agregó. La mezcla

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de reacción luego se calentó a temperatura ambiente y se agitó durante la noche. La reacción se apagó con solución NH_4Cl saturada y luego se extrajo con acetato de etilo dos veces. Las capas orgánicas combinadas se secaron ($MgSO_4$) y se concentraron. El producto sin refinar se purificó por HPLC preparativa para dar sólido amarillento como sal TFA. (85 mg, 15% de rendimiento)

^1H RMN (400 MHz, CD_3OD) δ 3.91 (m, 3 H), 7.09 (dd, J=9.05, 2.45 Hz, 1 H), 7.17 (d, J=2.45 Hz, 1 H), 7.37 (s, 1 H), 7.42 (m, 1 H), 7.92 (m, 1 H), 8.08 (d, J=8.07 Hz, 1 H), 8.18 (d, J=9.05 Hz, 1 H), 8.65 (d, J=4.89 Hz, 1 H). MS m/z 253 (MH^+).

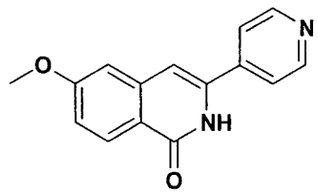
Etapa 2 (Esquema de reacción 3, Etapa 1):



Sal TFA de 6-Metoxi-3-piridin-2-il-2H-isoquinolin-1-ona (85 mg, 0.232 mmol) se calentó bajo reflujo con $POCl_3$ (3.0 mL) durante 2 días. Luego $POCl_3$ se destiló completamente y el residuo se apagó con hielo. Luego se neutraliza con solución de NaOH 10 N y el sólido café se colectó como producto puro. (62 mg, 99% de rendimiento). MS m/z 271 (MH^+).

000724

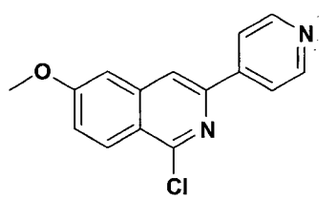
Los siguientes intermediarios se preparan como se describe en la presente y pueden ser incorporados en los compuestos de la fórmula 1



A una solución de N,N-Dietil-4-metoxi-2-metil-benzamida (332 mg, 1.5 mmol) en THF (15 mL) a -78°C, t-BuLi (1.7 M solución en pentano, 1.3 mL, 2.25 mmol) se agregó. La solución roja resultante se agitó a -78°C durante 10 min, luego 4-cianopiridina (164 mg, 1.575 mmol) se agregó. La mezcla de reacción luego se calentó a temperatura ambiente y se agitó durante la noche. La reacción se apagó con solución NH_4Cl saturada y el precipitado amarillo se colectó como producto puro. (145 mg, 38% de rendimiento)

^1H RMN(CD_3OD, 400 MHz) δ 3.91 (s, 3 H), 7.18 (dd, J=8.8 Hz, 2.8 Hz, 1 H), 7.26 (m, 2 H), 8.06 (d, J=6.0 Hz, 2H), 8.16 (d, J=8.8 Hz, 1H), 8.84 (d, J=6.0 Hz, 2H). MS m/z 253 (MH^+).

Etapa 2 (Esquema de reacción 3, etapa 1):

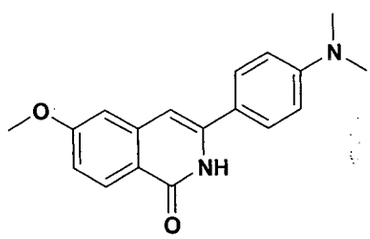


000725

6-Metoxi-3-piridin-4-il-2H-isoquinolin-1-ona (134 mg, 0.531 mmol) se calentó bajo reflujo con $POCl_3$ (6.0 mL) durante 5 días. Luego $POCl_3$ se destiló y el residuo se apagó con hielo. Se neutralizó luego con solución $NaHCO_3$ saturada y el sólido café se colectó como producto puro. (125 mg, 87% de rendimiento)

^1H RMN (DMSO-d^6, 400 MHz) δ 3.99 (s, 3 H), 7.53 (dd, *J*=9.04 Hz, 2.44 Hz, 1 H), 7.59 (d, *J*=2.69 Hz, 1 H), 8.26 (d, *J*=9.05 Hz, 1 H), 8.30 (d, *J*=5.38 Hz, 2 H), 8.73 (s, 1 H), 8.85 (d, *J*=6.36 Hz, 2 H). MS m/z 271 (MH^+).

Los siguientes intermediarios se preparan como se describe en la presente y pueden ser incorporados en los compuestos de la fórmula 1

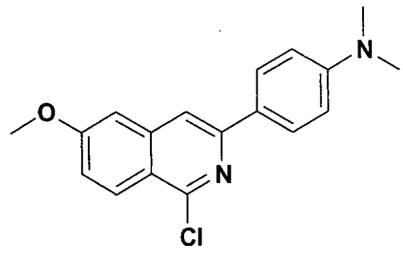


A una solución de N,N-Dietil-4-metoxi-2-metil-benzamida (332 mg, 1.5 mmol) en THF (15 mL) a -78°C, t-BuLi (1.7 M solución en pentano, 1.3 mL, 2.25 mmol) se agregó. La solución roja resultante se agitó a -78°C durante 10 min, luego 4-dimetilamino benzonitrilo (219 mg, 1.5 mmol) se agregó. La mezcla de reacción luego se calentó a temperatura ambiente y se agitó durante la noche. La reacción se apagó

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con solución NH_4Cl saturada y el precipitado amarillo se colectó y trituró con éter para dar un sólido blanco opaco como producto puro. (247 mg, 56% de rendimiento)

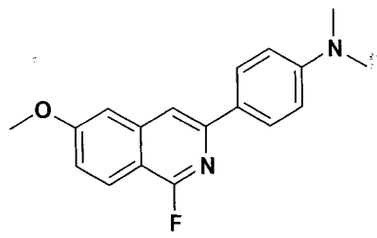
^1H RMN(DMSO-d^6, 400 MHz) δ 2.97 (s, 6 H), 3.87 (s, 3 H), 6.72 (s, 1 H), 6.78 (d, *J*=8.80 Hz, 2 H), 6.97 (dd, *J*=8.80, 2.45 Hz, 1 H), 7.10 (d, *J*=2.45 Hz, 1 H), 7.65 (d, *J*=8.80 Hz, 2 H), 8.05 (d, *J*=8.80 Hz, 1 H), 11.11 (s, 1 H). MS m/z 295 (MH^+).



3-(4-Dimetilamino-fenil)-6-metoxi-2H-isoquinolin-1-ona (245 mg, 0.83 mmol) se calentó bajo reflujo con $POCl_3$ (10.0 mL) durante 2 días. Luego $POCl_3$ se destiló y el residuo se apagó con hielo. Luego se neutraliza con 10 N de solución NaOH y luego se extrajo con acetato de etilo dos veces. Las capas orgánicas se combinaron y se secaron (MgSO4). La evaporación del solvente dió un sólido anaranjado como producto (215 mg, 83% de rendimiento)

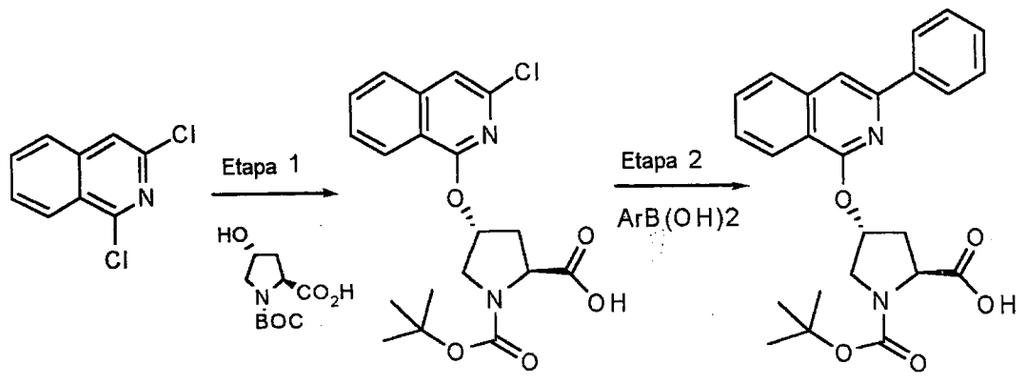
^1H RMN (400 MHz, CD_3OD) δ 3.01 (s, 6 H), 3.96 (s, 3 H), 6.88 (d, *J*=9.05 Hz, 2 H), 7.20 (dd, *J*=9.17, 2.57 Hz, 1 H), 7.28 (d, *J*=2.45 Hz, 1 H), 7.94 (s, 1 H), 7.96 (d, *J*=9.05 Hz, 2 H), 8.13 (d, *J*=9.29 Hz, 1 H). MS m/z 313 (MH^+).

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Una mezcla de [4-(1-Cloro-6-metoxi-isoquinolin-3-il)-fenil]-dimetil-amina (110 mg, 0.35 mmol) y difluoruro ácido de tetrabutil fosfonio (0.5 g) se calentó a 140°C en un reactor de microondas Smith durante 20 min. Luego se agregó agua y se extrajo con acetato de etilo. La capa orgánica se separó, se lavó con agua y se secó ($MgSO_4$). La evaporación del solvente dió un sólido de color café como producto. (85 mg, 82% de rendimiento). MS m/z 297 (MH^+).

Método C



Etapa 1:

A una solución de N-BOC-3-(*R*)-hidroxi-L-prolina (6.22 g, 26.9 mmol) en DMF (250 mL) a 0°C se agregó NaH (60%, 3.23 g,

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80.8 mmol) en varias porciones. La suspensión formada se agitó a esta temperatura durante 30 min. 1,3-dicloro-isoquinolina (5.33 g, 26.9 mmol) se agregó como sólido en una porción y la mezcla final se agitó a temperatura ambiente durante 12 h. Se apagó con 5% de ácido cítrico enfriado (ac.), se extrajo con EtOAC (300 mL). La fase acuosa se extrajo otra vez con EtOAC. Las capas orgánicas combinadas se lavaron con 5% de ácido cítrico (ac.) y salmuera respectivamente, se secó sobre $MgSO_4$, se filtró. El filtrado se evaporó *in vacuo* hasta secarse para proporcionar 10.53 g (99.8%) de éster de 1-terc-Butilo del ácido 4-(6-metoxi-isoquinolin-1-iloxi)-pirrolidin-1,2-dicarboxílico como una espuma blanca. Este material se usó en la siguiente etapa de reacción como sin refinar sin purificación adicional.

^{1}H RMN (CD_3OD) δ 1.43, 1.44 (rotámeros, 9H), 2.39-2.44 (m, 1H), 2.68-2.72 (m, 1H), 3.80-3.90 (m, 2H), 4.44-4.52 (m, 1H), 5.77 (a, 1H), 7.39 (s, 1H), 7.58 (t, *J*=7.3 Hz, 1H), 7.71-7.78 (m, 2H), 8.16 (d, *J*=7.5 Hz, 1H). MS *m/z* 392 (M^++H).

Etapa 2:

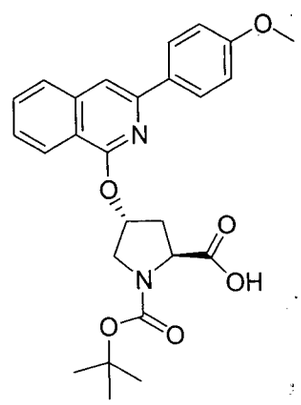
Una mezcla de éster de 1-terc-Butilo del ácido 4-(6-metoxi-isoquinolin-1-iloxi)-pirrolidin-1,2-dicarboxílico (39 mg, 0.10 mmol), ácido fenilborónico (14.6 mg, 0.12 mmol), terc-butóxido de sodio (38 mg, 0.40 mmol) y $((t\text{-}Bu)_2POH)_2PdCl_2$

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(POPd) (5 mg, 0.01 mmol) en THF (2 mL) se calentó a reflujo durante 4 h. Después de enfriarse, la mezcla formada se apagó con 5% de ácido cítrico (ac.) y luego se extrajo con EtOAc (20 mL). La capa orgánica se lavó con salmuera, se secó sobre $MgSO_4$, se filtró, se evaporó. El residuo se purificó por HPLC preparativa para proporcionar 36 mg (83%) del producto deseado como una espuma blanca.

^{1}H RMN (CD_3OD) δ 1.43, 1.45 (rotámeros, 9H), 2.51-2.56 (m, 1H), 2.74-2.82 (m, 1H), 3.88-3.92 (m, 1H), 3.98-4.01 (m, 1H), 4.50-4.57 (m, 1H), 5.95 (a, 1H), 7.36-7.39 (m, 1H), 7.45-7.48 (m, 2H), 7.55 (t, *J*=7.3 Hz, 1H), 7.70 (t, *J*=7.5 Hz, 1H), 7.84-7.89 (m, 2H), 8.14-8.17 (m, 3H), 9.05 (a, 1H). MS *m/z* 435 (M^++H).

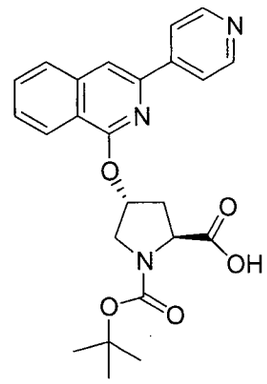
Los siguientes intermediarios se preparan como se describe en la presente y pueden ser incorporados en los compuestos de la fórmula 1



Preparado usando ácido 4-metoxifenilborónico

^{1}H RMN (CD_3OD) δ 1.40, 1.45 (rotámeros, 9H), 2.50-2.55 (m, 1H), 2.73-2.81 (m, 1H), 3.81-3.89 (m, 4H), 3.98-4.01 (m, 1H), 4.50-4.57 (m, 1H), 5.93 (a, 1H), 7.02 (d, *J*=9.0 Hz, 2H), 7.50 (t, *J*=7.3 Hz, 1H), 7.67 (t, *J*=7.5 Hz, 1H), 7.73 (s, 1H), 7.83 (d, *J*=8.5 Hz, 1H), 8.09 (d, *J*=8.5 Hz, 2H), 8.15 (d, *J*=8.0 Hz, 1H). MS *m/z* 465 (M^++H).

El siguiente intermediario se preparó como se describe arriba:

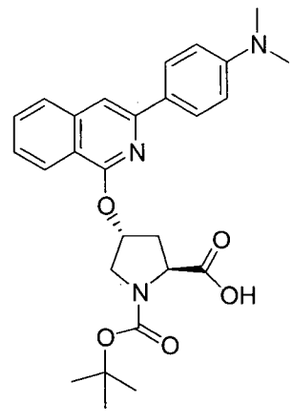


Preparado usando ácido 4-piridilborónico

^{1}H RMN (CD_3OD) δ 1.43, 1.46 (rotámeros, 9H), 2.53-2.56 (m, 1H), 2.80-2.89 (m, 1H), 3.90-3.93 (m, 1H), 4.00-4.05 (m, 1H), 4.50-4.57 (m, 1H), 6.00, 6.05(rotámeros, 1H), 7.80 (t, *J*=7.3 Hz, 1H), 7.87 (t, *J*=7.5 Hz, 1H), 8.08 (d, *J*=8.5 Hz, 1H), 8.32 (d, *J*=8.0 Hz, 1H), 8.49 (s, 1H), 8.84 (d, *J*=6.0 Hz, 2H), 8.84 (d, *J*=6.5 Hz, 2H. MS *m/z* 436 (M^++H).

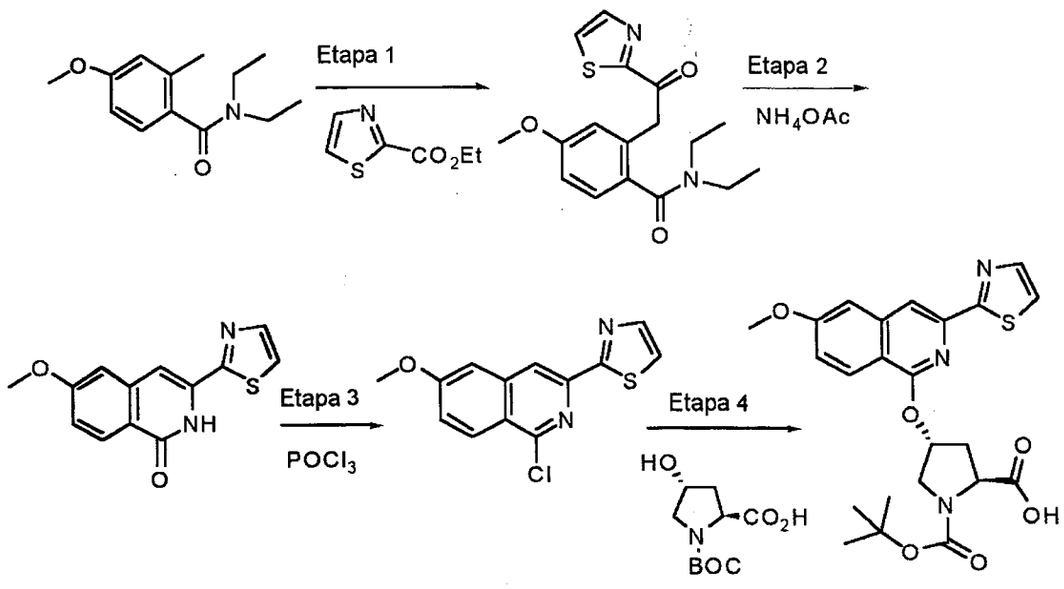
Los siguientes intermediarios se preparan como se describe en la presente y puede ser incorporados en los compuestos de la fórmula 1

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Preparado usando ácido 4-N,N-dimetilamino-fenilborónico. MS *m/z* 478 (M^++H).

Método D



Etapa 1:

A una solución de N,N-dietil-4-metoxi-2-metil-benzamida (633 mg, 2.9 mmol) en THF (15 mL) a -78°C se agregó n-BuLi (2.3 mL de 2.5 M en hexano, 5.74 mmol) gota a gota. La

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solución roja formada se mantuvo a esta temperatura durante 30 min adicionales antes de ser transferida por cánula a una solución de éster etílico del ácido tiazol-2-carboxílico (A. Medici et al, Tetrahedron Lett. 1983, p2901) (450 mg, 2.9 mmol) en THF (5 mL) a -78°C. La solución verde oscura final se mantuvo a esta temperatura durante 2 h con agitación. Se apagó con NH_4Cl saturada (ac) y luego se extrajo con EtOAc (50 mL). La capa orgánica se lavó con NH_4Cl saturada (ac) y salmuera, se secó, se purificó por cromatografía de columna instantánea, se eluyó con 2:1 EtOAc: hexano para proporcionar 405 mg (45%) del producto deseado como un aceite viscoso blanco opaco.

^1H RMN ($CDCl_3$) δ 1.08 (t, J=7.0 Hz, 6H), 3.22 (a, 2H), 3.44 (a, 2H), 3.79 (s, 3H), 4.59 (s, 2H), 6.79-6.81 (m, 1H), 6.86 (d, J=2.5 Hz, 1H), 7.16 (d, J=8.5 Hz, 1H), 7.66 (d, J=3.0 Hz, 1H), 8.00 (d, J=3.0 Hz, 1H).

MS m/z 333 (M^++H).

Etapa 2:

Una mezcla de N,N-dietil-4-metoxi-2-(2-oxo-2-tiazol-2-il-etil)-benzamida (405 mg, 1.22 mmol) y NH_4OAc (3.0 g, 38.9 mmol) se calentó a 140°C en un tubo sellado durante 1 h. La solución derretida se vació en agua enfriada con hielo, se filtró, se lavó la torta a fondo con agua. El sólido de color café seco, (240 mg, 76%) se usó como sin refinar durante la

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siguiente reacción sin purificación adicional. MS *m/z* 259 (M^++H).

Etapa 3:

Este producto, 1-cloro-6-metoxi-3-tiazol-2-il-isoquinolina, se preparó como se describe arriba excepto que se usó 6-metoxi-3-tiazol-2-il-2H-isoquinolin-1-ona.

^{1}H RMN ($CDCl_3$) δ 3.97 (s, 3H), 7.16 (d, *J*=4.0 Hz, 1H), 7.27-7.31 (m, 1H), 7.46 (d, *J*=5.0 Hz, 1H), 7.93 (d, *J*=5.5 Hz, 1H), 8.22 (d, *J*=15.5 Hz, 1H), 8.39 (s, 1H). MS *m/z* 277 (M^++H).

Etapa 4:

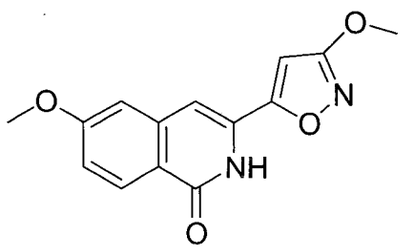
Este producto se preparó por el mismo método como se describe excepto usando 1-cloro-6-metoxi-3-tiazol-2-il-isoquinolina.

^{1}H RMN (CD_3OD) δ 0.97-1.09 (m, 12H), 1.24-1.29 (m, 10H), 1.44-1.46 (m, 1H), 1.87-1.90 (m, 1H), 2.20-2.26 (m, 1H), 2.30-2.36 (m. 1H), 2.65-2.71 (m, 1H), 2.93-2.96 (m, 1H), 3.96 (s, 3H), 4.12-4.27 (m, 2H), 4.38-4.52 (m, 2H), 5.12 (d, *J*=10.5 Hz, 1H), 5.29 (d, *J*=17.5 Hz, 1H), 5.69-5.74 (m, 1H), 5.99 (a, 1H), 7.14 (d, *J*=9.0 Hz, 1H), 7.33 (s, 1H), 7.66 (d, *J*=3.5 Hz, 1H), 7.93 (d, J=3.0 Hz, 1H), 8.05 (s, 1H), 8.11 (d, *J*=9.0 Hz, 1H), 9.14 (a, 1H).

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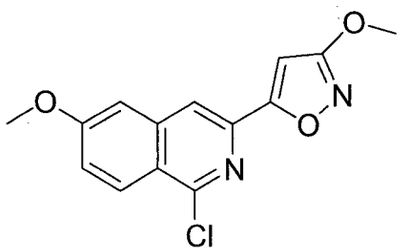
MS *m/z* 797 (M^++H).

Los siguientes intermediarios se preparan como se describe en la presente y pueden ser incorporados en los compuestos de la fórmula 1



La 6-metoxi-3-(3-metoxi-isoxazol-5-il)-2H-isoquinolin-1-ona se preparó usando N,N-dietil-4-metoxi-2-[2-(3-metoxi-isoxazol-5-il)-2-oxo-etil]-benzamida.

^{1}H RMN (DMSO-d_6) δ 3.89 (s, 3H), 3.97 (s, 3H), 7.01 (s, 1H), 7.14-7.16 (m, 2H), 7.43 (s, 1H), 8.13 (d, *J*=8.5 Hz, 1H). MS *m/z* 273 (M^++H).

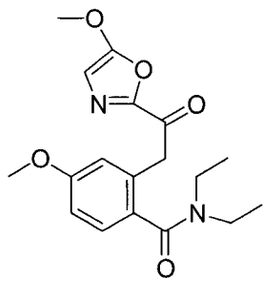


La 1-cloro-6-metoxi-3-(3-metoxi-isoxazol-5-il)-isoquinolina se preparó usando 6-metoxi-3-(3-metoxi-isoxazol-5-il)-2H-isoquinolin-1-ona

^{1}H RMN ($CDCl_3$) δ 3.97 (s, 3H), 4.04 (s, 3H), 6.60 (s, 1H), 7.17 (d, *J*=2.5 Hz, 1H), 7.31-7.33 (m, 1H), 8.02 (s, 1H), 8.23 (d, *J*=9.0 Hz, 1H).

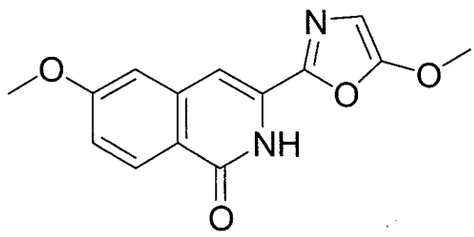
MS *m/z* 291, 293 (M^++H)

Los siguientes intermediarios se preparan como se describe en la presente y pueden ser incorporados en los compuestos de la fórmula 1



N,N-dietil-4-metoxi-2-[2-(5-metoxi-oxazol-2-il)-2-oxo-etil]-benzamida, se preparó usando el éster etílico del ácido 5-metoxi-oxazol-2-carboxílico.

MS *m/z* 347 (M^++H).

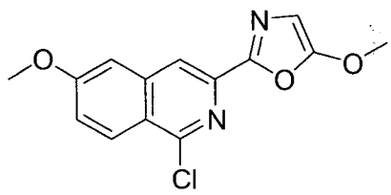


La 6-metoxi-3-(5-metoxi-oxazol-2-il)-2H-isoquinolin-1-ona, se preparó usando N,N-dietil-4-metoxi-2-[2-(5-metoxi-oxazol-2-il)-2-oxo-etil]-benzamida.

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^{1}H RMN (DMSO-d_6) δ 3.94 (s, 3H), 4.01 (s, 3H), 6.34 (s, 1H), 6.99 (d, *J*=2.0 Hz, 1H), 7.12-7.14 (m, 1H), 7.25 (s, 1H), 8.32 (d, *J*=9.0 Hz, 1H).

MS *m/z* 274 (M^++H).

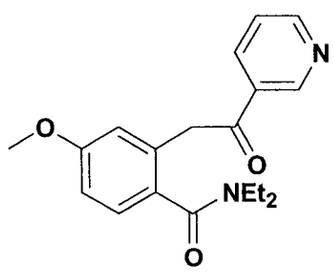


La 1-cloro-6-metoxi-3-(5-metoxi-oxazol-2-il)-isoquinolina, se preparó usando 6-metoxi-3-(5-metoxi-oxazol-2-il)-2H-isoquinolin-1-ona.

^{1}H RMN ($CDCl_3$) δ 3.96 (s, 3H), 4.00 (s, 3H), 6.34 (s, 1H), 7.12 (d, *J*=2.5 Hz, 1H), 7.28-7.31 (m, 1H), 8.13 (s, 1H), 8.23 (d, *J*=9.0 Hz, 1H).

MS *m/z* 291, 293 (M^++H).

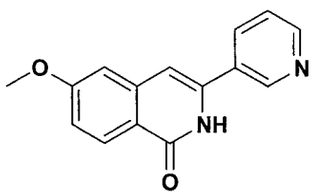
Los siguientes intermediarios se preparan como se describe en la presente y pueden ser incorporados en los compuestos de la fórmula 1



A una solución de N,N-Dietil-4-metoxi-2-metil-benzamida (332 mg, 1.5 mmol) en THF (15 mL) a -78°C, t-BuLi (1.7 M

solución en pentano, 2.12 mL, 3.6 mmol) se agregó. La solución roja resultante se agitó a -78°C durante 10 min, luego nicotinato de metilo (206 mg, 1.5 mmol) se agregó. La mezcla de reacción se agitó a -78°C durante 2h. Luego la reacción se apagó con solución NH_4Cl saturada y luego se extrajo con acetato de etilo dos veces. Las capas orgánicas combinadas se secaron ($MgSO_4$) y se concentró. El producto sin refinar se purificó por HPLC preparativa para dar aceite espeso de color amarillo como sal TFA. (124 mg, 19% de rendimiento).

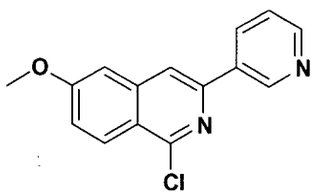
MS m/z 349 ($M+Na^+$).



N,N-Dietil-4-metoxi-2-(2-oxo-2-piridin-3-il-etil)-benzamida (120 mg, 0.272 mmol) se calentó con acetato de amonio (1 g) durante 3 hr. Luego se enfrió y se agregó agua. Se extrajo con acetato de etilo y la capa orgánica se separó. Luego se secó ($MgSO_4$) y se concentró para dar un producto sólido de color café como producto. (65 mg, 95% de rendimiento)

^1H RMN (400 MHz, DMSO-d^6) δ 3.89 (s, 3 H), 6.93 (s, 1 H), 7.10 (dd, *J*=8.80, 2.45 Hz, 1 H), 7.19 (d, *J*=2.45 Hz, 1 H), 7.52 (dd, *J*=7.46, 4.77 Hz, 1 H), 8.15 (m, 2 H), 8.64 (dd, *J*=4.89, 1.47 Hz, 1 H), 8.96 (d, *J*=1.71 Hz, 1 H), 11.51 (s, 1 H).

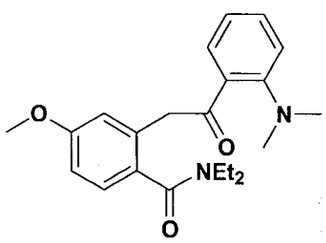
MS m/z 253 (MH^+).



6-Metoxi-3-piridin-3-il-2H-isoquinolin-1-ona (65 mg, 0.258 mmol) se calentó bajo reflujo con $POCl_3$ (2.5 mL) durante 7 días. Luego $POCl_3$ se destiló y el residuo se apagó con hielo. Luego se neutraliza con 10 N de solución NaOH y luego se extrajo con acetato de etilo dos veces. Las capas orgánicas combinadas se secaron ($MgSO_4$) y se concentraron para dar un sólido amarillo como producto. (27 mg, 39% de rendimiento).

MS m/z 271 (MH^+).

Los siguientes intermediarios se preparan como se describe en la presente y pueden ser incorporados en los compuestos de la fórmula 1



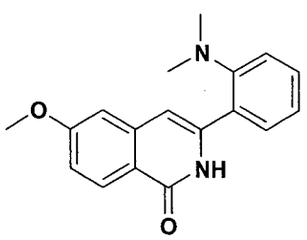
A una solución de N,N-Dietil-4-metoxi-2-metil-benzamida (332 mg, 1.5 mmol) en THF (15 mL) a -78°C, t-BuLi (1.7 M solución en pentano, 2.2 mL, 3.75 mmol) se agregó. La solución roja resultante se agitó a -78°C durante 10 min,

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luego éster metílico del ácido N,N-dimetilantranílico (269 mg, 1.5 mmol) se agregó. La mezcla de reacción se agitó a -78°C durante 2h. Luego la reacción se apagó con solución NH_4Cl saturada y luego se extrajo con acetato de etilo dos veces. Las capas orgánicas combinadas se secaron ($MgSO_4$) y se concentraron. El producto sin refinar se purificó por HPLC preparativa para dar un aceite espeso de color amarillo como producto. (256 mg, 46% de rendimiento)

^{1}H RMN (400 MHz, CD_3OD) δ 0.99-1.13 (m, 6 H), 3.23-3.31 (m, 8 H), 3.39 (m, 2 H), 3.82 (s, 3 H), 4.35 (s, 2 H), 6.91 (dd, *J*=8.44, 2.57 Hz, 1 H), 6.99 (d, *J*=2.45 Hz, 1 H), 7.22 (d, *J*=8.56 Hz, 1 H), 7.69 (t, *J*=7.70 Hz, 1 H), 7.84 (m, 1 H), 7.96 (d, *J*=8.31 Hz, 1 H), 8.18 (d, *J*=7.83 Hz, 1 H).

MS m/z 369(MH^+).

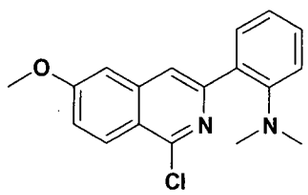


2-[2-(2-Dimetilamino-fenil)-2-oxo-etil]-N,N-dietil-4-metoxi-benzamida (250 mg, 0.678 mmol) se calentó con acetato de amonio (1.5 g) durante 2 hr. Luego se enfrió y se agregó agua. Se extrajo con acetato de etilo y la capa orgánica se separó. Luego se secó ($MgSO_4$) y se concentró para dar un sólido de color amarillo como producto. (125 mg, 63% de rendimiento).

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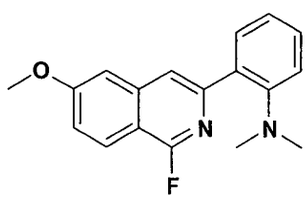
^{1}H RMN (400 MHz, CD_3OD) δ 2.95 (s, 6 H), 3.92 (s, 3 H), 6.92 (s, 1 H), 7.12 (dd, *J*=8.80, 2.45 Hz, 1 H), 7.16 (d, *J*=2.45 Hz, 1 H), 7.35 (m, 1 H), 7.55 (m, 2 H), 7.63 (d, *J*=7.83 Hz, 1 H), 8.20 (d, *J*=9.05 Hz, 1 H).

MS m/z 295 (MH^+).



3-(2-Dimetilamino-fenil)-6-metoxi-2H-isoquinolin-1-ona (125 mg, 0.425 mmol) se calentó bajo reflujo con $POCl_3$ (4.0 mL) durante un día. Luego $POCl_3$ se destiló y el residuo se apagó con hielo. Luego se neutraliza con 10 N de solución NaOH y luego se extrajo con acetato de etilo dos veces. Las capas orgánicas se combinaron y se secaron ($MgSO_4$). La evaporación del solvente dió un sólido de color café como producto (82 mg, 62% de rendimiento)

MS m/z 313 (MH^+).



Una mezcla de [2-(1-Cloro-6-metoxi-isoquinolin-3-il)-fenil]-dimetil-amina (82 mg, 0.262 mmol) y difluoruro ácido de tetrabutil fosfonio (1.0 g) se calentó a 140°C en un

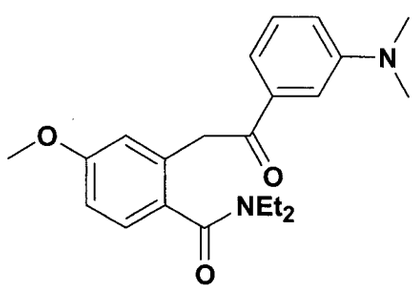
000741

reactor de microondas Smith durante 20 min. Luego se agregó agua y luego se extrajo con acetato de etilo. La capa orgánica se separó, se lavó con agua y se secó ($MgSO_4$). La evaporación del solvente dió el producto sin refinar el cual se purificó por HPLC preparativa para proporcionar un aceite de color amarillo como producto. (85 mg)

^{1}H RMN (400 MHz, CD_3OD) δ 3.41 (s, 6 H), 4.00 (s, 3 H), 7.42 (dd, *J*=9.05, 2.45 Hz, 1 H), 7.53 (s, 1 H), 7.71 (m, 2 H), 7.99 (m, 1 H), 8.16 (m, 2 H), 8.31 (s, 1 H).

MS m/z 297 (MH^+).

Los siguientes intermediarios se preparan como se describe en la presente y pueden ser incorporados en los compuestos de la fórmula 1



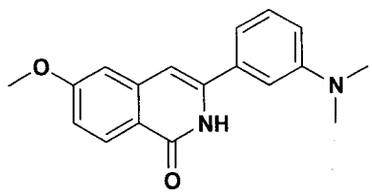
A una solución de N,N-Dietil-4-metoxi-2-metil-benzamida (332 mg, 1.5 mmol) en THF (15 mL) a -78°C, t-BuLi (1.7 M solución en pentano, 2.2 mL, 3.75 mmol) se agregó. La solución roja resultante se agitó a -78°C durante 10 min, luego éster metílico del ácido (3-dimetilamino)benzoico (269 mg, 1.5 mmol) se agregó. La mezcla de reacción se agitó a

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-78°C durante 2h. Luego la reacción se apagó con solución NH_4Cl saturada y luego se extrajo con acetato de etilo dos veces. Las capas orgánicas combinadas se secaron ($MgSO_4$) y se concentraron. El producto sin refinar se purificó por HPLC preparativa para dar un aceite espeso de color amarillo como sal TFA. (245 mg, 33% de rendimiento)

1H RMN (400 MHz, CD_3OD) δ 1.01 (t, *J*=6.85 Hz, 3 H), 1.09 (m, 3 H), 3.11 (s, 6H), 3.21 (m, 2 H), 3.40 (m, 2 H), 3.79 (s, 3 H), 4.39 (s, 2 H), 6.84-6.91 (m, 2 H), 7.19 (d, *J*=8.32 Hz, 1 H), 7.35 (m, 1 H), 7.49 (t, *J*=8.07 Hz, 1 H), 7.66-7.71 (m, 2 H).

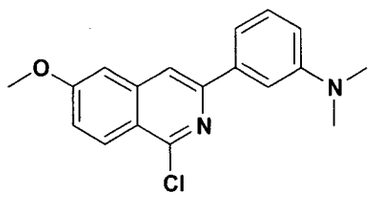
MS m/z 369(MH^+).



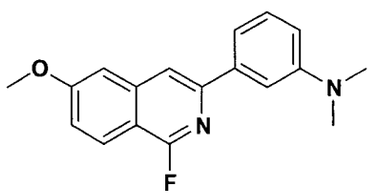
2-[2-(3-Dimetilamino-fenil)-2-oxo-etil]-N,N-dietil-4-metoxi-benzamida (240 mg, 0.497 mmol) se calentó con acetato de amonio (2.0 g) durante 2.5 hr. Luego se enfrió y se agregó agua. Un sólido de color café se colectó como producto puro. (95 mg, 65% de rendimiento)

1H RMN (400 MHz, CD_3OD) δ 2.98 (s, 6 H), 3.88 (s, 3 H), 6.74-6.87 (m, 2 H), 7.01-7.07 (m, 3 H), 7.18 (d, *J*=2.44 Hz, 1 H), 7.28 (t, *J*=7.82 Hz, 1 H), 8.10 (d, *J*=8.80 Hz, 1 H). MS m/z 295 (MH^+).

000743



3-(3-Dimetilamino-fenil)-6-metoxi-2H-isoquinolin-1-ona (92 mg, 0.312 mmol) se calentó bajo reflujo con $POCl_3$ (3.0 mL) durante 2 días. Luego $POCl_3$ se destiló y el residuo se apagó con hielo. Luego se neutraliza con una solución $NaHCO_3$ saturada y luego se extrajo con acetato de etilo dos veces. Las capas orgánicas se combinaron y se secaron ($MgSO_4$). La evaporación del solvente dió un aceite espeso de color café como producto. (72 mg, 74% de rendimiento). MS m/z 313 (MH^+).

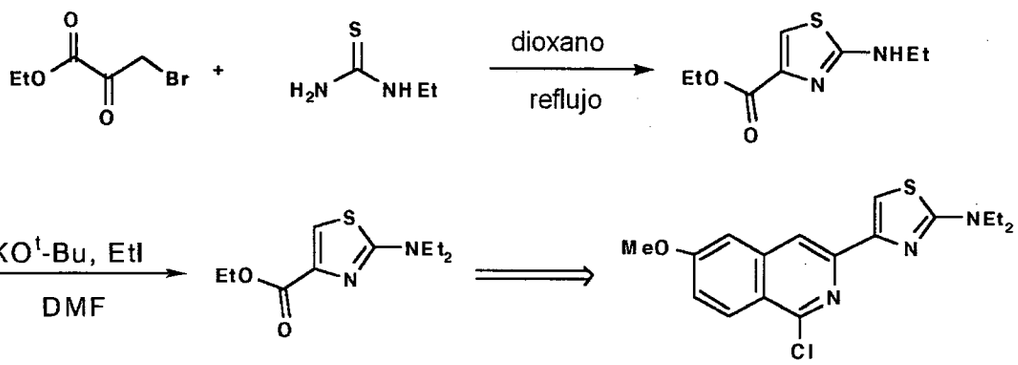


Una mezcla de [3-(1-Cloro-6-metoxi-isoquinolin-3-il)-fenil]-dimetilamina (72 mg, 0.23 mmol) y difluoruro ácido de tetrabutil fosfonio (0.5 g) se calentó a 140°C en un reactor de microondas Smith durante 20 min. Luego se agregó agua y luego se extrajo con acetato de etilo. La capa orgánica se separó, se lavó con agua y se secó ($MgSO_4$). La evaporación del solvente dió un aceite de color café como producto. (58 mg, 85% de rendimiento).

MS m/z 297 (MH^+).

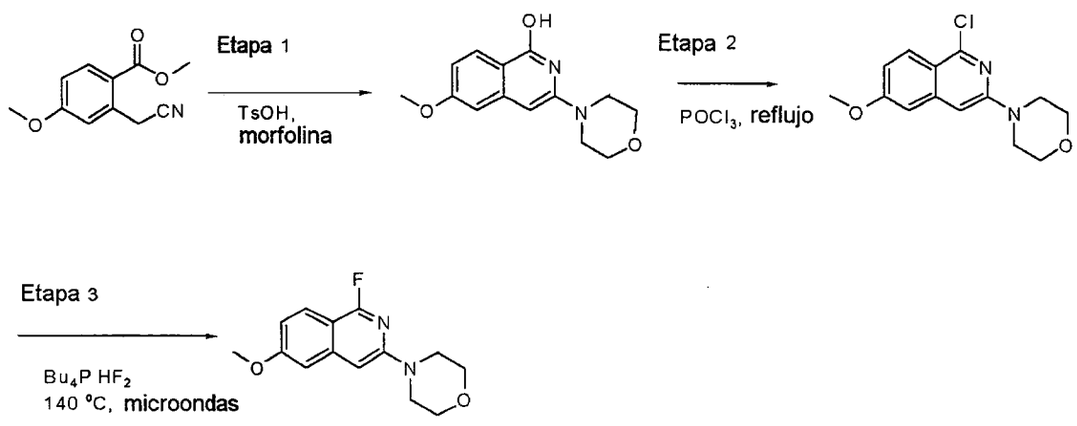
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Los siguientes intermediarios se preparan como se describe en la presente y pueden ser incorporados en los compuestos de la fórmula 1



La condensación del bromopiruvato de etilo con tiourea de etilo en reflujo de dioxano proporcionó el tiazol monoalquilamino como sal HBr en rendimiento cuantitativo. La alquilación de éster etílico del ácido 2-etilamino-tiazol-4-carboxílico con EtI en DMF proporcionando éster etílico del ácido 2-dietilamino-tiazol-4-carboxílico.

Método E



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Etapa 1:

Una suspensión de éster metílico del ácido 2-cianometil-4-metoxi-benzoico (1.9g y TsOH. H_2O (0.15 g, mmol) en morfolina 5 mL) se puso a reflujo durante 4 h y se removió el solvente *in vacuo*. El residuo se volvió a cristalizar del EtOAc/hexanos con gotas de MeOH para proporcionar el producto (0.43 g, 17%). MS *m/z* 266 (M^++1).

Etapa 2:

Una mezcla de 6-metoxi-3-morfolin-4-il-isoquinolin-1-ol (0.298 g, 1.15 mmol) en $POCl_3$ (20 mL) se puso a reflujo durante 2 h, se removió el solvente *in vacuo* y se enfrió, se agregó agua. El pH se ajusto a >11 por la adición de 1.0 N de NaOH. La capa acuosa se extrajo con EtOAc. El extracto se secó ($MgSO_4$), se removió el solvente *in vacuo* para proporcionar el producto (0.299g, 94%). MS *m/z* 279 (M^++1).

Etapa 3:

Una mezcla de 1-Cloro-6-metoxi-3-morfolin-4-il-isoquinolina (0.050g, 0.18 mmol) y dicloruro ácido de tetrabutil fosfonio (0.8 g, 2.8 mmol) [Synlett ***1992***, (4), 345-6] se calentó a 140°C en microondas durante 10 min. La mezcla de reacción se diluyó con EtOAc y se filtró a través de una precolumna ISCO 25g con una capa de gel de silicio en lo alto, se removió el solvente para proporcionar el producto (0.037 mg, 77%): ^{1}H RMN (CLOROFORMO-D) δ

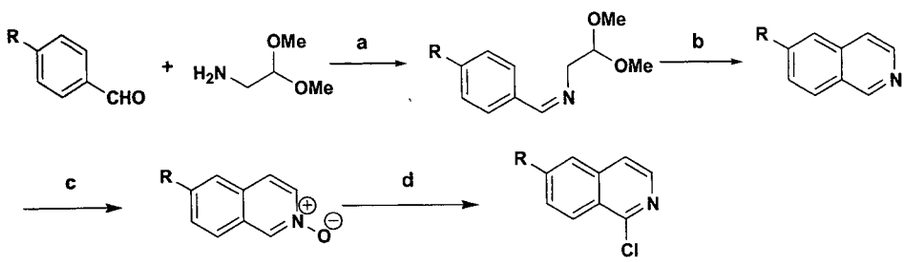
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ppm 3.48 (m, 4 H), 3.84 (m, 4 H), 3.89 (s, 3 H), 6.46 (d, *J*=1.22 Hz, 1 H), 6.85 (s, 1 H), 6.90 (dd, *J*=9.16, 2.44 Hz, 1 H), 7.82 (d, *J*=8.85 Hz, 1 H). MS *m/z* 263 (M^++1).

Método F

Isoquinolinas de 6-fluoro y 6-alquilo usadas en la preparación de los compuestos de la fórmula 1 se preparan por medio de una síntesis Pomeranz-Fritsch (procedimiento típico: Preparación de 1,1-biisoquinolina 8,8-disubstituida ópticamente activa, K. Hirao, R. Tsuchiya, Y. Yano, H. Tsue, *Heterocycles* 42(1) 1996, 415-422) como se indica a continuación. Los productos se convierten en los derivados de 1-cloro por medio de intermediarios N-óxido.

Esquema de Reacción Sintético General



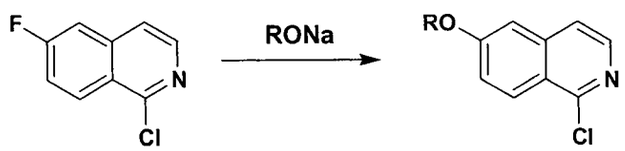
Los reactivos y condiciones de reacción: (a) reflujo en benceno, eliminación azeotrópica de agua; (b) primera etapa: cloroformiato de etilo, fosfito de trimetilo en THF, segunda etapa: tetracloruro de titanio en cloroformo; (c) MCPBA en CH_2Cl_2; (d) $POCl_3$ en benceno.

R	Isoquinolina, rendimiento	1-Cloruro, rendimiento combinado
F	20	43
Et	76	65
i-Pr	14	18
t-Bu	47	55

Preparación de intermediarios de isoquinolina 6-isopropoxilo y 6-*terc*-Butoxilo:

Algunos 6-alcoxi-1-cloro isoquinolinas se preparan por un desplazamiento directo, ipso, de 6-fluoro-1-cloroisoquinolina con los iones de metal de alcoxido correspondientes como terc-butóxido de potasio (53%) e isopropóxido de sodio (54%).

Esquema de reacción Sintético General



R = aniones de alcóxidos tal como *terc*-Bu, iso-Pr

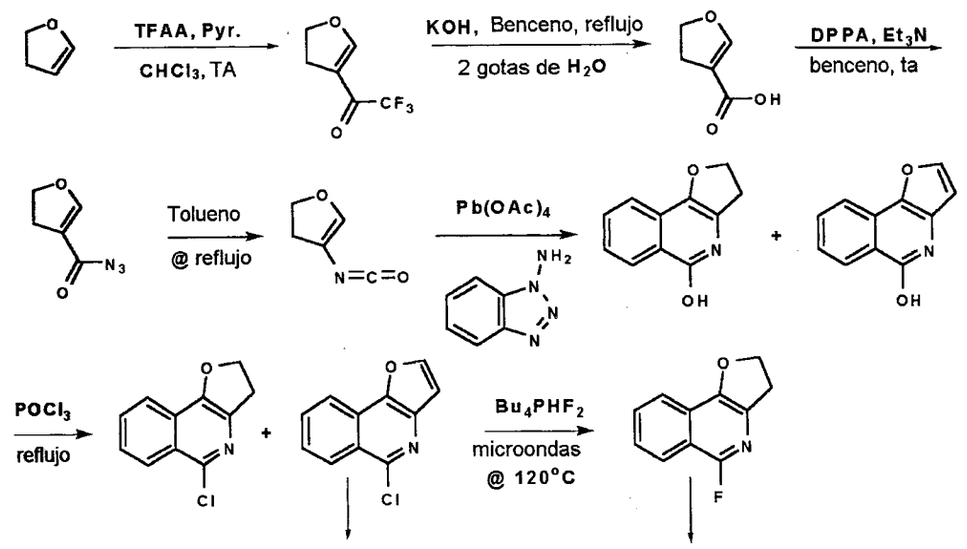
La 6-fluoro-1-cloroisoquinolina se sometió a un desplazamiento nucleofílico aromático con isopropóxido de sodio y terc-butóxido de potasio en DMF para dar el 6-

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isopropoxilo correspondiente (54%): ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 1.43 (d, *J*=6.11 Hz, 6 H) 4.76 (m, *J*=6.11 Hz, 1 H) 7.08 (d, *J*=2.45 Hz, 1 H) 7.29 (dd, *J*=9.29, 2.45 Hz, 1 H) 7.50 (d, *J*=5.62 Hz, 1 H) 8.18 (d, *J*=5.87 Hz, 1 H) 8.24 (d, *J*=9.29 Hz, 1 H) e isoquinolinas 6-*terc*-Butoxil-1-cloro (55%): ^{1}H RMN (400 MHz, CLOROFORMO-d) δ ppm 1.48 (s, 9 H) 7.31 (m, 2 H) 7.47 (d, J=5.62 Hz, 1 H) 8.18 (d, J=5.62 Hz, 1 H) 8.21 (d, J=9.78 Hz, 1 H) respectivamente como el producto mayor. Estas 6-alcoxil-1-cloro isoquinolinas se incorporan en los compuestos de la fórmula 1 como se describe en la presente.

Método G

Esquema de reacción Sintético General



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Este síntesis hacen uso de las tecnologías descritas, en parte, en las siguientes referencias:

(1) Hojo, Masaru; Masuda, Ryoichi; Sakaguchi, Syuhei; Takagawa, Makoto, *Synthesis* (1986), (12), 1016-17

(2) Rigby, James H.; Holsworth, Daniel D.; James, Kelly. Vinil Isocianatos In Synthesis. [4 + 2] Cycloaddition Reactions con Benzyne Addends. *Journal Of Organic Chemistry* (1989), 54(17), 4019-20

(3) Uchibori, Y.; Umeno, M.; Yoshiokai, H.; *Heterociclos*, 1992, 34 (8), 1507-1510

Estudios Biológicos

Los ensayos de enzima de complejo proteasa VHC NS3/4A y ensayos de replicón de VHC basados en células se utilizaron en la presente descripción, y se prepararon, condujeron y validaron como sigue:

Generación del complejo de proteasa VHC NS3/4A recombinante

Los complejos de proteasa HCV NS3, derivados de la cepa BMS, cepa H77 o cepa J4L6S, se generaron como se describe enseguida. Estas proteínas recombinantes purificadas se generaron para su uso en un ensayo homogéneo (véase posteriormente) para proporcionar una indicación de cómo los compuestos efectivos de la presente descripción inhibirían la actividad proteolítica de VHC NS3.

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El suero de pacientes infectados con VHC se obtuvo del Dr. T. Wright, San Francisco Hospital. Una plantilla de ADNc de longitud completa producido por ingeniería (ácido desoxirribonucléico complementado) del genoma del VHC (cepa BMS) se construyó de fragmentos de ADN obtenidos por transcripción inversa-PCR (RT-PCR) de ARN de suero (ácido ribonucléico) y usando cebadores seleccionados con base en la homología entre otras cepas de genotipo 1a. De la determinación de la secuencia de genoma completa, el genotipo 1a se asignó al VHC aislado de conformidad con la clasificación de Simmonds et al. (Véase P Simmonds, KA Rose, S Graham, SW Chan, F McOmish, BC Dow, EA Follett, PL Yap and H Marsden, *J. Clin. Microbiol.*, 31(6), 1493-1503 (1993)). La secuencia de aminoácido de la región no estructural, NS2-5B, se mostró que es >97% idéntica al genotipo del VHC 1a (H77) y 87% idéntica al genotipo 1b (J4L6S). Los clones infecciosos, H77 (genotipo 1a) y J4L6S (genotipo 1b) se obtuvieron de R. Purcell (NIH) y las secuencias se publican en el Genbank (AAB67036, véase Yanagi, M., Purcell, R.H., Emerson, S.U. y Bukh, J. *Proc. Natl. Acad. Sci. U.S.A.* 94(16), 8738-8743 (1997); AF054247, ver Yanagi, M., St Claire,M., Shapiro,M., Emerson,S.U., Purcell,R.H. and Bukh,J. *Virology* 244 (1), 161-172. (1998)).

Las cepas H77 y J4L6S se usaron para la producción de los complejos de proteasa NS3/4A recombinante. El ADN que codifica el complejo de proteasa NS3/4A de VHC recombinante (aminoácidos 1027 a 1711) para estas cepas se manipuló como se describe por P. Gallinari et al. (ver Gallinari P, Paolini C, Brennan D, Nardi C, Steinkuhler C, De Francesco R. *Biochemistry* 38(17):5620-32, (1999)). Brevemente, la extemidad solubilizada de tres lisinas se agregó en el extremo 3' de la región que codifica NS4A. La cisteína en la posición P1 del sitio de desdoblamiento NS4A-NS4B (aminoácido 1711) se cambió a glicina para evitar el desdoblamiento proteolítico de la etiqueta de lisina. Adicionalmente, la cisteína para la mutación de serina se introdujo por PCR en la posición del aminoácido 1454 para prevenir el desdoblamiento autolítico en el dominio de helicasa NS3. El fragmento de ADN variante se clonó en el vector de expresión bacterial pET21b (Novagen) y el complejo NS3/4A se expresó en Escherichia coli cepa BL21 (DE3) (Invitrogen) siguiendo el protocolo descrito por P. Gallinari et al. (véase Gallinari P, Brennan D, Nardi C, Brunetti M, Tomei L, Steinkuhler C, De Francesco R., *J Virol.* 72(8):6758-69 (1998)) con modificaciones. Brevemente, la expresión del complejo de proteasa NS3/4A se indujo con 0.5 milimolar (mM) de isopropil β-D-1-

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tiogalactopiranósido (IPTG) durante 22 horas (h) a 20°C. Una fermentación típica (1 Litro (L)) proporciona aproximadamente 10 gramos de la pasta celular húmeda. Las células se vuelven a suspender en solución amortiguadora de lisis (10 mL/g) que consiste de 25 mM *N*-(2-Hidroxietil)Piperazina-*N'*-(2-ácido etan sulfónico) (HEPES), pH 7.5, 20% glicerol, 500 mM cloruro de sodio (NaCl), 0.5% Triton X-100, 1 microgramo/mililitro ("µg/mL") lisozima, 5 mM cloruro de magnesio ($MgCl_2$), 1 µg/ml DnasaI, 5mM β-Mercaptoetanol (βME), inhibidor de proteasa-ácido etilendiamina tetracético (EDTA) libre (Roche), homogenizado e incubado durante 20 minutos a 4°C. El homogenado se sonicó y clarificó por ultra-centrifugación a 235000 g durante 1 hora a 4°C. Se agregó imidazol al sobrenadante hasta una concentración final de 15 mM y el pH se ajusta hasta 8.0. El extracto de proteína sin refinar se cargó en una columna de níquel-ácido nitrilotriacético (Ni-NTA) previamente equilibrada con solución amortiguadora B (25 mM HEPES, pH 8.0, 20% glicerol, 500 mM NaCl, 0.5% Triton X-100, 15 mM imidazol, 5 mM βME). La muestra se cargó a una relación de flujo de 1 mL/min. La columna se lavó con 15 volúmenes de columna de la solución amortiguadora C (igual como la solución amortiguadora B excepto con 0.2% Triton X-100). La proteína se eluyó con 5 volúmenes de columna de solución

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amortiguadora D (igual como la solución amortiguadora C excepto con 200 mM Imidazol).

Las fracciones que contienen el complejo NS3/4A se agruparon y cargaron en una columna de desalación Superdex-S200 previamente equilibrada con solución amortiguadora D (25 mM HEPES, pH 7.5, 20% glicerol, 300 mM NaCl, 0.2% Triton X-100, 10 mM βME). La muestra se cargó a una relación de flujo de 1 mL/min. Las fracciones que contienen el complejo de proteasa NS3/4A se agruparon y concentraron hasta aproximadamente 0.5 mg/ml. La pureza de los complejos de proteasa NS3/4A, derivados de las cepas BMS, H77 y J4L6S, se juzgaron que van a ser mayores al 90% por SDS-PAGE y análisis de espectrometría de masa. La enzima se almacenó a -80°C, se descongela en hielo y se diluye antes de usarse en solución amortiguadora de ensayo.

Ensayos de Péptido FRET para observar actividad proteolítica NS3/4A del VHC

El propósito de este ensayo *in vitro* fue medir la inhibición de los complejos de NS3 proteasa del VHC derivados de las cepas de BMS, H77 o J4L6S como se describió anteriormente, por los compuestos de la presente invención. Este ensayo proporciona una indicación de que tan efectivos podrían ser los compuestos de la presente

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invención en la inhibición de la actividad proteolítica NS3 del VHC.

Con objeto de monitorear la actividad de NS3/4A proteasa de VHC, se usó un substrato de péptido NS3/4A. El substrato fue RET S1 (Resonance Energy Transfer Depsipeptide Substrate; AnaSpec, Inc. cat # 22991) (péptido FRET), descrito por Taliani et al. en Anal. Biochem. 240(2):60-67 (1996). La secuencia de este péptido se basa vagamente en el sitio de desdoblamiento natural NS4A/NS4B para la proteasa NS3 de VHC excepto que hay una ligadura éster en vez de un enlace amida en el sitio de desdoblamiento. El péptido también contiene un donador de fluorescencia, EDANS, cerca de un extremo del péptido y un aceptor, DABCYL, cerca del otro extremo. La fluorescencia del péptido se apaga por transferencia de energía de resonancia intermolecular (RET) entre el donador y aceptor, pero como la proteasa NS3 desdobla el péptido los productos se liberan del RET por apagado y la fluorescencia del donador se vuelve aparente.

El substrato de péptido se incubó con uno de los tres complejos NS3/4A de proteasa recombinantes, en ausencia o presencia de un compuesto de la presente descripción. Los efectos inhibidores del compuesto se determinaron al monitorear la formación del producto de reacción fluorescente en tiempo real usando un Cytofluor Series

4000.

Los reactivos fueron como sigue: HEPES y Glicerol (Ultrapuro) se obtuvieron de GIBCO-BRL. Sulfóxido de dimetilo (DMSO) se obtuvo de Sigma. El β-Mercaptoetanol se obtuvo de Bio Rad.

Solución amortiguadora de ensayo: 50 mM HEPES, pH 7.5; 0.15 M NaCl; 0.1% Triton; 15% Glicerol; 10 mM βME. Substrato: 2 µM concentración final (de una solución de reserva 2 mM en DMSO almacenada a -20°C). La proteasa NS3/4A de VHC tipo 1a (1b), concentración final 2-3 nM (de una solución de reserva 5 µM en 25 mM HEPES, pH 7.5, 20% glicerol, 300 mM NaCl, 0.2% Triton-X100, 10 mM βME). Para compuestos con potencias que se acercan al límite del ensayo, el ensayo se hizo más sensible al agregar 50 µg/ml de Albúmina de Suero de Bovino (Sigma) a la solución amortiguadora de ensayo y se reduce la concentración de proteasa final hasta 300 pM.

El ensayo se realizó en una placa negra de poliestireno de 96 cavidades de Falcon. Cada cavidad contuvo 25 µl del complejo de proteasa NS3/4A en solución amortiguadora de ensayo, 50 µl de un compuesto de la presente descripción en solución amortiguadora de ensayo/DMSO al 10% y 25 µl de substrato de solución amortiguadora de ensayo. También se preparó un control (sin compuesto) en la misma placa de ensayo. Se mezcló el complejo de enzimas con un compuesto o

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una solución de control por 1 minuto antes de iniciar la reacción enzimática por la adición del substrato. La placa de ensayo se leyó inmediatamente usando un Cytofluor Series 4000 (Perspective Biosystems). El instrumento se fijó para leer una emisión de 340 nm y excitación de 490 nm a 25°C. Las reacciones se siguieron generalmente por aproximadamente 15 minutos.

Se calculó el porcentaje de inhibición con la siguiente ecuación:

$$100-[(\delta F_{inh}/\delta F_{con})x100]$$

en donde δF es el cambio en la fluorescencia sobre un intervalo lineal de la curva. Se aplicó un ajuste de una curva no lineal a los datos de concentración-inhibición y se calculó una concentración efectiva al 50% (IC_{50}) por el uso de un programa de cómputo de ajuste Excel XLfit usando la ecuación, y=A+((B-A)/(1+((C/x)^D))).

Los compuestos de la presente descripción, que se probaron contra más de un tipo de complejo NS3/4A, se encontraron que tienen propiedades inhibidoras similares no obstante que los compuestos demuestran uniformemente una potencia mayor contra las cepas 1b en comparación con la cepa 1a.

Ensayos de Especificidad

Se realizaron los ensayos de especificidad para demostrar la selectividad *in vitro* de los compuestos de la

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presente descripción para inhibir la proteasa NS3/4A del VHC en complejo en comparación con otra serina o cisteína proteasas.

Las especificidades de los compuestos de la presente invención se determinaron contra una diversidad de serinas proteasas: elastasa de neutrofilo humano (HNE), elastasa pancreática porcina (PPE), y quimiotripsina pancreática humana y una cisteina proteasa: la catepsina B del hígado humano. En todos los caso, se usó un protocolo de formato de placa de 96 cavidades, usando ya sea un substrato colorimétrico de p-nitroanilina (pNA) o Amino-Metil-Coumarina fluorométrico (AMC) específico para cada enzima se usó como se describió previamente (Solicitud de Patente No. WO00/09543) con algunas modificaciones a los ensayos de la serina proteasa. Todas las enzimas se adquirieron de Sigma, EMDbiosciences mientras que los substratos fueron de Bachem, Sigma y EMDbiosciences.

El ensayo pNA para cimotripsina incluye una pre incubación de inhibidor-enzima de 1 hora a temperatura ambiente, seguida por la adición de un substrato e hidrólisis hasta ~15% de conversión como se mide en un lector de microplacas Spectramax Pro. Las concentraciones de compuesto variaron desde 100 a 0.4 μM dependiendo de su potencia. Los ensayos de catepsina B, HNE, y PPE cada uno

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se inició por la adición de substrato al enzima-inhibidor previamente incubado durante 10 minutos a temperatura ambiente e hidrólisis hasta 15% de conversión como se mide en Cytofluor.

Las condiciones finales para cada ensayo fueron como siguen:

clorohidrato de Tris(hidroximetilo)aminometano 50mM (Tris-HCl)pH8, 0.5M sulfato de sodio (Na_2SO_4), 50mM NaCl, 0.1 mM EDTA, 3% DMSO, 0.01% Tween- 20 con 100 µM succ-AAPF-pNA y 250nM de Cimotripsina.

50mM tris-HCl, pH 8.0, 50 mM NaCl, 0.1mM EDTA, 3% DMSO, 0.02% Tween-20, 5 µM succ-AAPV-AMV y 20nM HNE o 8 nM PPE;

100mM NaOAC (acetato de sodio) pH 5.5, 3% DMSO, 1mM TCEP (clorohidrato de Tris(2-carboxietil) fosfina), 5nM Catepsina B (solución de reserva de enzima activada en solución amortiguadora que contiene 20mM TCEP antes del uso), y 2 µM Z-FR-ZMC diluido en H_2O.

Se calculó el porcentaje de inhibición usando la formula:

$$[1-((Uv_{inh}-Uv_{blank})/Uv_{ctl}-Uv_{blank}))] \times 100$$

Se aplicó un ajuste de curva no lineal a los datos de concentración inhibición, y se calculó la concentración efectiva al 50% (IC_{50}) por el uso de un programa de computo de ajuste Excel XLfit.

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Generación de Replicón VHC

Se estableció un sistema de células enteras del replicón de VHC como se describe en Lohmann V, Korner F, Koch J, Herian U, Theilmann L, Bartenschlager R., Science 285(5424):110-3 (1999). Este sistema permite evaluar los efectos de los compuestos de proteasa de VHC en la replicación de ARN de VHC. Brevemente, al usar la secuencia de la cepa 1b de VHC descrita en el documento de Lohmann (número de acceso AJ238799), se sintetizó un ADNc de VHC por Operon Technologies, Inc. (Alameda, CA), y el replicón de longitud completa se ensambló entonces en el plásmido pGem9zf(+) (Promega, Madison, WI) uando técnicas de biología molecular estándar. El replicón consiste de (i) el 5' UTR VHC fusionado a los primeros 12 aminoácidos de la proteína capsida, (ii) el gen de neomicina fosfotransferasa (neo), (iii) el IRES del virus de encefalomiocarditis (EMCV), y (iv) genes NS3 hasta NS5B VHC y el 3' UTR VHC. Los ADN del plásmido se linearizaron con ScaI y los transcritos de ARN se sintetizaron *in vitro* usando el kit de transcripción T7 MegaScript (Ambion, Austin, TX) de conformidad con las instrucciones del fabricante. Los transcritos *in vitro* del ADNc se transfectaron en la línea celular de hepatoma humana, HUH-7. La selección para células que expresan

constitutivamente el replicón HCV se alcanzó en presencia de un marcador seleccionable, neomicina (G418). Las líneas celulares resultantes se caracterizaron para producción de ARN de hebra positiva y negativa y producción de proteína durante el tiempo.

Ensayo FRET de Replicón VHC

El ensayo FRET de replicón VHC se desarrolló para monitorear los efectos inhibidores de los compuestos descritos en la descripción en la replicación viral de VHC. Las células HUH-7, que expresan constitutivamente el replicón VHC, se hicieron crecer en Medio Eagle Modificado de Dulbecco (DMEM) (Gibco-BRL) que contiene suero de becerro fetal al 10% (FCS) (Sigma) y 1 mg/ml G418 (Gibco-BRL). Las células se sembraron la noche anterior (1.5 x 10^4 células/cavidad) en placas estériles de cultivo de tejido de 96 cavidades. Los controles de compuesto y sin compuesto se prepararon en DMMS que contiene 4% FCS, 1:100 penicilina/estreptomicina (Gibco-BRL), 1:100 L-glutamina y 5% DMSO en la placa de dilución (0.5% DMSO concentración final en el ensayo). Las mezclas compuesto/DMSO se agregaron a las células e incubaron durante 4 días a 37°C. Después de 4 días, las células se evalúan primero para citotoxicidad usando azul alamar (Trek Diagnotstic Systems) para una lectura CC_{50}. La toxicidad del compuesto (CC_{50}) se determinó al agregar

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1/10^{avo} de volumen de azul alamar al medio que incuba las células. Después de 4 horas, la señal de fluorescencia de cada cavidad se leyó, con una longitud de onda de excitación a 530 nm y una emisión de longitud de onda de 580 nm, usando el Cytofluor Series 4000 (Perspective Biosystems). Las placas se enjuagan a fondo con solución salina amortiguada en fosfato (PBS) (3 veces 150 µl). Las células se lisaron con 25 µl de un reactivo de ensayo de lisis que contiene un substrato de proteasa VHC (5X reactivo de lisis de cultivo celular de luciferasa de célula (Promega #E153A) diluido con 1X con agua destilada, el NaCl agregado a 150 mM final, el substrato péptido FRET (como se describe para el ensayo de enzima de arriba) diluido hasta 10 µM final de una solución de reserva 2 mM en 100% DMSO. La placa se colocó entonces en el instrumento Cytofluor 4000 que se ha colocado a 340 nm excitación/490 nm emisiones, modo automático durante 21 ciclos y el lector de placa en un modo cinético. Las determinaciones EC_{50} se llevaron a cabo como se describe para las determinaciones IC_{50}.

Ensayo del Reporte de Luciferasa del Replicón VHC

Como un ensayo secundario, las determinaciones EC_{50} del ensayo FRET de replicón se confirmaron en un ensayo del gen informador de luciferasa de replicón. La utilización de un ensayo del gen informador de luciferasa

de replicón se describió primero por Krieger et al (Krieger N, Lohmann V, y Bartenschlager R, J. Virol. 75(10):4614-4624 (2001)). La construcción de replicón descrito para el ensayo FRET se modificó al insertar ADNc que codifica una forma humanizada del gen de luciferasa Renilla y una secuencia ligadora fusionada directamente el extremo 3' del gen de luciferasa. Este inserto se introdujo en la construcción de replicón usando un sitio de restricción Asc1 localizado en el núcleo, directamente en dirección ascendente del gen marcador de neomicina. La mutación adaptativa en la posición 1179 (serina a isoleucina) también se introdujo (Blight KJ, Kolykhalov, AA, Rice, CM, Science 290(5498): 1972-1974). Una línea de célula estable que expresa constitutivamente esta construcción de replicón VHC se generó como se describe arriba. El ensayo del gen informador de luciferasa se estableció como se describe para el ensayo FRET de replicón de VHC con las siguientes modificaciones. Después de 4 días en un incubador 37°C/5% CO_2, las células se analizaron para actividad de luciferasa Renilla usando el Sistema de Ensayo de Luciferasa Dual-Glo Promega. El medio (100 µl) se removió de cada cavidad que contiene las células. A los restantes 50 µL del medio, se agregaron 50 µl del reactivo de Dual-Glo luciferasa, y las placas se sacuden durante 10 minutos hasta 2 horas a temperatura

ambiente. El reactivo Dual-Glo Stop & Glo (50 µl) se agregó entonces a cada cavidad, y las placas se sacudieron nuevamente durante 10 minutos hasta 2 horas adicionales a temperatura ambiente. Las placas se leyeron en un Packard TopCount NXT usando un programa de luminiscencia.

El porcentaje de inhibición se calculó usando la fórmula siguiente:

$$\% \text{ control} = \frac{\text{señal de luciferasa promedio en cavidades experimentales (+ compuesto)}}{\text{señal de luciferasa promedio en cavidades de control DMSO (- compuesto)}}$$

Los valores se graficaron y se analizaron usando Xlfit para obtener el valor EC_{50}.

Los compuestos representativos de la descripción se evaluaron en los ensayos de enzima de VHC, ensayo de célula de replicón VHC y/o en varios de los ensayos de especificidad resumidos. Por ejemplo, el compuesto 18 se encontró que tiene un IC_{50} de 3.4 nanomolar (nM) contra la cepa NS3/4A BMS en el ensayo de enzima. Se obtuvieron los valores de potencia similares con las cepas H77 (IC_{50} de 1.2 nM) y J4L6S (IC_{50} de 0.9 nM) publicadas. El valor EC_{50} en el ensayo FRET de replicón fue 9 nM y 1.1 nM en el ensayo de Luciferasa de replicón.

En los ensayos de especificidad, el mismo compuesto se encontró que tiene la siguiente actividad: HLE > 1.56

μM; PPE > 1.56 μM; quimiotripsina > 50 μM; Catepsina B > 50 μM. Estos resultados indican que esta familia de compuestos es altamente específica para la proteasa NS3 y muchos de estos miembros inhiben la replicación del replicón de VHC.

Se entenderá que los compuestos de la presente descripción pueden inhibir todos los genotipos del VHC.

Los compuestos de la descripción actual se probaron y encontraron que tienen actividades en los intervalos como sigue:

Intervalo de Actividad IC_{50} (cepa NS3/4A BMS): A es > 0.2 μM; B es 0.02-0.2 μM; C es 0.6-20 nM.

Intervalos de Actividad EC_{50} (para compuestos probados): A es > 1 μM; B es 0.1-1 μM; C es 3-100 nM.

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Tabla 2

Número de Compuesto	Proteasa VHC (IC50)	Pro Replicón de VHC (EC50)
409 - primer isómero	B	
409 - segundo isómero	A	
201A	4.00	4.23
201B	B	C
202A	C	C

202B	660.00	1298.00
203A	4.00	1.54
203B	B	C
204 primer isómero	C	C
204 segundo isómero	A	A
205 primer isómero	C	C

- 000767

205 segundo isómero	A	C
206 primer isómero	C	C
206 segundo isómero	A	A
207 primer isómero	C	C
207 segundo isómero	A	A
208 primer isómero	C	C

208 segundo isómero	A	
209 primer isómero	C	C
209 segundo isómero	A	A
210 primer isómero	C	C
210 segundo isómero	B	B
211 primer isómero	C	C

000769

211 segundo isómero	A	C
212 primer isómero	A	B
212 segundo isómero	C	C
213 primer isómero	A	B
213 segundo isómero	C	C
214 primer isómero	C	B

000770

214 segundo isómero	A	
215B	830.00	5494.00
215A	C	C
216 primer isómero	C	C
216 segundo isómero	A	
217 primer isómero	C	C

000771

217 segundo isómero	A	
218 primer isómero	C	C
218 segundo isómero	A	A
219 primer isómero	A	A
219 segundo isómero	C	C
220 primer isómero	C	C

000772

220 segundo isómero	A	B
221 primer isómero	C	B
221 segundo isómero	B	A
222	C	C
223 primer isómero	C	B
223 segundo isómero	A	A

224 primer isómero	C	B
224 segundo isómero	A	B
226 primer isómero	C	C
226 segundo isómero	A	
227 primer isómero	C	C
227 segundo isómero	A	A

030774

231 primer isómero	C	C
231 segundo isómero	A	A
232 primer isómero	C	C
232 segundo isómero	B	C
233A	B	B
233B	1300.00	2628.00

234 primer isómero	B	B
234 segundo isómero	A	A
235 primer isómero	A	
235 segundo isómero	C	C
236	A	A

990778

6 segundo isómero	C	B
16	C	C
17	C	C
21	C	C
35	C	C
36	73.00	1424.00

886779

37	C	C
38A	C	C
38B	5000.00	7712.00
200A	C	C
200B	160.00	195.40
242	C	C

000780

243	C	C
22 primer isómero	C	C
22 segundo isómero	C	B
407 primer isómero	C	B
407 segundo isómero	C	B
408 primer isómero	C	C

000781

408 segundo isómero	A	B
410	A	C
411	A	B
7	B	C
8	B	C
9	C	C

080782

10	C	C
11	C	C
12 primer isómero	C	C
12 segundo isómero	B	B
13 primer isómero	B	C
13B	1200.00	5740.00

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14 primer isómero	C	C
14 segundo isómero	A	B
15 primer isómero	C	C
15B	1900.00	3376.00
18	C	C
19 primer isómero	C	C

000734

19B	1000.00	1850.00
20 primer isómero	C	C
20 segundo isómero	B	B
23	C	C
24A	26.00	593.20
24 segundo isómero	A	A

000785

25	C	C
26 primer isómero	C	C
26B	1300.00	3189.00
27A	3.00	4.09
27 segundo isómero	B	C
28 primer isómero	C	C

000786

28 segundo isómero	B	B
29A	C	B
29B	249.00	14890.00
32A	1.00	3.59
32B	A	A
33	2.00	8.19

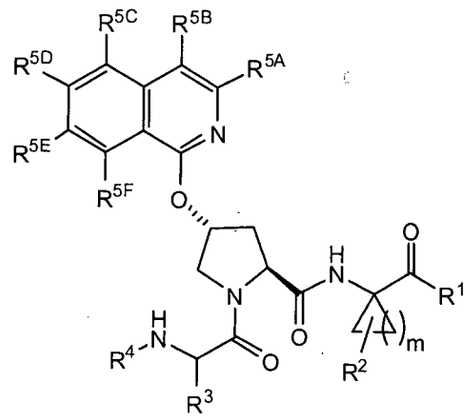
000787

Será evidente para aquellos expertos en el arte que la presente descripción no se limita a los ejemplos ilustrativos precedentes, y que puede incluirse en otras formas específicas sin salirse de los atributos esenciales de la misma. Por lo tanto se desea que los ejemplos se consideren en todos los aspectos como ilustrativos y no restrictivos, se hace referencia a las reivindicaciones adjuntas, en vez de los ejemplos precedentes, y todos los cambios que vienen dentro del significado y intervalo de equivalencia de las reivindicaciones, por lo tanto, se pretenden que se abarquen en la presente.

000788

REIVINDICACIONES

1. Un compuesto de la fórmula (I)



(I)

o una sal farmacéuticamente aceptable de la misma, caracterizado porque

m es 1, 2, ó 3;

R^1 se selecciona de hidroxi y $-NHSO_2R^6$; en donde R^6 se selecciona de alquilo, arilo, cicloalquilo, (cicloalquil)alquilo, heterociclilo, y $-NR^aR^b$, en donde el alquilo, el cicloalquilo y la parte cicloalquilo del (cicloalquil)alquilo están opcionalmente substituidos con uno, dos, o tres substituyentes seleccionados de alquenilo, alcoxi, alcoxialquilo, alquilo, arilalquilo, arilcarbonilo, ciano, cicloalquenilo, (cicloalquil)alquilo, halo, haloalcoxi, haloalquilo, y (NR^eR^f)carbonilo;

R^2 se selecciona de hidrógeno, alquenilo, alquilo, y cicloalquilo, en donde el alquenilo, alquilo, y cicloalquilo están opcionalmente substituidos con halo;

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R^3 se selecciona de alquenilo, alcoxialquilo, alcoxicarbonilalquilo, alquilo, arilalquilo, carboxialquilo, cianoalquilo, cicloalquilo, (cicloalquil)alquilo, haloalcoxi, haloalquilo, (heterociclil)alquilo, hidroxialquilo, (NR^cR^d)alquilo, y (NR^eR^f)carbonilalquilo;

R^4 se selecciona de fenilo y un anillo parcialmente o completamente insaturado de cinco o seis miembros que contiene opcionalmente uno, dos, tres, o cuatro heteroátomos seleccionados de nitrógeno, oxígeno, y azufre; en donde cada uno de los anillos es opcionalmente substituido con uno, dos, tres, o cuatro substituyentes independientemente seleccionados de alcoxi, alcoxicarbonilo, alquilo, alquilcarbonilo, alquilsulfanilo, carboxi, ciano, cicloalquilo, cicloalquiloxi, halo, haloalquilo, haloalcoxi, $-NR^cR^d$, (NR^eR^f)carbonilo, (NR^eR^f)sulfonilo, y oxo; con la condición de que cuando R^4 es un anillo substituido de seis miembros todos los substituyentes en el anillo diferentes a fluoro deberán estar en las posiciones meta y/o para con relación al punto de enlace del anillo a la porción de molécula precursora;

R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^{5E} y R^{5F} son cada uno independientemente seleccionados de hidrógeno, alcoxi, alcoxicarbonilo, alquilo, alquilcarbonilo, arilo, carboxi, ciano, cianoalquilo, cicloalquilo, halo, haloalquilo, haloalcoxi, heterociclilo, hidroxi, hidroxialquilo, nitro,

000790

$-NR^cR^d$, (NR^cR^d)alquilo, (NR^cR^d)alcoxi, (NR^eR^f)carbonilo, y (NR^eR^f)sulfonilo; o

dos grupos R^5 adyacentes, junto con los átomos de carbono a los cuales son enlazados, forman un anillo parcialmente o completamente insaturado de cuatro a siete miembros que contiene opcionalmente uno o dos heteroátomos independientemente seleccionados de nitrógeno, oxígeno, y azufre, en donde el anillo está opcionalmente substituido con uno, dos, o tres grupos independientemente seleccionados de alcoxi, alquilo, ciano, halo, haloalcoxi, y haloalquilo;

R^a y R^b son independientemente seleccionados de hidrógeno, alcoxi, alquilo, arilo, arilalquilo, cicloalquilo, (cicloalquil)alquilo, heterociclilo, y heterociclilalquilo; o R^a y R^b junto con el átomo de nitrógeno al cual son enlazados forman un anillo monocíclico heterocíclico de cuatro a siete miembros;

R^c y R^d son independientemente seleccionados de hidrógeno, alcoxialquilo, alcoxicarbonilo, alquilo, alquilcarbonilo, arilalquilo, y haloalquilo; y

R^e y R^f son independientemente seleccionados de hidrógeno, alquilo, arilo, arilalquilo, y heterociclilo; en donde el arilo, la parte arilo del arilalquilo, y el heterociclilo están opcionalmente substituidos con uno o dos substituyentes independientemente seleccionados de alcoxi, alquilo, y halo.

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2. El compuesto de conformidad con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, caracterizado porque R^1 es $-NHSO_2R^6$.

3. El compuesto de conformidad con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, caracterizado porque

m es 1 ó 2;

R^1 es $-NHSO_2R^6$; en donde R^6 se selecciona de alquilo, arilo, cicloalquilo, (cicloalquil)alquilo, heterociclilo, y $-NR^aR^b$, en donde el alquilo, cicloalquilo y la parte cicloalquilo del (cicloalquil)alquilo están opcionalmente substituidos con uno, dos, o tres substituyentes seleccionados de alquenilo, alcoxi, alcoxialquilo, alquilo, arilalquilo, arilcarbonilo, ciano, cicloalquenilo, (cicloalquil)alquilo, halo, haloalcoxi, haloalquilo, y (NR^eR^f)carbonilo;

R^2 se selecciona de alquenilo, alquilo, y cicloalquilo, en donde el alquenilo, alquilo, y cicloalquilo están opcionalmente substituidos con halo;

R^3 se selecciona de alquenilo y alquilo;

R^4 se selecciona de fenilo y un anillo parcialmente o completamente insaturado de cinco o seis miembros que contiene opcionalmente uno, dos, tres, o cuatro heteroátomos seleccionados de nitrógeno, oxígeno, y azufre; en donde cada uno de los anillos está opcionalmente substituido con uno,

030792

dos, tres, o cuatro substituyentes independientemente seleccionados de alcoxi, alcoxicarbonilo, alquilo, alquilcarbonilo, alquilsulfanilo, carboxi, ciano, cicloalquilo, cicloalquiloxi, halo, haloalquilo, haloalcoxi, $-NR^cR^d$, (NR^eR^f)carbonilo, (NR^eR^f)sulfonilo, y oxo; con la condición de que cuando R^4 es un anillo de seis miembros substituido todos los substituyentes en el anillo diferentes a fluoro deberán estar en las posiciones meta y/o para con relación al punto de enlace del anillo a la porción de molécula precursora;

R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^{5E} y R^{5F} son cada uno independientemente seleccionados de hidrógeno, alcoxi, alcoxicarbonilo, alquilo, alquilocarbonilo, arilo, carboxi, ciano, cianoalquilo, cicloalquilo, halo, haloalquilo, haloalcoxi, heterociclilo, hidroxi, hidroxialquilo, nitro, $-NR^cR^d$, (NR^cR^d)alquilo, (NR^cR^d)alcoxi, (NR^eR^f)carbonilo, y (NR^eR^f)sulfonilo; o

dos grupos R^5 adyacentes, junto con los átomos de carbono a los cuales son enlazados, forman un anillo parcialmente o completamente insaturado de cuatro a siete miembros que contiene opcionalmente uno o dos heteroátomos independientemente seleccionado de nitrógeno, oxígeno, y azufre, en donde el anillo está opcionalmente substituido con uno, dos, o tres grupos independientemente seleccionados de alcoxi, alquilo, ciano, halo, haloalcoxi, y haloalquilo;

R^a y R^b son independientemente seleccionados de hidrógeno, alcoxi, alquilo, arilo, arilalquilo, cicloalquilo, (cicloalquil)alquilo, heterociclilo, y heterociclilalquilo; o R^a y R^b junto con el átomo de nitrógeno al cual son enlazados forman un anillo monocíclico heterocíclico de cuatro a siete miembros;

R^c y R^d son independientemente seleccionados de hidrógeno, alcoxialquilo, alcoxicarbonilo, alquilo, alquilcarbonilo, arilalquilo, y haloalquilo; y

R^e y R^f son independientemente seleccionados de hidrógeno, alquilo, arilo, arilalquilo, y heterociclilo; en donde el arilo, la parte arilo del arilalquilo, y el heterociclilo están opcionalmente substituidos con uno o dos substituyentes independientemente seleccionados de alcoxi, alquilo, y halo.

4. Un compuesto de conformidad con la reivindicación 3, o una sal farmacéuticamente aceptable del mismo, caracterizado porque R^6 se selecciona de cicloalquilo no sustituido y $-NR^aR^b$.

5. Un compuesto de conformidad con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, caracterizado porque

m es 1;

R^1 es $-NHSO_2R^6$; en donde R^6 es cicloalquilo no sustituido;

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R^2 es alquenilo;

R^3 se selecciona de alquenilo y alquilo;

R^4 se selecciona de fenilo y un anillo parcialmente o completamente insaturado de cinco o seis miembros que contiene opcionalmente uno, dos, tres, o cuatro heteroátomos seleccionados de nitrógeno, oxígeno, y azufre; en donde cada uno de los anillos está opcionalmente substituido con uno, dos, o tres substituyentes independientemente seleccionados de alcoxi, alcoxicarbonilo, alquilo, alquilcarbonilo, carboxi, ciano, cicloalquilo, cicloalquiloxi, halo, haloalquilo, haloalcoxi, $-NR^cR^d$, (NR^eR^f)carbonilo, (NR^eR^f)sulfonilo, y oxo; con la condición de que cuando R^4 es un anillo substituido de seis miembros, todos los substituyentes en el anillo diferentes a fluoro deberán estar en las posiciones meta y/o para con relación al punto de enlace del anillo a la porción de molécula precursora;

R^{5A}, R^{5B}, R^{5C}, R^{5D}, R^{5E} y R^{5F} son cada uno independientemente seleccionados de hidrógeno, alcoxi, arilo, y $-NR^cR^d$; o

dos grupos R^5 adyacentes, junto con el átomo de carbono al cual son enlazados, forman un anillo parcialmente o completamente insaturado de seis miembros que contiene opcionalmente uno o dos heteroátomos independientemente seleccionado de nitrógeno, oxígeno, y azufre, en donde el anillo está opcionalmente substituido con uno, dos, o tres

grupos independientemente seleccionados de alcoxi, alquilo, ciano, halo, haloalcoxi, y haloalquilo;

R^c y R^d son independientemente seleccionados de hidrógeno, alcoxicarbonilo, alquilo, alquilcarbonilo y arilalquilo; y

R^e y R^f son independientemente seleccionados de hidrógeno, alquilo, arilo, y arilalquilo.

6. El compuesto de conformidad con la reivindicación 5, o una sal farmacéuticamente aceptable del mismo, caracterizado porque R^4 es fenilo opcionalmente substituido con uno, dos o tres substituyentes independientemente seleccionados de alcoxi, alcoxicarbonilo, alquilo, alquilcarbonilo, carboxi, ciano, cicloalquilo, cicloalquiloxi, halo, haloalquilo, haloalcoxi, $-NR^cR^d$, (NR^eR^f)carbonilo, (NR^eR^f)sulfonilo, y oxo; con la condición que todos los substituyentes en el anillo diferente a fluoro deberán estar en las posiciones meta y/o para con relación al punto de enlace del anillo a la porción de molécula precursora;

7. El compuesto de conformidad con la reivindicación 5, o una sal farmacéuticamente aceptable del mismo, caracterizado porque R^4 es un anillo completamente insaturado de seis miembros que contiene un átomo de nitrógeno; en donde el anillo es opcionalmente substituido con uno, dos o tres substituyentes independientemente seleccionados de alcoxi,

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alcoxicarbonilo, alquilo, alquilcarbonilo, carboxi, ciano, cicloalquilo, cicloalquiloxi, halo, haloalquilo, haloalcoxi, $-NR^cR^d$, (NR^eR^f)carbonilo, (NR^eR^f)sulfonilo, y oxo; con la condición que todos los substituyente en el anillo diferente a fluoro deberán estar en las posiciones meta y/o para con relación al punto de enlace del anillo a la porción de molécula precursora.

8. Un compuesto, caracterizado porque se selecciona de:

N-(4,6-dimetil-2-piridinil)-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

N-(4,6-dimetil-2-piridinil)-D-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

N-(5-(trifluorometil)-2-piridinil)valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

N-(4,6-dimetoxi-1,3,5-triazin-2-il)-3-metil-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

N-(4,6-dimetoxi-1,3,5-triazin-2-il)valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

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N-(4,6-dimetoxi-2-pirimidinil)valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

N-(4,6-dimetil-2-pirimidinil)-D-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

N-(4,6-dimetil-2-pirimidinil)-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

N-2-piridilvalil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

N-(4-metoxi-2-piridinil)valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

N-(4-(trifluorometil)-2-piridinil)valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

N-(4-metil-2-piridinil)valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

N-(4-ciano-2-piridinil)valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

3-metil-N-2-piridil-L-valil-(4R)-N-((1R,2S)-1-

((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

3-metil-N-2-piridil-D-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

3-metil-N-3-piridil-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

3-metil-N-3-piridil-D-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

N-(4,6-dimetil-2-piridinil)-3-metil-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

N-(4,6-dimetil-2-piridinil)-3-metil-D-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

3-metil-N-fenil-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

3-metil-N-fenil-D-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

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N-(4,6-dimetil-2-piridinil)valil-(4R)-N-((1R,2S)-1-((dimetilsulfamoil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

N-(4,6-dimetil-2-piridinil)valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((3-(dimetilamino)-6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

N-(4,6-dimetil-2-piridinil)-3-metilvalil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((3-(dimetilamino)-6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

3-metil-N-fenil-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((3-(dimetilamino)-6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

3-metil-N-fenil-D-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((3-(dimetilamino)-6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

3-metil-N-fenil-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((3,6-dimetoxi-1-isoquinolinil)oxi)-L-prolinamida;

3-metil-N-fenil-D-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((3,6-dimetoxi-1-isoquinolinil)oxi)-L-prolinamida;

N-(4,6-dimetil-2-piridinil)valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((3,6-dimetoxi-1-isoquinolinil)oxi)-L-prolinamida;

N-(4,6-dimetil-2-piridinil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(4,6-dimetil-2-piridinil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

3-metil-N-(4-metil-5-nitro-2-piridinil)valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-5-pirimidinil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-5-pirimidinil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

3-metil-N-(5-metil-3-piridinil)valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

3-metil-N-(6-metil-3-piridinil)-L-valil-(4R)-4-((7-

030891

cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

3-metil-N-(6-metil-3-piridinil)-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

3-metil-N-(5-(trifluorometil)-3-piridinil)-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

3-metil-N-(5-(trifluorometil)-3-piridinil)-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

3-metil-N-(6-metil-2-piridinil)-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

3-metil-N-(6-metil-2-piridinil)-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(2,6-dimetil-4-piridinil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-

000852

((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(2,6-dimetil-4-piridinil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(4,6-dicloro-2-piridinil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(4,6-dicloro-2-piridinil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(5-cloro-3-piridinil)-3-metilvalil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(4-etil-1,3-tiazol-2-il)-3-metil-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

N-(5,6-dihidro-4H-1,3-tiazin-2-il)-3-metil-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-

030813

prolinamida;

N-(5,6-dihidro-4H-1,3-tiazin-2-il)-3-metil-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-3-(4-(trifluorometoxi)fenil)-1-isoquinolinil)oxi)-L-prolinamida;

3-metil-N-(6-metil-2-piridinil)-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((3-(dimetilamino)-5-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

3-metil-N-(6-metil-2-piridinil)-D-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((3-(dimetilamino)-5-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

N-(3-fluorofenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(3-fluorofenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(3-metoxifenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(3-metoxifenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-

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((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

3-metil-N-(3-(metilcarbamoil)fenil)-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

3-metil-N-(3-(metilcarbamoil)fenil)-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(3-cianofenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(3-cianofenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(4-(terc-butoxicarbonil)fenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(4-(terc-butoxicarbonil)fenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-

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prolinamida;

N-(4-cianofenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(4-cianofenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(3-(terc-butilsulfamoil)fenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(3-(terc-butilsulfamoil)fenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

3-metil-N-(3-sulfamoilfenil)-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

3-metil-N-(3-sulfamoilfenil)-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

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N-(2,3-difluorofenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(2,3-difluorofenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(4-carboxifenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(4-carboxifenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(3-(terc-butoxicarbonil)fenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(3-(terc-butoxicarbonil)fenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(3-carboxifenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-

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metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(3-carboxifenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(3-(terc-butilcarbamoil)fenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(3-(terc-butilcarbamoil)fenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

3-metil-N-fenil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

3-metil-N-fenil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(4-(terc-butilsulfamoil)fenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-

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((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(4-(terc-butilsulfamoil)fenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

3-metil-N-(4-sulfamoilfenil)-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

3-metil-N-(4-sulfamoilfenil)-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

3-metil-N-(3-((1-metil-1-feniletil)carbamoil)fenil)-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

3-metil-N-(3-((1-metil-1-feniletil)carbamoil)fenil)-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(3-carbamoilfenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-

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prolinamida;

N-(3-carbamoilfenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(3-(dimetilcarbamoil)fenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(3-(dimetilcarbamoil)fenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(3-(dimetilsulfamoil)fenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(3-(dimetilsulfamoil)fenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(3,4-difluorofenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

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N-(3,4-difluorofenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(4-(dimetilcarbamoil)fenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(4-(dimetilcarbamoil)fenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

3-metil-N-(4-((1-metil-1-feniletil)carbamoil)fenil)-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

3-metil-N-(4-((1-metil-1-feniletil)carbamoil)fenil)-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(4-(etilsulfamoil)fenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(4-(etilsulfamoil)fenil)-3-metil-D-valil-(4R)-4-((7-

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cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(4-(dimetilsulfamoil)fenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(4-(dimetilsulfamoil)fenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(4-carbamoilfenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(4-carbamoilfenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

3-metil-N-(3-(metilsulfamoil)fenil)-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

3-metil-N-(3-(metilsulfamoil)fenil)-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-

((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(3-(isopropoxicarbonil)fenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(3-(isopropoxicarbonil)fenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(3-(metoxicarbonil)fenil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(3-(metoxicarbonil)fenil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-1-((2S)-2-((4-etoxi-1,2,5-tiadiazol-3-il)amino)butanoil)-L-prolinamida;

(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-1-((2R)-2-((4-etoxi-1,2,5-tiadiazol-3-

il)amino)butanoil)-L-prolinamida;

N-(2-fluorofenil)-3-metil-D-valil-(4R)-4-[(7-cloro-4-metoxi-1-isoquinolinil)oxi]-N-((1R,2S)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-L-prolinamida;

N-(2-fluorofenil)-3-metil-L-valil-(4R)-4-[(7-cloro-4-metoxi-1-isoquinolinil)oxi]-N-((1R,2S)-1-{[(ciclopropilsulfonil)amino]carbonil}-2-vinilciclopropil)-L-prolinamida;

N-(3,4-difluorofenil)-3-metil-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((9-metoxi-4-metil-3,4-dihidro-2H-[1,4]oxazino[3,2-c]isoquinolin-6-il)oxi)-L-prolinamida;

N-(3,4-difluorofenil)-3-metil-D-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((9-metoxi-4-metil-3,4-dihidro-2H-[1,4]oxazino[3,2-c]isoquinolin-6-il)oxi)-L-prolinamida;

N-(6-metoxi-3-piridinil)-3-metil-L-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

N-(6-metoxi-3-piridinil)-3-metil-D-valil-(4R)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-4-((6-metoxi-1-isoquinolinil)oxi)-L-prolinamida;

N-(6-metoxi-3-piridinil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(6-metoxi-3-piridinil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

N-(6-(difluorometoxi)-3-piridinil)-3-metil-L-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida; y

N-(6-(difluorometoxi)-3-piridinil)-3-metil-D-valil-(4R)-4-((7-cloro-4-metoxi-1-isoquinolinil)oxi)-N-((1R,2S)-1-((ciclopropilsulfonil)carbamoil)-2-vinilciclopropil)-L-prolinamida;

o una sal farmacéuticamente aceptable de los mismos.

9. Una composición, caracterizada porque comprende un compuesto de conformidad con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo, y un portador farmacéuticamente aceptable.

10. La composición de conformidad con la reivindicación 9, caracterizada además porque comprende al menos un compuesto adicional que tiene actividad anti-VHC.

11. La composición de conformidad con la reivindicación

10, caracterizada porque al menos uno de los compuestos adicionales es un interferón o una ribavirina.

12. La composición de conformidad con la reivindicación 11, caracterizada porque el interferón se selecciona de interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A, e interferón tau linfoblastoide.

13. La composición de conformidad con la reivindicación 10, caracterizada porque al menos uno de los compuestos adicionales se selecciona de interleucina 2, interleucina 6, interleucina 12, un compuesto que mejora el desarrollo de una respuesta de célula T auxiliar tipo 1, ARN de interferencia, ARN antisentido, Imiqimod, ribavirina, un inhibidor de 5'-monofosfato deshidrogenasa inosina, amantadina, y rimantadina.

14. La composición de conformidad con la reivindicación 10, caracterizada porque al menos uno de los compuestos adicionales es efectivo para inhibir la función de un objetivo seleccionado de metaloproteasa de VHC, serina proteasa de VHC, polimerasa de VHC, helicasa de VHC, proteína NS4B de VHC, entrada de VHC, ensamble de VHC, salida de VHC, proteína NS5A de VHC, e IMPDH para el tratamiento de una infección por VHC.

15. Un método de tratamiento de una infección por VHC en un paciente, caracterizado porque comprende administrar al

paciente una cantidad terapéuticamente efectiva de un compuesto de conformidad con la reivindicación 1, o una sal aceptable farmacéuticamente del mismo.

16. El método de conformidad con la reivindicación 15, caracterizado porque comprende además administrar al menos un compuesto adicional que tiene actividad anti-VHC antes de, después o simultáneamente con el compuesto de conformidad con la reivindicación 1, o una sal farmacéuticamente aceptable del mismo.

17. El método de conformidad con la reivindicación 16, caracterizado porque al menos uno de los compuestos adicionales es un interferón o una ribavirina.

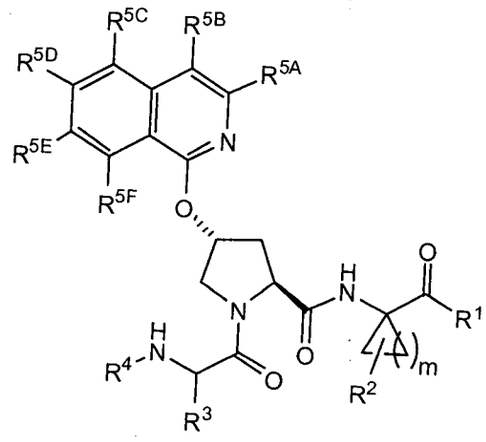
18. El método de conformidad con la reivindicación 17, caracterizado porque el interferón se selecciona de interferón alfa 2B, interferón alfa pegilado, interferón de consenso, interferón alfa 2A, e interferón tau linfoblastoide.

19. El método de conformidad con la reivindicación 16, caracterizado porque al menos uno de los compuestos adicionales se selecciona de interleucina 2, interleucina 6, interleucina 12, un compuesto que mejora el desarrollo de una respuesta de célula T auxiliar tipo 1, ARN de interferencia, ARN antisentido, Imiqimod, ribavirina, un inhibidor de 5'-monofosfato deshidrogenasa inosina, amantadina, y rimantadina.

20. El método de conformidad con la reivindicación 16, caracterizado porque al menos uno de los compuestos adicionales es efectivo para inhibir la función de un objetivo seleccionado de metaloproteasa de VHC, serina proteasa de VHC, polimerasa de VHC, helicasa de VHC, proteína HCV NS4B, entrada de VHC, ensamble de VHC, salida de VHC, proteína NS5A de VHC, e IMPDH para el tratamiento de una infección por VHC.

RESUMEN DE LA INVENCION

Se describen inhibidores del virus de Hepatitis C que tienen la fórmula general



También se describen composiciones que comprenden los compuestos y métodos de uso de los compuestos para inhibir el VHC.

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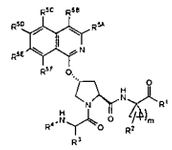
Industria y Comercio
SUPERINTENDENCIA

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

(21) N° de solicitud:	(51) Int Cl: C07D 401/12; A61K 31/4709; A61P 31/14; C07D 401/14; C07D 417/14 ; C07K 5/00
22) Fecha de solicitud:	(71)Solicitante(s) BRISTOL-MYERS SQUIBB COMPANY
(30) Prioridad (31) ***No.*** 32) ***Fecha*** (33) ***País*** 60/865,034 09.11.2006 US 11/934,840 05.11.2007 US	(72) Inventor(es) SIN, Ny; VENABLES, Brian Lee; Y OTROS
	(74) Apoderado: **ALVARO CORREA ORDOÑEZ**
(85) Fecha limite inicio fase nacional: 09-06-2009 (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud: 08.11.2007 No. de solicitud PCT/US2007/084012	(87) Publicación internacional Fecha: 22.05.2008 N° publicación: WO/2008/060927
(54) Titulo: INHIBIDORES DEL VIRUS DE LA HEPATITIS C	

Reivindicación(es):

1. Un compuesto de la fórmula (I)



(I)

o una sal farmacéuticamente aceptable de la misma, caracterizado porque

m es 1, 2, ó 3;

R1 se selecciona de hidroxi y –NHSO2R6; en donde R6 se selecciona de alquilo, arilo, cicloalquilo, (cicloalquil)alquilo, heterociclilo, y –NRaRb, en donde el alquilo, el cicloalquilo y la parte cicloalquilo del (cicloalquil)alquilo están opcionalmente substituidos con uno, dos, o tres substituyentes seleccionados de alquenilo, alcoxi, alcoxialquilo, alquilo, arilalquilo, arilcarbonilo, ciano, cicloalquenilo, (cicloalquil)alquilo, halo, haloalcoxi, haloalquilo, y (NReRf)carbonilo;

R2 se selecciona de hidrógeno, alquenilo, alquilo, y cicloalquilo, en donde el alquenilo, alquilo, y cicloalquilo están opcionalmente substituidos con halo;

R3 se selecciona de alquenilo, alcoxialquilo, alcoxicarbonilalquilo, alquilo, arilalquilo, carboxialquilo, cianoalquilo, cicloalquilo, (cicloalquil)alquilo, haloalcoxi, haloalquilo, (heterociclil)alquilo, hidroxialquilo, (NRcRd)alquilo, y (NReRf)carbonilalquilo;

R4 se selecciona de fenilo y un anillo parcialmente o completamente insaturado de cinco o seis miembros que contiene opcionalmente uno, dos, tres, o cuatro heteroátomos seleccionados de nitrógeno, oxígeno, y azufre; en donde cada uno de los anillos es opcionalmente substituido con uno, dos, tres, o cuatro substituyentes independientemente seleccionados de alcoxi, alcoxicarbonilo, alquilo, alquilcarbonilo, alquilsulfanilo, carboxi, ciano, cicloalquilo, cicloalquiloxi, halo, haloalquilo, haloalcoxi, –NRcRd, (NReRf)carbonilo, (NReRf)sulfonilo, y oxo; con la condición de que cuando R4 es un anillo substituido de seis miembros todos los substituyentes en el anillo diferentes a fluoro deberán estar en las posiciones meta y/o para con relación al punto de enlace del anillo a la porción de molécula precursora;

R5A, R5B, R5C, R5D, R5E y R5F son cada uno independientemente seleccionados de hidrógeno, alcoxi, alcoxicarbonilo, alquilo, alquilcarbonilo, arilo, carboxi, ciano, cianoalquilo, cicloalquilo, halo, haloalquilo, haloalcoxi, heterociclilo, hidroxi, hidroxialquilo, nitro, –NRcRd, (NRcRd)alquilo, (NRcRd)alcoxi, (NReRf)carbonilo, y (NReRf)sulfonilo; o

dos grupos R5 adyacentes, junto con los átomos de carbono a los cuales son enlazados, forman un anillo parcialmente o completamente insaturado de cuatro a siete miembros que contiene opcionalmente uno o dos heteroátomos independientemente seleccionados de nitrógeno, oxígeno, y azufre, en donde el anillo está opcionalmente substituido con uno, dos, o tres grupos independientemente seleccionados de alcoxi, alquilo, ciano, halo, haloalcoxi, y haloalquilo;

Ra y Rb son independientemente seleccionados de hidrógeno, alcoxi, alquilo, arilo, arilalquilo, cicloalquilo, (cicloalquil)alquilo, heterociclilo, y heterociclilalquilo; o Ra y Rb junto con el átomo de nitrógeno al cual son enlazados forman un anillo monocíclico heterocíclico de cuatro a siete miembros;

Rc y Rd son independientemente seleccionados de hidrógeno, alcoxialquilo, alcoxicarbonilo, alquilo, alquilcarbonilo, arilalquilo, y haloalquilo; y

Re y Rf son independientemente seleccionados de hidrógeno, alquilo, arilo, arilalquilo, y heterociclilo; en donde el arilo, la parte arilo del arilalquilo, y el heterociclilo están opcionalmente substituidos con uno o dos substituyentes independientemente seleccionados de alcoxi, alquilo, y halo.

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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 : C07D 401/12; A61K 31/4709; A61P 31/14; C07D 401/14; C07D 417/14 ; C07K 5/00

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

(72) Inventor(es) SIN, Ny; VENABLES, Brian Lee; SUN, Li-Qiang; SIT, Sing-Yuen; CHEN, Yan; SCOLA, Paul Michael.

(74) Apoderado: ALVARO CORREA ORDOÑEZ

(30) Prioridad	(31) *No. Prioridad*	32) *Fecha*	(33) *País*
	60/865,034	09.11.2006	US
	11/934,840	05.11.2007	US

(85) Fecha inicio fase nacional: 09-06-2009

(86) Datos relativos a la presentación de la solicitud PCT
Fecha de presentación de la solicitud: 08.11.2007
No. de solicitud PCT/US2007/084012

(87) Publicación internacional
Fecha: 22.05.2008
N° publicación: WO/2008/060927

(54) Titulo: INHIBIDORES DEL VIRUS DE LA HEPATITIS C

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Industria y Comercio
SUPERINTENDENCIA

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

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

(21) N° de solicitud: (22) Fecha de solicitud:

(51) Clasificación Internacional : C07D 401/12; A61K 31/4709; A61P 31/14; C07D 401/14; C07D 417/14 ; C07K 5/00

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

(72) Inventor(es) SIN, Ny; VENABLES, Brian Lee; SUN, Li-Qiang; SIT, Sing-Yuen; CHEN, Yan; SCOLA, Paul Michael.

(74) Apoderado: ALVARO CORREA ORDOÑEZ

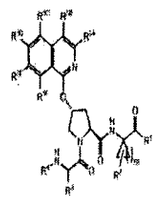
(30) Prioridad

(31) *No. Prioridad*	32) *Fecha*	(33) *País*
60/865,034	09.11.2006	US
11/934,840	05.11.2007	US

(85) Fecha límite inicio fase nacional: 09-06-2009

(86) Datos relativos a la presentación de la solic. PCT
Fecha de presentación de la solicitud: 08.11.2007
No. de solicitud PCT/US2007/084012

(87) Publicación internacional:
Fecha:
No. Publicación :



(54) Titulo: INHIBIDORES DEL VIRUS DE LA HEPATITIS C

(57) Resumen: Se describen inhibidores del virus de Hepatitis C que tienen la fórmula general. También se describen composiciones que comprenden los compuestos y métodos de uso de los compuestos para inhibir el VHC.

822

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

2009/004

RECIBO OFICIAL DE CAJA : 09 - 18,514
FECHA : MARZO 6 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-047361- -00000-0000
Fecha: 2009-05-11 15:36:01 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 826

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	VR PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	14472172	06/03/2009	75,329,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN		540,000.00
		TOTAL :	$	540,000.00

SON: QUINIENTOS CUARENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

823

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

2009/004

RECIBO OFICIAL DE CAJA : 09 - 18,408
FECHA : MARZO 6 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-047361- -00000-0000

Fecha: 2009-05-11 15:36:01 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONAL!
Act. 411 PRESENTACION Folios: 826

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	14472172	06/03/2009	75,329,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-08 PRORROGA DE TERMINOS	31 PRORROGA DE TERMINOS	81,000.00
		TOTAL : $	81,000.00

SON: OCHENTA Y UNO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

824

NIT : 800176089-2

2009/001

RECIBO OFICIAL DE CAJA : 09 - 2,341
FECHA : ENERO 13 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-047361- -00000-0000
Fecha: 2009-05-11 15:36:01 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 826

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	RECIBO DE CAJA			2233	09/01/2009	5,904,000.00

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

CANT.	RENTISTICO		CONCEPTO		TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	998	VALOR COMPLEMENTO TARIFA A#O ANTR	32,000.00
				TOTAL : $	32,000.00

SON: TREINTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

825

2008/023

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-047361- -00000-0000
Fecha: 2009-05-11 15:36:01 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 826

CERTIFICACION DE EXCEDENTE : 08 - 100,364
FECHA : DICIEMBRE 26 DE 2008

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	120646805	24/12/2008	46,377,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS	6,000.00
		TOTAL : $	6,000.00

SON: SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

826

2008/023

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 08 - 100,365
FECHA : DICIEMBRE 26 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-047361- -00000-0000
Fecha: 2009-05-11 15:36:01 Dep. 2020 NUECREACION
Tra. 11 PATENTEIY!I Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 826

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BAKER & MCKENZIE	CONSIGNACION	BANCO DE BOGOTA	062754387	120646805	24/12/2008	46,377,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVCIOS ADMINISTRATIVOS	6,000.00
		TOTAL : $	6,000.00

SON: SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER SUSTITUIDA POR NINGUN RECIBO.

BAKER & McKENZIE

Baker & McKenzie Colombia S.A.
Av. 82 No. 10 - 62 Piso 6
Bogotá, Colombia

NIT: 900.034.906-9
Tel: +57 1 634 1500
Fax: +57 1 376 2211
www.bakernet.com

Señores

Centro de Documentación e Información

SUPERINTENDENCIA DE INDUSTRIA Y CO

E. S.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-129339- -00000-0000

Fecha: 2008-12-04 16:12:05 Dep. 2000 DESPROPINDUS
Tra. 334 REMISIINFORMA Eve:
Act. 411 PRESENTACION Folios: 6

Referencia: Archivo de poder general para Bristol-Myers Squibb Company

Apoderados: Alvaro Correa-Ordoñez y/o Olga Georgette Otero y/o Ricardo Metke y/o Juan Pablo Concha

SOLICITUD DE ARCHIVO DE PODER GENERAL DE ACUERDO CON LA CIRCULAR EXTERNA NO. 007 DEL 10 DE SEPTIEMBRE DE 2008

ÁLVARO CORREA ORDÓÑEZ, mayor de edad y vecino de Bogotá D.C., identificado según aparece al pie de mi firma, en mi condición de apoderado de la sociedad en referencia, manifiesto lo siguiente:

1. En atención a lo dispuesto en la Circular Externa No. 007 del 10 de septiembre de 2008, la cual implementó el procedimiento para archivo de poderes generales para los asuntos en materia de Propiedad Industrial ante la Superintendencia de Industria y Comercio, solicito el archivo del poder otorgado por la sociedad Bristol-Myers Squibb Company domiciliada en New Jersey, Estados Unidos de América, a mi favor.

2. En consecuencia, solicito se me informe el número de radicación en el archivo de poderes generales para consulta y referencia en futuros trámites para esta sociedad.

Atentamente,

ÁLVARO CORREA ORDÓÑEZ
C.C.No.79.143.366 de Usaquén
T.P.20.281

Anexo: Copia autentica del Poder de Abogado

BOGATM/BOGDMS-139874.DOC

827

POD-4002

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

PODER OTORGADO POR BRISTOL-MYERS SQUIBB COMPANY

APOSTILLA

1. PAÍS: ESTADOS UNIDOS DE AMÉRICA

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

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

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

CERTIFICADO

5. EN TRENTON, NUEVA JERSEY

6. EL 28 DE JUNIO DE 2007

7. POR BRADLEY ABELOW, TESORERO DE NUEVA JERSEY

8. N° A295716

9. SELLO (APARECE ADHERIDO SELLO DORADO)

10. FIRMA (FIRMADO) BRADLEY ABELOW

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

Dado y suscrito el 30 de mayo de 2007

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

JAIME A. GARAVITO

COTEJO ... ONCE DE ESTE CIRCULO HAGO CONSTAR QUE ÉSTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA.

02 DIC 2008

BOGOTÁ, D.C. - COLOMBIA
ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

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

CERTIFICACIÓN NOTARIAL

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

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

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

[Firmado] SALLY B. HANSEN, Notario Público

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

[Aparece sello realzado]

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

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

BOGDM5 # 82106

JAIME A. GARAVITO B.
TRADUCTOR E INTERPRETE
Res. 034 de Enero 11 de 19
MINISTERIO DE JUSTICIA

COMO NOTARIO ONCE DE ESTE CONSTAR QUE ÉSTA COPIA COINCIDE CON EL QUE HE TENIDO A LA VISTA.
02 DIC 2008
BOGOTÁ, D.C. - COLOMBIA
ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

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

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

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

CERTIFIED

5. AT TRENTON, NEW JERSEY

6. THE 28TH DAY OF JUNE 2007

7. BY: Bradley Abelow, NEW JERSEY TREASURER

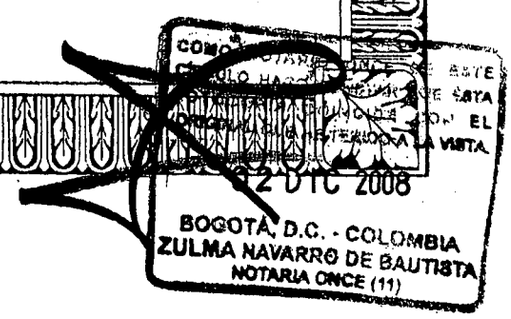
8. NO. A295716

9. SEAL/STAMP:

10. SIGNATURE

Bradley Abelow





830

BAKER & MCKENZIE

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

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

POWER OF ATTORNEY

The undersigned.

BRISTOL–MYERS SQUIBB COMPANY

domiciled in

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

declares that it hereby grants to

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

with domicile at Av. 82 No. 10 – 62, 6Th floor, of Bogotá D. C., Colombia, a full and sufficient power of attorney to obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models, industrial designs, integrated circuits, layout-designs and vegetal varieties; the registration of trademarks, denominations of origin, commercial names, trade emblems, slogans and domain names; its renewal, assignments, change of name or domicile, voluntary cancellation; and the registration of licenses of use of the above rights; b)Processes of protection to the consumer, unfair competition, oppositions, cancellations, nullity, precautionary injunctions, infringement, granting of licenses, writ mandamus, the protection of trade secrets, and in general the civil, penal, an administrative processes relating to those rights. And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

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

Done and subscribed in

On the 30 day of May of 2007

Signature of the person issuing the Power

Anastasia P. Winslow
Senior Patent Counsel

PODER DE ABOGADO

La abajo firmada,

BRISTOL–MYERS SQUIBB COMPANY

domiciliada en

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

declara por el presente que otorga a

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

con domicilio en la Av. 82 No. 10 – 62 Piso 6 en Bogotá D. C., Colombia, poder especial amplio y suficiente, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera autoridades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, diseños industriales, esquemas de trazado de circuitos integrados y variedades vegetales; el registro de marcas, denominaciones de origen, nombres comerciales, enseñas, lemas comerciales y nombres de dominio; su renovación, traspaso, cambio de nombre o domicilio, cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Los procesos para la protección del consumidor, competencia desleal, oposiciones, cancelaciones, nulidades, medidas cautelares, infracciones, concesión de licencias, la tutela, la protección de secretos industriales, y en general procesos civiles, penales, administrativos relacionados con estos derechos. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del caso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

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

Dado y firmado en

A los 30 días del mes de mayo de 2007

Firma de la persona que firma el Poder

COMO [illegible] ONCE DE ESTE CÍRCULO HAGO CONSTAR QUE ÉSTA FOTOCOPIA COINCIDE CON EL [illegible] QUE HE TENIDO A LA VISTA.

02 DIC 2008

BOGOTÁ D.C. - COLOMBIA
ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

83

NOTARIAL CERTIFICATION

On this 30 day of May

2007 , the undersigned Notary

CERTIFIES

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

set his hand on the foregoing document.

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

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

4. That the judicial person **BRISTOL-MYERS SQUIBB COMPANY**
having its home office in

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

is duly organized, has present legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.

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

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

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

CERTIFICACION NOTARIAL

A los 30 días del mes de mayo

de 2007 , el suscrito Notario

DA FE

1 Que Anastasia P. Winslow

mayor y domiciliado en Princeton, NJ
Estados Unidos de América

suscribió de su puño y letra el documento que antecede.

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

3 Que el otorgante ha suscrito el referido documento en su carácter de

Abogados de Patentes Senior
de la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**

4 Que la persona jurídica **BRISTOL-MYERS SQUIBB COMPANY**

con sede en

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

está legalmente constituida, que tiene existencia legal actual y que el acto para el cual se otorga el poder está comprendido entre los que constituyen su objeto social.

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

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

El Notario Público HACE CONSTAR QUE ÉSTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA.
02 OCT 2008
BOGOTÁ, D.C. - COLOMBIA
ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

832

Industria y Comercio

SUPERIN

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-047361- -00000-0000

Fecha: 2009-05-11 15:36:01 Dep: 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 826

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN (X) MODELO DE UTILIDAD ( )	( )	( )
-Indicación de que se solicita la concesión de una patente.		
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	X	( )
-Descripción de la invención.	X	( )
-Dibujos de ser estos pertinentes.	X	( )
-Comprobante de Pago de las tasas establecidas.	X	( )
COMPLETA (X) INCOMPLETA		
DISEÑO INDUSTRIAL ( )	( )	( )
-Indicación de que se solicita el registro de Diseño Industrial.		
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
-Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )		
-Indicación de que se solicita el registro de Diseño Industrial.		
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
-Representación gráfica del Esquema Trazado.	( )	( )
-Comprobante de Pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable: _____

Fecha: Mayo 11/09

833

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 March 2003 (27.03.2003)

PCT

(10) International Publication Number
WO 03/024971 A1

(51) International Patent Classification[7]: C07D 487/04, A61P 29/00

(21) International Application Number: PCT/US02/30135

(22) International Filing Date:
20 September 2002 (20.09.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/323,625 20 September 2001 (20.09.2001) US

(71) Applicant: **THE PROCTER & GAMBLE COMPANY** [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US).

(72) Inventors: **CLARK, Michael, Phillip**; 10563 S. State Route 48, Loveland, OH 45140 (US). **LAUFER-SWEILER, Matthew, John**; 4251 Green Arbors Lane, Cincinnati, OH 45249 (US). **DJUNG, Jane, Far-Jine**; 5747 W. Fountain Cr., Mason, OH 45040 (US). **NATCHUS, Michael, George**; 555 Waterview Trail, Alpharetta, GA 30022 (US). **DE, Biswanath**; 11269 Cornell Woods Drive, Cincinnati, OH 45241 (US).

(74) Agents: **REED, T., David** et al.; The Procter & Gamble Company, 6110 Center Hill Road, Cincinnati, OH 45224 (US).

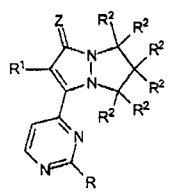
(81) Designated States *(national)*: AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID,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

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

Published:
— *with international search report*

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

(54) Title: 6,7-DIHYDRO-5H-PYRAZOLO[1,2-A]PYRAZOL-1-ONES WHICH CONTROL INFLAMMATORY CYTOKINES



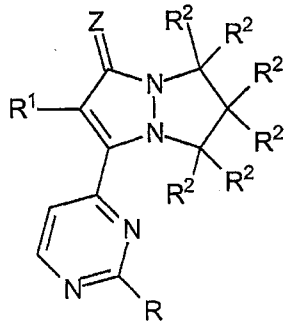
(I)

(57) Abstract: The present invention relates to compound which are capable of preventing the extracellular release of inflammatory cytokines, said compounds, including all enantiomeric and diasteriomeric forms and pharmaceutically acceptable salts thereof, have the formula (I): wherein R comprises ethers or amines; R1 is: a) substituted or unsubstituted aryl; or b) substituted or unsubstituted heteroaryl; each R?2¿ unit is independently selected from the group consisting of: a) hydrogen; b) -(CH¿2?)¿j?O(CH¿2?)nR?8¿; c) -(CH¿2?)¿j?NR?9a¿R?9b¿; d) -(CH¿2?)¿j?CO¿2?R?10¿; e) -(CH¿2?)¿j?OCO?2¿R?10¿ f) -(CH¿2?)¿j?CON(R?10¿)¿2? g) -(CH¿2?)¿j?OCON(R?10¿)¿2?; h) two R?2¿ units can be taken together to form a carbonyl unit; i) and mixtures thereof; R?8¿, R?9a¿, R?9b¿, and R?10¿ are each independently hydrogen, C¿1?-C¿4? alkyl, and mixtures thereof; R?9a¿ and R?9b¿ can be taken together to form a carbocyclic or heterocyclic ring comprising from 3 to 7 atoms; two R?10¿ units can be take together to form a carbocyclic or heterocyclic ring comprising from 3 to 7 atoms; j is an index from 0 to 5, n is an index from 0 to 5;Z is O, S, NR?11¿, or NOR?11¿; R?11¿ is hydrogen or C¿1?-C¿4? alkyl.

WO 03/024971 A1

What is claimed is:

1. A compound, including all enantiomeric and diasteriomeric forms and pharmaceutically acceptable salts thereof, said compound having the formula:



wherein R is:

a) $-O[CH_2]_kR^3$; or

b) $-NR^{4a}R^{4b}$;

R^3 is substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted hydrocarbyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl or alkylenearyl, substituted or unsubstituted heteroaryl or alkyleneheteroaryl; the index k is from 0 to 5;

R^{4a} and R^{4b} are each independently:

a) hydrogen; or

b) $-[C(R^{5a}R^{5b})]_mR^6$;

each R^{5a} and R^{5b} are independently hydrogen, $-OR^7$, $-N(R^7)_2$, $-CO_2R^7$, $-CON(R^7)_2$; C_1-C_4 linear, branched, or cyclic alkyl, and mixtures thereof; R^6 is hydrogen, $-OR^7$, $-N(R^7)_2$, $-CO_2R^7$, $-CON(R^7)_2$; substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted aryl heterocyclic, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^7 is hydrogen, a water-soluble cation, C_1-C_4 alkyl, or substituted or unsubstituted aryl; the index m is from 0 to 5;

R^1 is:

a) substituted or unsubstituted aryl; or

b) substituted or unsubstituted heteroaryl;

each R^2 unit is independently selected from the group consisting of:

a) hydrogen;

b) $-(CH_2)_jO(CH_2)_nR^8$;

c) $-(CH_2)_jNR^{9a}R^{9b}$;

d) $-(CH_2)_jCO_2R^{10}$;

e) $-(CH_2)_jOCO_2R^{10}$

f) $-(CH_2)_jCON(R^{10})_2$;

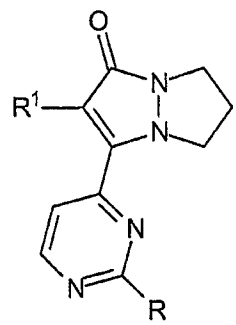
g) $-(CH_2)_jOCON(R^{10})_2$;

h) two R^2 units can be taken together to form a carbonyl unit;

l) and mixtures thereof;

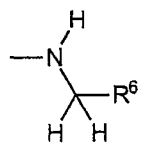
R^8, R^{9a}, R^{9b}, and R^{10} are each independently hydrogen, C_1-C_4 alkyl, and mixtures thereof; R^{9a} and R^{9b} can be taken together to form a carbocyclic or heterocyclic ring comprising from 3 to 7 atoms; two R^{10} units can be take together to form a carbocyclic or heterocyclic ring comprising from 3 to 7 atoms; j is an index from 0 to 5, n is an index from 0 to 5; Z is O, S, NR^{11}, or NOR^{11}; R^{11} is hydrogen or C_1-C_4 alkyl.

2. A compound according to Claim 1 having the formula:

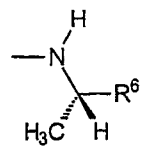


wherein R is an ether unit having the formula $-OR^3$ wherein R^3 is selected from the group consisting of phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluoro-phenyl, 2,6-difluorophenyl, 2-cyanophenyl, 3-cyanophenyl, 2-trifluoromethylphenyl, 4-trifluoromethylphenyl, 2-methylphenyl, 4-methylphenyl, 2,4-dimethylphenyl, 3-N-acetyl-aminophenyl, 2-methoxyphenyl, 4-methoxyphenyl, and 3-benzo[1,3]dioxol-5-yl;

an amino unit having the formula:



or an amino unit having the formula:



wherein R^6 is selected from the group consisting of hydrogen, methyl, ethyl, vinyl, cyclopropyl, cyclohexyl, methoxymethyl, methoxyethyl, 1-hydroxy-1-methylethyl, carboxy,